AN INVESTIGATION INTO THE IMPACT OF CONGENITAL ANOMALIES ON INFANT MORBIDITY AND MORTALITY



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This dissertation is my original work.



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Table I: Abbreviations

Abbreviation	Term
ALF	Anonymised linking field.
aOR	Adjusted odds ratio.
aRRR	Adjusted relative risk ratios.
BINOCAR	British and Irish Network of Congenital Anomaly Researchers.
BMI	Body mass index.
BPA	British Paediatric Association.
CAPSNet	Canadian Pediatric Surgery Network.
CARIS	Congenital Anomaly Register and Information Service for Wales.
CAROBB	Congenital Anomaly Register for Oxfordshire, Berkshire and Buckinghamshire.
CCASS	Canadian Congenital Anomalies Surveillance System.
CDC	Centers for Disease Control and Prevention.
CDH	Congenial diaphragmatic hernia.
CHD(s)	Congenital heart defect(s).
CI	Confidence interval.
CPQCC	California Perinatal Quality Care Collaborative.
ECMO	Extracorporeal membrane oxygenation.
EMSYCAR	East Midlands and South Yorkshire Congenital Anomalies Register.
EUROCAT	The European Surveillance of Congenital Anomalies.
FASP	Fetal Anomaly Screening Programme.
FMI	Fraction of missing information.
HES	Hospital Episodes Statistics in England.
HS-CHD	Haemodynamically significant congenital heart disease
ICBDSR	International Clearinghouse for Birth Defects Surveillance and Research.
ICD-9-CM	The International Classification of Diseases and Related Health Problems-Ninth Revision-Clinical Modification.
ICD-10 RCPCH	The Royal College of Paediatrics and Child Health adaptation of the 10th revision of the International Classification of Diseases and Related Health Problems.
IGRP	Information Governance Review Panel.
IQR	Interquartile range.
KID	Kids' Inpatient Database.
LRT	Likelihood ratio test.
MAR	Missing at random.
MCAR	Missing completely at random.
MCDK	Multicystic renal dysplasia.
MeSH terms	Medical Education Subject Headings terms.
MI	Multiple imputation.
MNAR	Missing not at random.
MOOSE checklist	Meta-analysis of Observation Studies in Epidemiology checklist.
NCCHD	National Community Child Health Database.
NICU	Neonatal Intensive Care Unit.
NorCAS	Northern Congenital Abnormality Survey.
NSQIP-P	The American College of Surgeons' National Surgery Quality Improvement Program-Pediatric database.
NTD(s)	Neural tube defect(s).

Table I (continued): Abbreviations

Abbreviation	Term
NWIS	The NHS Wales Information Service, previously known as Health Solution Wales (HSW).
OFC	Orofacial clefts.
ONS	Office for National Statistics.
OPCS-4	Classification of Surgical Operations and Procedures 4th Revision.
PDA	Patent ductus arteriosus.
PEDW	Patient Episode Database for Wales.
PICU	Paediatric intensive care unit.
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses.
PROSPERO	The International Prospective Register of Systematic Reviews.
RCPCH	Royal College of Paediatrics and Child Health.
RoB	Risk of bias.
RR	Relative risk.
RSV	Respiratory Syncytial Virus.
SAIL databank	The Secure Anonymised Information Linkage databank.
SDGs	Sustainable Development Goals.
SQL	Structured Query Language.
SURE	Safe User of Research data Environments.
SWCAR	South West Congenital Anomaly Register.
TOF and OA	Tracheoesophageal fistula and oesophageal atresia.
TOPFA	Termination of pregnancy for fetal abnormality.
TPN	Total parenteral nutrition.
UN	The United Nations.
uOR	Unadjusted (or crude) odds ratio.
uRRR	Unadjusted (or crude) relative risk ratios.
URTIs	Upper respiratory tract infections.
UTI	Urinary tract infection.
VON	Vermont Oxford Network.
WANDA	Wessex Antenatally Detected Anomalies Register.
WHO	The World Health Organisation.

Table II: Terms and definitions.

Term	Definition
Anencephaly	Partial or total absence of the scalp, skull and brain tissue.
Anomaly-specific admissions	Refers to the primary cause of admissions due to congenital and chromosomal anomalies as defined by the ICD chapter headings.
APGAR score	A scoring method to assess the condition of a newborn child at birth, named after Dr. Virginia Apgar, an anaesthesiologist. It is determined by the appearance, pulse, respiratory effort, muscle tone and reflex of the newborn.
Birth hospitalisation	Refers to admissions of healthy babies solely for birth in hospital.
Birth prevalence rate of an anomaly	Calculated by the total number of births (live and still) cases of an anomaly divided by the total number of births (live and still), expressed per 1,000 or per 10,000 total births.
Cochrane Q test	As chi-square statistics to assess whether the observed differences are compatible with chance alone.
Complex gastroschisis	Refers to gastroschisis with a bowel perforation, necrosis or atresia.
Congenital anomalies	CARIS definition: structural, metabolic, endocrine or genetic defects, as well as rare diseases of genetic or hereditary origin, present in the child/ fetus at the end of pregnancy, even if not detected until after the birth. CDC definition: abnormalities of body structure or function that are present at birth and are of prenatal origin. EUROCAT definition: structural defects (i.e. including congenital malformations, deformations, disruptions and dysplasias) and chromosomal abnormalities that occur during intrauterine life.
Congenital heart defects (CHDs): severity classification.	Least severe CHDs include ventricular septal defect (VSD), atrial septal defect (ASD) and pulmonary valve stenosis. Moderate severe CHDs include common arterial truncus, transposition of great vessels, atrioventricular septal defect (AVSD), tetralogy of Fallot (ToF), pulmonary valve atresia, aortic valve atresia/ stenosis, coarctation of aorta and total anomalous pulmonary venous return. Most severe CHDs include single ventricle, tricuspid atresia and stenosis, Ebstein's anomaly, hypoplastic left heart and hypoplastic right heart.
Day Case	Refers to patients who were admitted electively for treatment or care that did not require an overnight hospital stay.
Encephalocele	Herniation of the brain and/or meninges through a defect in the skull.
Encephalocele neonatal/infant mortality rate (NMR/IMR)	Calculated by the number of neonates/infants with encephalocele who died, divided by the total number of all livebirths in a population in the relevant time period; expressed per 100, 000 livebirths.
Encephalocele neonatal/infant case fatality	Calculated by the number of neonates/infants with encephalocele who died, divided by the number of all neonates/infants born with encephalocele in the relevant population; expressed as the proportion (%) of livebirths affected by encephalocele.
Episode	The period in which a patient was under the care of one consultant within a provider spell.

Table II (continued): Terms and definitions.

Term	Definition
Fixed-effects model	A method in meta-analysis to estimate the combined effect as the common effect size, assuming that there is one true effect size which is shared by all the included studies.
Fraction of missing information (FMI)	A parameter-specific measure to quantify the loss of information due to missing data and considered as a better guide to the efficiency gain from multiple imputation than the proportion of missing data. Scaled between 0 and 1, a larger FMI indicates high variability and that the observed data in the imputation model do not provide much information about the missing data.
Frequency of hospitalisation	Calculated by the total number of spells per infant admitted.
Infant case fatality related to an anomaly	Calculated as the proportion of deaths of infants with an anomaly among total number of liveborn cases with that anomaly (as a percentage).
Infant death	Death of an infant occurring after birth until first year after birth.
Infant mortality rate (IMR)	Calculated by the total number of infant deaths in a study population divided by the total number of livebirths in the study population; expressed per 1,000 or 10,000 livebirths.
In-patients	Refers to the patients who were admitted to hospital and staying at least one night.
Isolated congenital anomaly (or disease)	Refers to single anomaly (or disease) which was diagnosed and reported to CARIS.
Livebirth prevalence rate of an anomaly	Calculated by the total number of livebirths cases of an anomaly divided by the total number of livebirths; expressed per 1,000 or per 10,000 livebirths.
Lower Layer Super Output Areas (LSOA)	A geographic hierarchy designed to improve the reporting of small area statistics in England and Wales.
Main cause of neonatal deaths	Refers to the earliest cause in the chain of events leading to neonatal death.
Major anomalies	Refer to anomalies included in the EUROCAT Subgroups of Congenital Anomalies as described in the EUROCAT Guide 1.4 (EUROCAT 2016).
Minor anomalies	Refer to anomalies of lesser medical, functional or cosmetic consequences as described in the EUROCAT Guide 1.4 (EUROCAT 2016).
Multiple imputation performed using chained equations (MICE)	A method to replace missing data using an iterative series of predictive models with fully conditional specification appropriate for the distributions of the affected variables simultaneously.
Neonatal death	Death of an infant occurring after birth until 28 days after birth.
ONS cause (of death) group hierarchical classification	A hierarchical classification developed to allow the infant deaths to be assigned to a specific category according to the likely timing of the damage leading to the death, so that comparison of neonatal and post-neonatal deaths can be possible following a change in deaths certificates for neonatal deaths and stillbirths whereby a single underlying cause of death was not assigned.

Table II (continued): Terms and definitions.

Term	Definition
Other-cause admissions	Refer to admissions due to any other causes except for congenital and chromosomal anomalies as defined by the ICD chapter headings.
Pattern of infant hospitalisation	This entails causes, frequency and length of hospital stay of infants in the first year after birth.
Person time (or at risk time, in days) to admission	For the first spell, person time was calculated from date of the admission minus the date of the Monday that occurred prior to the actual date of birth (as date of birth was considered as sensitive data and not provided. Only WoB was provided); hence, person time for the first spell was accurate to seven days. For the second spell onwards, person time was calculated from the admission date minus the discharge date of the prior admission.
Population, Exposure(s), Comparison(s) and Outcome (PECO)	A framework used to define research objectives and formulate literature search when conducting a systematic review.
Post-neonatal death	Death of an infant occurring after 28 days following birth until the first birthday.
Preterm birth	Birth of an infant before 37^{+0} complete weeks of gestation.
Primary cause of admission/ diagnosis	Refers to the diagnosis designated to the first episode of each spell.
Primary prevention	Refers to interventions aiming to prevent disease before it ever occurs (e.g. folic acid supplementation to prevent the occurrence of NTDs).
Random-effects model	A method in meta-analysis to estimate the mean of a distribution of effects, taking into account that the true effect size is likely to vary from one population to another due to different exposures; and therefore smaller studies are given weights more equally to larger size studies.
Rates of infant hospitalisation	Calculated by the number of admissions per person year in the first year after birth.
Secondary prevention	Refers to interventions aiming to reduce the impact of a disease that has already occurred (e.g. by detecting and treating the disease as soon as possible and appropriate).
Spell/ provider spell	Total continuous stay of a patient using a bed on premises controlled by the NHS health care provider. Spells were initiated with an admission episode and would end by either a discharge, transfer to another NHS provider or death. In 90% of cases, the provider spell consisted of just one consultant episode.
Spell duration or Length of stay (LOS)	Period of time (in days) between start date of provider spell and discharge date of the provider spell. For infants who were admitted from birth, the length of stay of that spell was calculated from the discharge date minus the date of the Monday that occurred prior to the actual date of birth (as date of birth was deemed sensitive data, and only WoB was provided). If admission and discharge were on the same date, the spell duration were set to 0.5 days to represent some extent of stay. Total LOS of an infant was calculated by the sum of duration (in days) of all the hospital spells across all admissions in infancy.

Table II (continued): Terms and definitions.

Term	Definition
Spell rank	Presented as the 1st, 2nd, 3rd spell etc. in the PEDW dataset. Spell rank order was derived using data from dates of admission and discharge specific to each infant.
Spina bifida	Herniation or exposure of the spinal cord and/ or meninges through an opening defect in the spine.
Spina bifida neonatal/infant mortality rate (NMR/ IMR)	Calculated by number of neonates/infants with spina bifida who died, divided by the total number of all livebirths in the population in the relevant time period; expressed per 100, 000 live births.
Spina bifida neonatal/infant case fatality	Calculated by the number of neonates/infants with spina bifida who died, divided by the number of all neonates/infants born with spina bifida in the relevant population; expressed as the proportion (%) of livebirths affected by spina bifida.
Spina bifida occulta	A mild form of spina bifida with no clinical consequence.
Tertiary prevention	Refers to interventions aiming to reduce the impact of an ongoing illness that has lasting effects (e.g. by reducing symptoms and improving the quality of life).
Townsend quintile	Refers to a measure of material deprivation within a population, which incorporates the variables of unemployment, car ownership, house ownership, and overcrowding of the household. The scale is from 1 (least deprived) to 5 (most deprived).
Underlying cause of post-neonatal deaths	Refers to the disease or condition which initiates an event or a series of events leading directly to death
Week of birth (WoB)	As date of birth was deemed identifiable data (hence not available in the PEDW dataset), NHS Wales Informatics Service (NWIS) provided data on WoB, which was the date of the Monday that occurred prior to the actual date of birth. WoB was used by Health Information Research Unit (HIRU).

Abstract

Background

Congenital anomalies consist of a heterogeneous group of conditions involving structural, metabolic, endocrine, and genetic defects that occur during intrauterine development; they contribute significantly to infant morbidity and mortality. However, little is known about how particular anomalies and their associated conditions lead to excess infant morbidity and mortality. Population-based study evidence is limited and inadequate to inform clinical and public health practices. The aim of this research is to investigate the impact of congenital anomalies on infant mortality and infant hospitalisation as a proxy for morbidity.

Methods

Two systematic reviews were conducted specifically to examine the contemporary evidence concerning infant mortality associated with spina bifida and encephalocele respectively, and a structured literature review to examine the contemporary evidence relating to infant hospitalisation associated with congenital anomalies.

A population-based cohort study was conducted using linked de-identified data from the Welsh national Congenital Anomaly Register and Information Service (CARIS) and Office for National Statistics (ONS) between 1998 and 2017. Descriptive statistics were used to analyse the rates and patterns of infant mortality by anomaly subgroup. Logistic regression was used to estimate the odds ratio for risk factors contributing to excess infant case fatality due to congenital anomalies; confounders were adjusted for in multivariable logistic regression analysis.

The second population-based cohort study used linked de-identified data from the Patient Episode Database for Wales (PEDW), CARIS and ONS between 1999 and 2016. Survival analysis was conducted to estimate the admission rate, and descriptive statistics to examine patterns of infant hospitalisation by anomaly subgroup. Multinomial logistic regression was carried out to

investigate the relative risk ratios of hospital admission in infancy for infants with congenital anomalies.

Results

Anomaly-related deaths represented almost one-third of all infant deaths. Multiple anomalies and structural anomalies involving vital organ systems were associated with the highest infant mortality rate and case fatality. Congenital anomalies and associated morbidities were the most common causes of death for infants with anomalies who died. Preterm birth was associated with a four-fold increased odds of infant case fatality in all anomaly subgroups. The effects of maternal ethnicity, maternal smoking, parity, infant sex, anomaly severity and surgery varied according to anomaly subgroups.

Infants with congenital anomalies were at a greater odds of more frequent and longer admissions compared to infants without an anomaly. Congenital anomalies and the associated diseases, and respiratory conditions were the most common primary causes of hospital admissions among infants with anomalies. Preterm birth, younger mother, maternal smoking and male sex (except for genitourinary anomalies) were independently associated with increased risks of anomaly-related infant hospitalisation.

Conclusions

Congenital anomalies and their associated complications are significant causes of infant hospitalisation and mortality, with various risk factors playing a significant role. Generalisability of the analytical findings beyond the UK may be limited due to variations in anomaly definitions, health care systems, admission thresholds, neonatal practices and registration of extremely premature births over time and between countries. Further studies should aim at using big data with large national population-based studies to minimise this heterogeneity.

Chapter 1: Introduction and Background

1.1 Introduction

1.1.1 Topic and Scope

The UK has one of the highest child death rates in Europe (Kurinczuk et al. 2009; Zeitlin and Mohangoo 2008). How particular causes of deaths have contributed to the high comparative infant mortality rate in the UK remains unclear. Congenital anomalies are structural and chromosomal abnormalities that occur during intrauterine development (EUROCAT 2019); they represent a wide spectrum of abnormalities in which the aetiology, birth prevalence, clinical characteristics and prognostic outcomes are heterogeneous (Springett et al. 2014). Congenital anomalies are a leading cause of infant morbidity and mortality, accounting for over one-third of all infant deaths in the UK (Kurinczuk et al. 2009; ONS 2010). For those infants who survive, disabilities and morbidities associated with congenital anomalies can have a life-changing and profound impact not only on the child's wellbeing and development, but also on their families, the health system and wider society.

Currently, in-depth population-based morbidity and mortality studies of infants with congenital anomalies are lacking, with most studies focused on a few specific anomaly groups. Variations in research settings, anomaly definitions and classifications, inclusion criteria, and health care systems between studies present major challenges in methodology. Current evidence is inadequate to robustly inform the planning of health care resources and public health interventions for infants with congenital anomalies.

My DPhil thesis consists a series of systematic reviews and population-based cohort studies with the common theme of investigating the impact of congenital anomalies on infant morbidity and mortality. This thesis aimed to generate novel epidemiological findings which will be informative for clinicians caring for babies who were born with congenital anomalies, parental counselling, as

well as future planning of health service and public health interventions aiming for reducing morbidity and mortality of infants born with congenital anomalies.

1.2 Background

1.2.1 Congenital anomalies

Definition

Congenital anomalies are also known as congenital abnormalities, malformations or birth defects. The European Surveillance of Congenital Anomalies (EUROCAT) defines congenital anomalies as structural defects (i.e. including congenital malformations, deformations, disruptions and dysplasias) and chromosomal abnormalities that occur during intrauterine life (EUROCAT 2019). However, there is no single universally agreed definition of what constitutes a congenital anomaly. Congenital anomalies may be detected prenatally, at birth, or manifest later in life (WHO 2018).

Heterogeneity

Congenital anomalies are comprised of a heterogeneous group of conditions in which the aetiology, birth prevalence, clinical characteristics and prognostic outcomes vary according to the anomaly subtypes (Table 1.1) (Springett et al. 2014). From the perspectives of disease severity and prognosis, congenital anomalies can be broadly categorised into major and minor anomalies. For example, the Centers for Disease Control and Prevention (CDC) makes the following distinction: major anomalies have a significant impact on infant mortality, morbidity and disability as a consequence of the anomalies, whereas minor anomalies pose a relatively limited clinical consequence for the affected individuals (CDC 2019). The European Surveillance of Congenital Anomalies (EUROCAT) describes minor anomalies as those with lesser medical, functional or cosmetic consequences in the anomaly classification (Appendices 1.1 and 1.2) (EUROCAT 2013). However, there is no clear or universally agreed definition or classification of major and minor

anomalies. Moreover, morphology varies drastically according to anomaly subtypes. For example, an anomaly can occur in isolation (e.g. isolated spina bifida) or as part of multiple defects (e.g. spina bifida with hydrocephalus as a secondary malformation, or spina bifida with a trisomy 21 as an unrelated major anomaly) (Rasmussen et al. 2003). In addition, the pattern of malformations can result from different pathogeneses (such as abnormal sequence, developmental field defect etc.) based on different biological mechanisms (Appendix 1.3) (Feldkamp et al. 2017).

Heterogeneity presents a major challenge to the epidemiological methodology of prognostic studies related to congenital anomalies. Although epidemiological studies classify anomalies or groups of anomalies according to their common aetiology wherever possible, so that further investigations of clinical or environmental factors contributing to morbidity and mortality can be specifically identified according to the anomaly (Wellesley et al. 2005), small sample sizes in rarer anomaly subtypes, variations in research settings, anomaly definitions, inclusion criteria, and health care systems between studies present major challenges.

Table 1.1: Descriptions of major groups and subgroups of congenital anomalies. (Statistical data from six BINOCAR registers[2]: NorCAS, EMSYCAR, CAROBB, WANDA, SWCAR and CARIS[3]; coverage: 36% of births in England and Wales: 2012). (Springett et al. 2014; CARIS 2020; Khoshnood et al. 2012).

Congenital anomalies	**Descriptions/ Pathologies**	**Birth prevalence in England and Wales per 10,000 total births (95% CI)**	**Risk factors**	**Treatment**	**Prognosis**
Group: Nervous system anomalies		*Overall: 26.4 (24.5-28.5)*			
Subgroup: Neural tube defects	Failure of complete closure of the neural tube.	12.5 (11.2-14.0)	Genetic factors, maternal obesity, diabetes, vitamin B9 (folate) and B12 deficiency, sodium valproate and previous fetus affected by an NTD. Protective factor: Intake of folic acid at least 3 months prior to pregnancy and up to end of the 12th week of pregnancy.	Anencephaly: none/ comfort care. Open spina bifida: Surgery within 72 hours after birth. Associated hydrocephalus: ventriculo-peritoneal shunt.	Anencephaly: death is inevitable. Spina bifida and encephalocele: variable range of disabilities: e.g. bladder and bowel dysfunction, paralysis, learning difficulties etc.
Anencephaly	Total or partial absence of the cranial vault, covering skin and brain tissue.	5.3 (4.4-6.2)			
Encephalocele	Herniation of the brain and/or meninges through a defect in the skull.	1.0 (0.7-1.5)			
Spina bifida	Non-closure of the spine resulting in herniation or exposure of the spinal cord and/ or meninges. Hydrocephalus may or may not be associated.	6.2 (5.3-7.3)			
Group: Congenital heart defects (CHDs)		*Overall: 60.2 (57.3-63.3)*			
Severe CHD[1]		22.6 (20.8-24.5)	Genetic factors, maternal smoking, alcohol intake, obesity, diabetes, rubella and sodium valproate.	Care plans for elective delivery and NICU stabilisation. Interventions vary from observations only to complex cardiac surgery depending on pathology.	Variable, depending on severity and presence of extra-cardiac malformations.
Hypoplastic left/ right heart	Underdevelopment of left/ right heart.	3.4 (2.7-4.2)/ 0.5 (0.2-0.8)			

Table 1.1 (continued): Descriptions of major groups and subgroups of congenital anomalies.

Congenital anomalies	Descriptions/ Pathologies	Birth prevalence in England and Wales per 10,000 total births (95% CI)	Risk factors	Treatment	Prognosis
Tricuspid atresia/ stenosis	Complete absence of/ narrowing of the tricuspid valve opening restricts blood flow between upper and lower part of right heart.	1.0 (0.6-1.4)	As above	As above	As above
Ebstein's anomaly	The septal and posterior leaflets of tricuspid valve are displaced.	0.5 (0.3-0.9)			
Single ventricle	Only one ventricle.	0.8 (0.5-1.3)			
Moderately severe[1]					
Tetralogy of Fallot	Ventricular septal defect, pulmonary stenosis, right ventricular hypertrophy and overriding aorta	4.3 (3.5-5.2)			
Transposition of great vessels	Abnormal spatial arrangement of great vessels (e.g. superior or inferior venae cavae, pulmonary artery or veins or the aorta).	3.9 (3.2-4.7)			
Coarctation of aorta	Narrowing of the aorta/ aortic arch.	4.0 (3.3-4.9)			
Atrioventricular septal defect	'Holes' between chambers of the right and left side of the heart.	4.4 (3.6-5.2)			
Aortic valve atresia/ stenosis	Absence of / narrowing of the aortic valve between left ventricle of the heart and the aorta.	1.4 (1.0-1.9)			
Pulmonary valve atresia	Absence of normal valvular opening from the right ventricle to the lungs.	0.7 (0.4-1.1)			
Common arterial truncus	Truncus arteriosus fails to divide into the pulmonary trunk and aorta.	0.6 (0.3-0.9)			
Total anomalous pulmonary venous return	Veins receive blood from the lungs to the heart do not attach normally to the left atrium.	0.8 (0.5-1.2)			

Table 1.1 (continued): Descriptions of major groups and subgroups of congenital anomalies.

Congenital anomalies	Descriptions/ Pathologies	Birth prevalence in England and Wales per 10,000 total births (95% CI)	Risk factors	Treatment	Prognosis
Total anomalous pulmonary venous return	Veins receive blood from the lungs to the heart do not attach normally to the left atrium.	0.8 (0.5-1.2)	As above	As above	As above
Least severe[1]					
Ventricular septal defect (VSD)	An abnormal opening that separates the lower two chambers of the heart.	27.6 (25.6-29.7)			
Atrial septal defect (ASD)	An abnormal opening that separates the top two chambers of the heart.	8.4 (7.3-9.5)			
Pulmonary valve stenosis	Narrowing of the outflow of blood flow from the right ventricle of the heart at the level of pulmonary valve.	3.8 (3.1-4.6)			
Group: Respiratory anomalies		*Overall: 9.8 (8.6-11.1)*			
Choanal atresia	Obstruction of the back of the nasal passage by abnormal bony or membraneous tissue due to failed recanalization of nasal fossae.	1.0 (0.7-1.5)	Not well known. Genetic factors and environmental toxins such as herbicides may play a role.	Stenting or surgery.	Survival outlook for babies without other problems is good.
Cystic adenomatous malformation of lung	Lobes of lung is replaced by non-working cystic abnormal lung tissue.	2.3 (1.8-3.0)	Not well known.	Surgery or conservative treatment varies depending on size and number of lesions. Ventilatory support after birth if necessary.	Mortality up to 30% of cases.
Group: Oro-facial clefts		*Overall: 14.3 (12.9-15.8)*			
Cleft lip +/- palate	Partial or complete clefting of the upper lip +/- palate	7.8 (6.8-9.0)	Genetic factors, maternal smoking, alcohol intake, malnutrition, viral infections, use of bronchodilators and certain anti-convulsant drugs.	Surgical repair usually within first six months of life.	Can cause feeding difficulties. 16% of cases have other structural abnormalities; 7% of cases are syndromic.

Table 1.1 (continued): Descriptions of major groups and subgroups of congenital anomalies.

Congenital anomalies	Descriptions/ Pathologies	Birth prevalence in England and Wales per 10,000 total births (95% CI)	Risk factors	Treatment	Prognosis
Group: Digestive system anomalies		*Overall: 18.1 (16.5-19.8)*			
Oesophageal atresia +/-tracheo-oesophageal fistula	Disconnection between upper part of the oesophagus and the lower part of the oesophagus and the stomach with or without abnormal connection to the trachea.	2.5 (1.9-3.1)	Family history	Surgery soon after birth.	Survival outlook for babies without other problems is good. Complications include dysphagia, gastro-oesophageal reflux disease, asthma-like symptoms, recurrent chest infection and tracheomalacia.
Duodenal atresia or stenosis	Absence or narrowing of a portion of lumen within the first part of small intestine.	1.8 (1.4-2.4)			
Anorectal atresia and stenosis	Imperforate anus.	2.8 (2.2-3.6)			Survival outlook for babies without other problems is good.
Hirschsprung's disease	Absence of nerve cells in the muscle of colon leading to problems with passing stool.	1.6 (1.2-2.2)			
Congenital diaphragmatic hernia	Protrusion of abdominal or retroperitoneal structures through a defect in the diaphragm into the chest cavity, typically at about 11-12 weeks gestation.	3.3 (2.6-4.0)		Ventilation and cardiovascular support at birth, and treatment of pulmonary hypertension if necessary. Early surgical repair once baby is stable. Most severe case requires Extracorporeal membrane oxygenation (ECMO).	Most cases are isolated; up to 40% of cases have other abnormalities; 20% have chromosomal abnormalities. Prognosis depends on severity, defect size, APGAR score, birthweight, presence of other structural and chromosomal abnormalities. Mortality rate is about 50% of cases.

Table 1.1 (continued): Descriptions of major groups and subgroups of congenital anomalies.

Congenital anomalies	Descriptions/ Pathologies	Birth prevalence in England and Wales per 10,000 total births (95% CI)	Risk factors	Treatment	Prognosis
Group: Abdominal wall defects		*Overall: 9.1 (8.0-10.3)*			
Gastroschisis	Loops of bowel herniate through an abdominal wall defect.	4.1 (3.4-5.0)	Maternal smoking, recreational drugs and young maternal age.	Early surgical repair once baby is stable. Primary or stage repair depending on the extent.	Morbidity relates to bowel atresia or necrosis. Some may develop feeding difficulty.
Exomphalos (Omphalocele)	Abdominal contents protrude through the abdominal wall into base of the umbilical cord and are covered by a peritoneal membrane.	4.3 (3.5-5.1)			Up to 80% have other serious abnormalities such as heart, chromosomal abnormalities or a syndrome. Mortality rate is about 10% for uncomplicated isolated cases.
Group: Genital		*Overall: 17.9 (16.3-19.6)*			
Hypospadias	Urinary opening is not at the usual location on the glans of penis.	13.3 (12.0-14.8)	Genetic, environmental and endocrine factors (low androgens, exposure to estrogen and toxins).	Corrective surgery.	Survival outlook for babies without other problems is good.
Indeterminate sex	The genital organs are not visually male or female.	0.9 (0.6-1.3)	Genetic and hormonal factors (e.g. Congenital adrenal hyperplasia), family history of infertility and genital abnormalities.	Multidisciplinary interventions include medical, surgical treatment and psychological therapy and support as appropriate.	Continuous medical care and monitoring for complications, such as infertility, cancer screenings, into adulthood are needed.

Table 1.1 (continued): Descriptions of major groups and subgroups of congenital anomalies.

Congenital anomalies	Descriptions/ Pathologies	Birth prevalence in England and Wales per 10,000 total births (95% CI)	Risk factors	Treatment	Prognosis
Group: Urinary anomalies		*Overall: 27.8 (25.8-29.9)*			
Bilateral renal agenesis (including Potter syndrome)	Absence of both kidneys resulting in anhydramnios, pulmonary hypoplasia, severe talipes, limb contractures and growth restriction.	1.5 (1.1-2.1)	Unknown.	No treatment at present.	Early neonatal death is common due to pulmonary hypoplasia.
Multicystic renal dysplasia (MCDK)	Abnormal development of internal structure of kidney.	5.9 (5.0-7.0)		Management for potential UTI and hypertension for unilateral MCDK. No treatment at present for bilateral MCDK.	Survival outlook for babies with unilateral MCDK without other problems is good, although there are risks of UTI and hypertension later in life. Most babies with bilateral MCDK will not survive.
Bladder extrophy +/- epispadia	Protrusion of the urinary bladder through a defect in the abdominal wall and/ or abnormal opening of the urethra.	0.5 (0.2-0.8)		Surgery	Survival outlook for babies without other problems is good.
Posterior urethral valve and/or prune belly	An obstructing membrane in the posterior male urethra causing outlet obstruction of the urinary bladder.	0.5 (0.3-0.9)			
Congenital hydronephrosis	Dilation of the renal pelvis +/- dilation of the renal calyces; can associated with renal impairment.	8.8 (7.7-10.0)		Conservative treatment e.g. antibiotics depending on the size and location of lesion. May require surgical stenting.	Survival outlook for babies without other problems is good.

Table 1.1 (continued): Descriptions of major groups and subgroups of congenital anomalies.

Congenital anomalies	Descriptions/ Pathologies	Birth prevalence in England and Wales per 10,000 total births (95% CI)	Risk factors	Treatment	Prognosis
Group: Limb		*Overall: 34.9 (32.6-37.2)*			
Limb reduction	A limb is reduced from its normal size or is completely missing during pregnancy.	4.9 (4.1-5.8)	Thalidomide, warfarin, valproic acid, misoprostol phenytoin and chorionic villus sampling.	Multidisciplinary care includes orthopaedic, surgical care, rehabilitation and follow-ups.	Survival outlook for babies without other problems is good.
Upper/lower limb reduction	Part of or the entire upper/ lower limb of a fetus fails to form.	3.2 (2.6-4.0)/ 1.9 (1.4-2.5)			
Club foot (talipes equinovarus)	One or both feet are rotated inwards and downwards	10.9 (9.7-12.3)	Genetic and environmental factors e.g. multiple births, position of the fetus, cerebral palsy and oligohydramnios.	Ponseti method: manipulation and cast of foot.	
Hip dislocation +/- dysplasia	'Ball and socket' joint of the hips doesn't properly develop and form.	4.9 (4.1-5.9)	Genetic and environmental factors, female sex, vaginal breech, large baby, reduced liquor, first born babies and multiple pregnancy, family history.	Conservative treatments such as Pavlik hip harness or Von Rosen splint, or surgical correction of the joint.	
Polydactyly	Having an additional fingers and/or toes.	7.3 (6.3-8.4)	Genetic factors.	Surgical correction.	
Syndactyly	Joined digits.	4.8 (4.0-5.7)			
Group: Other anomalies/ syndrome		-			
Skeletal dysplasia	Genetic mutations associated with severe abnormalities of bone growth and development (e.g. thanatophoric dysplasia, Type II osteogenesis imperfecta)	1.5 (1.1-2.1)	Genetic factors and family history.	None/ supportive.	Intrauterine death is common.
Genetic syndromes and microdeletions	Genetic disorders caused by deletions or duplications of genes on particular parts of chromosomes.	4.9 (4.1-5.9)	Genetic factors.	Genetic counseling and management of associated clinical problems.	Variable.

Table 1.1 (continued) Descriptions of major groups and subgroups of congenital anomalies.

Congenital anomalies	Descriptions/ Pathologies	Birth prevalence in England and Wales per 10,000 total births (95% CI)	Risk factors	Treatment	Prognosis
Group: Sequences		*Overall: 2.3 (1.8-3.0)*			
Group: Chromosomal anomalies		*Overall: 43.0 (40.5-45.6)*			
Down syndrome	Trisomy 21	23.3 (21.5-25.3)	Genetic factors and advanced maternal age.	Multidisciplinary. Genetic counseling, surgery for associated defects (e.g. cardiac, cleft lip/palate). Turner and Klinefelter syndromes: Estrogen replacement therapy.	No cure at present. Most babies with Patau and Edward syndromes will die before or shortly after birth. Survival outlooks for babies with Down, Turner and Klinefelter syndromes without other problems are good.
Patau syndrome	Trisomy 13	2.5 (2.0-3.2)			
Edward syndrome	Trisomy 18	6.7 (5.8-7.8)			
Turner syndrome	Girl has only single X chromosome, rather than usual two (XX).	3.2 (2.5-3.9)			
Klinefelter syndrome	Two or more X chromosomes in boy (47, XXY)	0.3 (0.1-0.6)			

[1]CHD severity category is based on criteria used by Khoshnood et al. (2012). [2]BINOCAR = British and Irish Network of Congenital Anomaly Researchers. [3]NorCAS = Northern Congenital Abnormality Survey; EMSYCAR = East Midlands and South Yorkshire Congenital Anomalies Register; CAROBB = Congenital Anomaly Register for Oxfordshire, Berkshire and Buckinghamshire; WANDA = Wessex Antenatally Detected Anomalies Register; SWCAR = South West Congenital Anomaly Register; CARIS = Congenital Anomaly Register and Information Service for Wales.

Classification of congenital anomalies

The ICD and BPA Classification Systems

The classification systems for congenital anomalies are based on a standard diagnostic coding tool to correctly and accurately record diagnostic information about anomalies in a standardised method (CDC 2019).

The International Classification of Diseases and Related Health Problems (ICD) and the Royal College of Paediatrics and Child Health (RCPCH)/ British Paediatric Association (BPA) extension code (i.e. an additional code for greater details) are the most commonly used classification systems for congenital anomalies. They were developed based on the knowledge of common embryologic and pathogenetic mechanisms (WHO 2004; Bedard et al. 2012).

The ICD and BPA systems allow each congenital anomaly to be coded and classified using a hierarchical order such that each anomaly is classified to one category only (Wellesley et al. 2005). For ICD-9, each congenital anomaly was diagnostically coded between 740 and 759 (and for ICD-10: between Q00 and Q99). ICD-9 was in use until 1998, after which ICD-10 has been widely used (National Health Centre for Health Statistics US 1980; WHO 2004).

These standardised diagnostic coding systems allow reliable comparisons over time, and between congenital anomaly registers (Dattani and Rowan 2002; ONS 2013).

Prevalence

In the UK, the birth prevalence rate of congenital anomaly is about 3% per year (Rankin et al. 2005). By convention, the frequency of occurrence of congenital anomalies is referred to as birth prevalence. This is because incidence of congenital anomalies cannot be measured accurately due to prenatal spontaneous loss of any fetus (i.e. miscarriages) affected by an anomaly or involved in an ectopic pregnancy. Hence, birth prevalence acknowledges that not all cases of congenital anomalies can be diagnosed or counted (Kurinczuk et al. 2010).

The birth prevalence rate of an anomaly is defined as:

$$\frac{\text{Total number of births (live and stillbirths) cases of an anomaly}}{\text{Total number of births (live and stillbirths)}}$$

Birth prevalence rate is expressed per 1,000 or per 10,000 total births (PHE 2017; Springett et al. 2014).

Estimates of birth prevalence vary from place to place depending on definitions of an anomaly, robustness of case notification system, and whether termination of pregnancies due to fetal abnormalities are included (Newton and Garner 2002). As a result, variations in birth prevalence between study populations are likely to be in large part due to methodology and reporting differences rather than true differences in underlying population incidence (Kurinczuk et al. 2010).

Population health

Congenital anomalies are an important public health concern for a variety of reasons. First, the birth prevalence of congenital anomalies has remained relatively static (representing approximately 2-3% of the livebirths) in the UK over the past two decades. Congenital anomalies are the second commonest cause of infant mortality in England and Wales (Kurinczuk et al. 2010). If the birth prevalence of congenital anomalies remains static and no new treatment and health policies are developed, congenital anomalies will remain a leading cause of infant mortality in the UK (Kurinczuk et al. 2009; Boyle et al. 2018).

Second, globally, the United Nations (UN) has set out the Sustainable Development Goals (SDGs) aiming to reduce under-5 mortality and end preventable child deaths under five years of age by 2030 (United Nations 2020), therefore it is vitally important to investigate the pattern and reduce the occurrence of mortality from congenital anomalies in high-income countries in order to address these goals.

Third, congenital anomalies represent a major cause of childhood morbidity and disability, and a leading cause of paediatric hospitalisation (Bishop et al. 2017; Colvin and Bower 2009). For many children with anomalies, the chronicity of the conditions and burden of hospitalisation can have a profound impact on the child's wellbeing and development, as well as on their families, the health care system and wider society. From a population health perspective, the standard of access to health provision and resource planning such as specialist services, surgeries and prescriptions are of public health concern (Dolk et al. 2010).

Fourth, successful implementation of primary and secondary prevention at a population level can have a significant impact on reducing birth prevalence and disease outcomes of certain anomalies. For example, research has shown that mandatory folic acid food fortification significantly reduces the occurrence and severity of neural tube defects (NTDs) (Liu et al. 2001; Shin et al. 2012; Bol et al. 2006; Wang et al. 2015); and the uptake of prenatal ultrasound screening significantly reduces the risk of anomaly-related neonatal death (Postoev et al. 2015). Importantly, in the UK, mandatory folic acid food fortification has not been implemented. Furthermore, the accuracy, access to and uptake of prenatal screening are variable, which is a public health concern.

1.2.2 Aetiology, prevention, termination of pregnancy and care pathways

Aetiology

The underlying causes of the majority of congenital anomalies are not known (Moore and Persaud 2003; Druschel et al. 1996). However, some anomalies are associated with certain predisposing risk factors or specific conditions, which can be generally categorised into three main groups:

1. Genetic causes

Genetic causes contribute about a quarter of all congenital abnormalities with a known aetiology (Moore and Persaud 2003). These include: chromosomal disorders e.g. Down syndrome; Mendelian single-gene defects e.g. cystic fibrosis and achondroplasia; and specific gene mutations e.g. Apert syndrome. Inheritance and recurrence are characteristic. Studies have shown that advanced maternal age > 35 years and consanguineous marriage are associated with a higher risk of congenital anomalies with a genetic origin (Czeizel 2005).

2. Environmental causes

Environmental causes have been shown to be associated with congenital anomalies for decades. They contribute about 15% of all congenital abnormalities (Czeizel 2005). These include for example, a) chemical and pharmacological exposures during pregnancy e.g. thalidomide-induced teratogenesis leading to limb defects, valproate embryopathy leading to midline defects, and warfarin-associated skeletal abnormalities (Clayton-Smith et al. 2019; Holmes 2002; Raivio et al. 1977); b) Infectious diseases exposures during pregnancy e.g. rubella infection associated eye and heart abnormalities, and sensorineural deafness (Givens et al. 1993); and c) other maternal conditions and lifestyles e.g. pre-gestational diabetes, obesity, smoking and alcohol consumption are associated with an increased risk of anomalies overall (Corrigan et al. 2009; Waller et al. 2007; Carmichael et al. 2012).

3. Complex or multifactorial causes

Multifactorial causes contribute about 60% of all congenital anomalies (Czeizel 2005). These include anomalies with potential polygenic predisposition and gene-environmental interaction, such as isolated NTDs, orofacial clefts, pyloric stenosis, hypospadias, undescended testis, and certain congenital heart defects (CHDs) belong to this aetiological group in which the conditions are caused by many contributing factors (Etheredge et al. 2012; Hobbs et al. 2010; Murray 2002; NIH 2020).

Prevention

Prevention strategies have been shown to have a significant impact on infant morbidity and mortality due to congenital anomalies.

Primary prevention aims to prevent the occurrence of an anomaly, hence it targets the preconception period by minimising maternal exposure to known risk factors (Czeizel 2005). Primary prevention has been shown to have a significant impact on reducing the birth prevalence and improving disease outcomes of certain anomalies. Examples include the uptake of periconceptional folic acid supplementation and the implementation of mandatory folic acid food fortification in reducing the occurrence or severity of NTDs (MRC Vitamin Study Research Group 1991; Czeizel 1998; Bol et al. 2006; Morris et al. 2016; Sayed et al. 2008; Cortés et al. 2012; Grosse et al. 2005; Berry et al. 1999), rubella vaccination in reducing the occurrence of congenital rubella syndrome (WHO 2018a), and prenatal screening and treatment for maternal diabetes, obesity and syphilis in reducing the incidence of anomalies overall (McCullough and Dolk 2017). The EUROCAT-EUROPLAN has produced a set of recommendations for the inclusion of primary prevention of congenital anomalies in national 'Rare Disease Plans' across Europe (Taruscio et al. 2014).

Secondary prevention aims to identify anomalies early in prenatal screening in order to reduce the risk of disease progression and complications by potential medical and/or surgical treatment and interventions. In the UK, the NHS Fetal Anomaly Screening Programme (FASP) aims to offer an equal access to prenatal screening for all eligible pregnant women in England. For example, prenatal screening for trisomies in the first and second trimesters, and detailed ultrasound scanning between 18^{+0} and 20^{+6} week gestation are offered to all pregnant women to detect potential anomalies (Appendix 1.4) (NICE 2008; PHE 2015a). However, the uptake of the tests is currently below national targets (Rowe et al. 2008; Gitsels – van der Wal et al. 2014) and detection rates vary by anomaly (Appendix 1.5). Although the survival of infants affected by

congenital anomalies would also depend on factors including the type and severity of the anomaly, access to medical and surgical treatment, and termination of pregnancy. Early prenatal diagnosis of congenital anomalies would help optimise the chance of survival of the affected infants by advanced planning of specialised care and transfer for delivery of the affected infants in a specialised centre (Riley et al. 1998). In utero treatment such as fetal surgery, which may alter the severity and progress of major congenital anomalies such as spina bifida, congenital diaphragmatic hernia and cystic adenomatoid malformation of the lung, are rarely performed (Adzick et al. 2011; Adzick et al. 1993; Nijagal et al. 2012).

Tertiary prevention aims to reduce the risk of complications due to an anomaly, and improve prognosis and quality of life through early medical and surgical interventions, multidisciplinary therapies and rehabilitation. Examples include early surgery for pyloric stenosis, undescended testis and some types of CHDs e.g. ventricular and atrial septal defects to achieve complete recovery (Czeizel 2005).

Termination of pregnancy for fetal abnormality and infant mortality rate

Prenatal diagnosis and termination of pregnancy (TOP) have significantly shifted the impact of congenital anomalies on infant mortality. Previous studies have suggested that advances in prenatal screening and diagnosis, and an increase in the uptake have a direct and significant impact on the gestational age at delivery of fetuses affected by detectable congenital anomalies at a population level. For example, in a large retrospectively population-based cohort study of all births (n = 461,083 livebirths and 3,991 stillbirths) in British Columbia conducted between 2000 and 2010, Joseph et al. (2013) have shown that the observed increase in stillbirths due to TOP was accompanied by a simultaneous decline in the prevalence of livebirths with congenital anomalies and rate of infant death. Studies from the EUROCAT, U.S., Canada and Russia have reported similar trends in the infant mortality rates for congenital anomalies and noted that prenatal screening and subsequent termination of pregnancy for fetal abnormality (TOPFA) significantly

contributes to the declines in late fetal death and the birth prevalence of congenital anomalies, and accounted for part of the observed declines in infant mortality rates over time (Liu et al. 2002; Liu et al. 2012a; Boyle et al. 2018; Best et al. 2020; Lee et al. 2001; Lin et al. 1999; Mansfield et al. 1999). Consequently, it is possible that late stillbirth and infant deaths due to serious or lethal anomalies have been replaced in part by TOP before 24 weeks' gestation following prenatal diagnosis (Liu et al. 2002; Liu et al. 2002a), although not all congenital anomalies can be diagnosed prenatally. However, due to the variations in severity between anomalies, it is acknowledged that TOPFA may not always have resulted in a reportable death of an infant if the termination had not been taken place, either because the pregnancy may have been miscarried prior to 24 weeks' gestation or the child may have survived beyond infancy especially for those with non-lethal anomalies (Bourke et al. 2005). Indeed, an analysis of TOPFA in England between 1991 and 2000 has estimated that of those aborted fetuses with congenital anomalies, 43% would have proved to have a lethal anomaly, 14% possibly had a lethal anomaly and 43% were potential survivors (Boyd et al. 1998). Further, Bourke et al. (2005) found that, in the case of anomalies of the nervous system, an increasing rate of TOPFA was accompanied by a decreasing IMR which was largely due to terminations for severe cases and a reduction in NTDs since 1996 with the increased consumption of folate (Bower et al. 2002); while an increase in TOP with chromosomal defects such as Down syndrome may not have affected the IMR as many of these TOP were for non-lethal defects (Khoshnood et al. 2004; Bell et al. 2003; O'Leary et al. 1996; Hurst et al. 1999). Therefore, although TOPFA has a significant impact on the overall trend and outcomes for liveborn infants with congenital anomalies over time, its role in reducing infant mortality is debatable.

Clinical Importance

Congenital anomalies represent a major cause of childhood morbidity and disability (CDC 2019). As the aetiology and disease outcomes vary enormously depending on the anomaly types (Dastgiri et al. 2003), consequently, the clinical consequence and prognosis vary between different types of anomalies; and the clinical treatment and management depend on different needs of the affected infants (Table 1.1) (Springett et al. 2014).

Children with anomalies often require hospitalisation. Compared to infants without an anomaly, infants with congenital anomalies are admitted to hospital more frequently and for longer stays (Colvin and Bower 2009). As a result, congenital anomalies can have a profound impact on the quality of life of the child and their families who can experience a substantial burden of health, emotional and economic stress (McCullough and Dolk 2017).

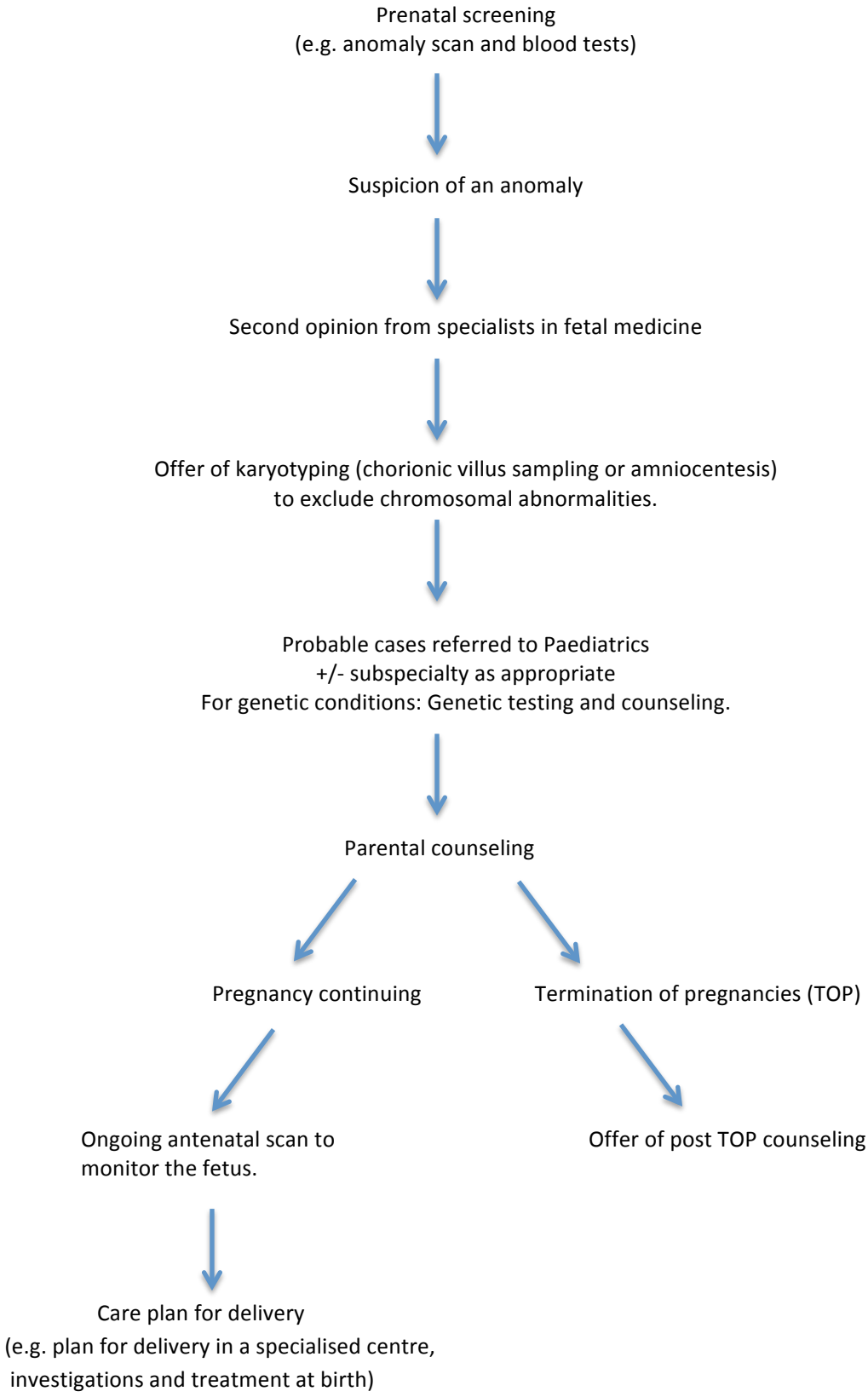
Care pathways

In the UK, all prenatally diagnosed or suspected anomalies are referred to specialists in fetal and neonatal medicine for a second opinion. At that point, further prenatal investigations including amniocentesis and karyotyping are offered to exclude chromosomal abnormalities. Depending on the specific anomaly and likely prognosis, specialists and multidisciplinary teams will be involved in a care plan for delivery (in a specialised centre if necessary), active treatment or palliative care, or termination of pregnancy (NHS 2012).

Postnatally, newborn babies with a suspected or confirmed anomaly will be clinically assessed, and further testing or treatment may be necessary. In addition, as part of routine postnatal care, all newborns will undergo newborn blood spot and hearing screening during the first week after birth (NHS 2015).

Common prenatal care and treatment pathways for congenital anomalies are summarised in Figure 1.1 and Table 1.1.

Figure 1.1: General prenatal care pathway for congenital anomalies within the NHS. (NHS 2012)



1.2.3 Infant mortality

Definition

Infant mortality is defined as deaths of babies before their first birthday (United Nations 1991). The infant mortality rate (IMR) is defined as:

$$\frac{\text{Total number of infant deaths in a study population}}{\text{Total number of livebirths in the study population}}$$

IMR is expressed per 1,000 live births.

IMR is calculated using both the neonatal and post-neonatal mortality rates (Davis et al. 2018). In the UK, the majority (70-75%) of infant deaths occur in the neonatal period, of which over three-quarters of neonatal deaths occur in the early neonatal period (0-6 days). IMR has long been used as an indicator of the overall health status of a population (Wolfe et al. 2014).

Causes and contributing factors

The UK has one of the highest child death rates in Europe; the IMR in the UK is above the 75th centile among EU15+ countries (Wolfe et al. 2014). However, comparison of IMR can be challenging due to changes in neonatal practice, and reporting and registration of extremely preterm births over time and between countries (Davis et al. 2018). The IMR in the UK had been declining from 12.0 deaths per 1,000 livebirths since the 1980s to an all-time low at 3.6 deaths per 1,000 livebirths in 2014. However, since then, the IMR has increased every year between 2014 and 2017, reaching 3.8 deaths per 1,000 livebirths in 2018 (ONS 2020). The main explanation for the increase in IMR since 2014 in the UK was that the changes in neonatal practice in the UK have led an increasing number of extremely preterm babies at less than 23 gestation weeks being born, even though the mortality of this group of extremely preterm babies remains high. In addition, the changes in reporting and registration of extremely preterm babies in the UK mean that babies are now registered as 'livebirths' if they show a sign of life at birth regardless of the gestation,

consequently the observed increase in IMR since 2014 can be explained by an increased number of early neonatal death among babies born < 24 weeks' gestation (Davis et al. 2018; Nath et al. 2020). The impact of these changes were evidenced from the ONS Birth statistics, which showed that the number of liveborn infants at less than 23 weeks' gestation has increased considerably (376 in 2014; 427 in 2015; 545 in 2016), 97% of whom died in the first week of life and consequently affected the overall IMR (ONS 2019c). Indeed, a recent study conducted by Nath et al. (2020) has shown that IMR continued to decrease after 2014 after excluding infants born < 24 weeks' gestation. Similarly, the study by Joseph et al. (2012) has shown that variations in the registration of the extreme gestation of viability can have a significant impact on reported IMRs.

Prematurity is the leading cause of infant mortality in the UK and globally (Lawn et al. 2005). Prematurity accounted for 50% of neonatal deaths and 14% of post-neonatal deaths in the UK in 2016 (ONS Statistical bulletin 2018). However, the EPICure studies have shown that the rate of infant mortality due to prematurity has been declining over time, which can be attributed to advances in prenatal screening, medical and surgical interventions (Santhakumaran et al. 2018; Costeloe et al. 2012). Other factors have been shown to have significant impact on infant mortality. For example, studies have shown that social inequalities are a major risk factor contributing to infant deaths overall (Nath et al. 2020). The IMR and risk of infant mortality significantly increases with maternal social deprivation and ethnic minority groups in the UK (Gray et al. 2009; Taylor-Robinson et al. 2019; Brown et al. 2006; Department of Health 2007; ONS 2019). Maternal age plays a significant role in which teenage mothers and mother aged > 35 years are at highest risk of infant mortality (Finlay et al. 2011; Babson et al. 2008; Friede et al. 1988). Furthermore, infant mortality is strongly linked to maternal health behaviours during pregnancy, for example maternal smoking and substance misuse have a negative impact on fetal development and significantly increase the risk of prematurity and perinatal death (RCPCH 2019; Pineles et al. 2016; Kposowa 2001; ONS 2019).

Causes of deaths and coding

Post-neonatal deaths (i.e. death of an infant occurring after 28 days following birth until the first birthday) in England and Wales are recorded using the standard death certificate (Appendix 1.6), where a single underlying cause of death is reported (Table 1.2). This death certificate is designed to identify the disease or condition which initiates an event or a series of events leading directly to death, and is recorded in part 1 of the certificate. Other conditions, which are parts of the series of events leading directly to death or contributing conditions, can also be recorded in the death certificate (Dattani and Rowan 2002; ONS 2020a).

Neonatal deaths (i.e. death of an infant occurring after birth until 28 days after birth) have been registered using a special death certificate instead of the standard death certificate since 1986, following the WHO recommendations (Appendix 1.7) (WHO 1977). This death certificate identifies the earliest cause in the chain of events leading to fetal or neonatal death by collecting information about the mother and the fetus or baby (Table 1.2). While the neonatal death certificate allows more flexibility to complete, its format makes it impossible to derive a single underlying cause of death (Dattani and Rowan 2002; ONS 2020a).

Table 1.2: Neonatal (and stillbirths) versus standard (i.e. post-neonatal) cause of death certificate. (Dattani and Rowan 2002)

Neonatal (and stillbirths) cause of death certificate	**Standard (i.e. post-neonatal) cause of death certificate[2]**
a. Main disease or conditions in infant (or fetus) b. Other diseases or conditions in infant (or fetus) c. Main maternal diseases or conditions affecting infant (or fetus) d. Other maternal diseases or conditions affecting infants (or fetus) e. Other relevant causes[1]	1(a). Disease or condition directly leading to death 1(b). Other disease or condition, if any, leading to 1(a) 1(c). Other disease or condition, if any, leading to 1(b). 2. Other significant condition contributing to the death but not related to the disease or condition causing it.
[1]*Circumstances which bear on the death but which cannot be described as a disease or condition of the infant or the mother.*	[2]*The death certificate used in England and Wales accords with the WHO recommendations in the ICD-10.*

To deal with coding issues, particularly for neonatal deaths which do not have a single recorded underlying cause, the UK Office for National Statistics (ONS) has developed a hierarchical classification system known as 'the ONS cause groups' to allow direct comparison of causes of neonatal and post-neonatal deaths. This system assigns a single cause group of deaths for neonates and postneonates to the first appropriate mutually exclusive categories i.e. the likely timing of the condition or damage leading to the death in relation to birth using computer algorithm based on the Wigglesworth classification (Table 1.3) (Dattani and Rowan 2002). In addition, with the move from ICD-9 to ICD-10 coding in 2001, the 'Bridge Coding Study' has shown that the vast majority of codes and classification comparing between ICD-9 and ICD-10 (i.e. the death statistics of a particular cause) were unchanged (Appendix 1.8), and the mortality proportions attributed to cause groups remained constant over time (Dattani and Rowan 2002; ONS 2011).

Table 1.3: The neonatal hierarchical classifications (ONS cause groupings) using categories by ICD-9 and ICD-10. (Dattani and Rowan 2002; Appendix 1.9)

ICD-9	**ICD-10**[1]
• *Before the onset of labour* 1. Congenital anomalies 2. Antepartum infections 3. Immaturity related conditions • *In or shortly after labour* 4. Asphyxia, anoxia or trauma • *Postnatal* 5. External conditions 6. Infections 7. Other specific conditions 9. Sudden infant deaths • *Unclassified* 0. Other conditions	• *Before the onset of labour* 1. Congenital anomalies 2. Antepartum infections 3. Immaturity related conditions • *In or shortly after labour* 4. Asphyxia, anoxia or trauma (intrapartum) 5. External conditions 6. Infections 7. Other specific conditions • *Cases of uncertain cause* 8a. Asphyxia, anoxia or trauma (antepartum) 8b. Remaining antepartum deaths 0. Other conditions (intrapartum by exclusion)
[1]*Cause of death in England and Wales has been coded to ICD-10 since January 2001.*	

Anomaly-related infant mortality

Congenital anomalies are the second most common cause of infant deaths in the UK, with a rate of 0.97 per 1,000 livebirths in 2017 (PHE 2019); and they are the leading cause of post-neonatal infant deaths. Overall, congenital anomalies account for over one-third of all infant deaths (ONS 2015). However, the majority of pregnancies and births affected by a congenital anomaly do not result in a stillbirth or infant death (ONS 2009), except for a few specific anomalies which are incompatible with life e.g. anencephaly. In theory, a congenital anomaly resulting in an infant death is not lethal during pregnancy but rather is associated with a high risk of early mortality due to the anomaly itself or associated complications.

In any single year, anomaly-related deaths result from more than 150 different causes or anomalies, hence there is a wide range of anomalies which are associated with infant mortality, and the risk of infant mortality varies enormously between different anomalies (ONS 2009; Kurinczuk et al. 2010). CHDs are the commonest cause of infant and neonatal death due to an anomaly, up to half of all anomaly-related infant deaths are CHD-related; these are followed by chromosomal defects and anomalies of the digestive system (PHE 2019). Although genitourinary and musculoskeletal anomalies are the commonest anomalies, the associated infant deaths due to these anomalies are relatively infrequent (PHE 2019; Springett et al. 2014; Kurinczuk et al. 2010).

The impact of congenital anomalies on infant mortality depends on various factors, including the implementation and effectiveness of public health interventions, health care systems, access to and uptake of prenatal diagnosis and effective treatment, legislation about termination of pregnancy, the presence of other competing causes of deaths, as well as the capacity to track all the anomaly cases and link with death registry; each of these factors can lead to variations in anomaly-related infant mortality between different study populations (Budd et al. 2015; van der Pal-de Bruin et al. 2002; Kurinczuk et al. 2010).

Furthermore, socio-demographic, maternal and infant characteristics play important roles as potential determinants of the excess infant morbidity and mortality from congenital anomalies. For example, previous studies have shown that inequalities in child mortality due to CHDs and NTDs exist in different maternal ethnic groups, infant's gestational age and birthweight categories (Best et al. 2017; Bol et al. 2006; Shin et al. 2012; Wong et al. 2001).

1.2.4 Anomaly-related infant morbidity and hospitalisation

Congenital anomalies are a major cause of infant and child morbidity (Billet et al. 2008; McCandless et al. 2004). The majority of infants born with congenital anomalies survive; and for those infants affected by a serious major anomaly such as congenital heart, gastrointestinal and chromosomal defects, their survival has significantly improved over time due to advances in medical and surgical treatment. This has led to a significant burden of hospitalisation on these children due to anomaly-associated complications, ongoing treatment and investigations compared to children born without a congenital anomaly (ONS 2009; Larsen et al. 2017; Colvin and Bower 2009; Bloemer et al. 2007; Bradnock et al. 2011). Infancy represents the most significant period of clinical manifestation and complications of congenital anomalies requiring hospitalisation, however, the chronicity of the diseases especially for those with complex needs often results in an increased risk of hospital admissions and repeated admissions throughout childhood and beyond (Bradnock et al. 2011; Sharp et al. 2000; Wynn et al. 2013; Benoist et al. 2016; Cauley et al. 2015). For example, there is evidence suggesting that the rate and frequency of hospitalisation of infants and children with major congenital anomalies has generally increased over time (Colvin and Bower 2009; Frid et al. 2002). In addition, infants and children with a complex or syndromal anomaly were admitted for a longer stay compared to the general paediatric population, or to those with a less complex or non-syndromal anomaly (Yoon et al. 1997; McCandless et al. 2004). Among children with anomalies who required hospitalisation,

anomaly-related complications and respiratory-related conditions are the most common causes for their admissions (Colvin and Bower 2009; Kristensen et al 2009; Synder 1999).

Previous studies of children with major congenital anomalies such as CHDs and Down syndrome suggest that hospitalisation is an useful indicator for morbidity and monitoring the disease outcomes, although a significant part of multidisciplinary rehabilitation service for children with disabilities as a result of congenital anomalies such as the physiotherapy, speech and language therapy were also carried out as outpatient (Thelin and Swanson 2006; Fitzsimons et al 2013; Watson 2000). Thus, quantifying service utilisation can help planning and commissioning of health services aiming to improve the quality of care of infants affected by congenital anomalies.

1.3 Research gaps and rationale of study

There are several general points that can be drawn from previous studies leading to the rationale for this project.

First, in-depth investigations of morbidity and mortality of infants with congenital anomalies are lacking, with the existing literature from high-income countries mainly focused on a few specific anomaly groups such as CHDs, NTDs, Down syndrome and certain gastrointestinal defects including gastroschisis and congenital diaphragmatic hernias. In the UK, population-based studies investigating mortality, morbidity and hospitalisation among infants affected by congenital anomalies have been lacking in the past few decades. An in-depth investigation into the impact of a wider group of congenital anomalies on infant morbidity and mortality is important and a public health priority to inform healthcare professionals caring for the affected babies, parental counselling as well as the planning of healthcare resources and commissioning of targeted specialised service for infants with congenital anomalies.

Second, heterogeneity presents a major challenge for prognostic studies of infants with congenital anomalies. Variations in health care systems, inclusion criteria, study populations,

anomaly definitions and classifications between studies present a major challenge in epidemiological methodology and analyses of anomaly-related prognostic studies. This study aimed to identify and investigate the main potential factors leading to heterogeneity through the conduct of a series of systematic reviews of the literature and population-based cohort studies, and to make recommendations to strengthen methodology for future studies.

Third, emerging evidence suggests that socio-demographic, clinical and interventional factors (e.g. social deprivation, implementation of folic acid food fortification, and advances in medical and surgical interventions) are important determinants of the excess infant morbidity and mortality due to congenital anomalies (Kalucy et al. 1994; Bol et al. 2006; Borman and Cryer 1990). Hence, the nature and clinical characteristics associated with congenital anomalies leading to excess infant morbidity and mortality warrant further investigations. Such knowledge would have significant implications for clinical practice and public health prevention aiming to reduce infant morbidity and mortality due to congenital anomalies.

Therefore, this thesis sets to generate novel epidemiological findings about the impact of a wider group of congenital anomalies on infant morbidity and mortality, and to address the research gaps by conducting a series of systematic reviews and population-based cohort studies using robust methodology and national datasets.

Chapter 2: Aims and Objectives

The overall aim of this DPhil study was:

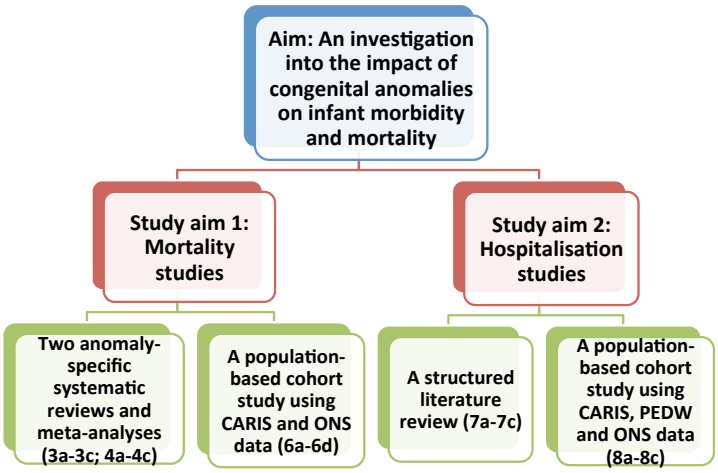
- **To investigate the impact of congenital anomalies on infant morbidity and mortality.**

The overall aim consisted of two main study aims as follows:

1. To investigate the nature and clinical characteristics of congenital anomalies leading to infant death;
2. To investigate the patterns, reasons for and outcomes of hospitalisation comparing infants with congenital anomalies and infants without congenital anomalies.

Figure 2.1 summarises the main components and methodological approaches for investigation.

Figure 2.1: Main components and methodological approaches for investigation



Each of the main study aims consisted of one or more systematic/ structured reviews, followed by a population-based cohort study. The specific objectives of each of these studies are described as follows.

For main study aim 1:

- Systematic reviews and meta-analyses

Two systematic reviews and meta-analyses on infant mortality associated with spina bifida (Chapter 3) and encephalocele (Chapter 4) were conducted with the specific objectives to investigate:

3a & 4a) Spina bifida- specific and encephalocele- specific neonatal and infant mortality rates over time;

3b & 4b) Spina bifida- specific and encephalocele- specific neonatal and infant case fatality over time;

3c & 4c) Socio-demographic and clinical factors associated with mortality in the first year for infants affected by spina bifida/ encephalocele.

These systematic reviews aimed to review and update the contemporary evidence and identify research gaps relating to the contribution of congenital anomalies to infant mortality from these major anomalies of the nervous system.

Note: Neural tube defects (NTDs) were chosen for the systematic reviews as part of the objectives of study aim 1 as anomalies of the nervous system are the second most common leading cause of anomaly-related infant deaths in which NTDs contribute a significant part. A systematic review had been previously conducted to investigate the survival of infants born with congenital heart defects (Best and Rankin 2016), which are the most common leading cause of anomaly-related infant deaths.

- First main data analysis of this study

A population-based cohort study was conducted using linked de-identified data from the Congenital Anomaly Register and Information Service (CARIS) for Wales and the Office of National Statistics (ONS) to investigate the nature and clinical features of the anomalies which lead to

death versus survival in the first year after birth in infants affected by an anomaly (Chapter 6). The specific objectives were:

6a) To estimate the infant mortality rates by anomaly;

6b) To describe the cause of death of infants with an anomaly;

6c) To describe and compare the characteristics of infants with congenital anomalies who survived and those who died;

6d) To examine the risk factors contributing to death versus survival of infants with an anomaly.

This study aimed to generate novel epidemiological findings of the impact of a wider group of congenital anomalies on infant mortality.

For main study aim 2:

- Structured literature review

A structured literature review of hospitalisation of infants born with congenital anomalies (Chapter 7) was conducted with the specific objectives:

7a) To describe the rates of hospitalisation by anomaly subgroups;

7b) To describe the pattern (i.e. causes, frequency and length of stay) of hospitalisation by anomaly subgroups;

7c) To describe the risk factors for hospitalisation of infants with a congenital anomaly.

This structured literature review aimed to update the contemporary study evidence and identify research gaps relating to the rate, patterns of and outcomes of hospitalisation comparing infants with and without congenital anomalies.

- Second main data analysis of this study

A population-based hospital episodes study was conducted using linked de-identified data from Patient Episode Database for Wales (PEDW), CARIS and ONS to investigate the patterns, reasons for and outcomes of hospitalisation comparing infants with anomalies who died with survivors (Chapter 8), the specific objectives were:

8a) To compare the rates of hospitalisation in the first year after birth between infants with and without congenital anomalies;

8b) To describe the patterns of hospitalisation in the first year after birth in infants with and without congenital anomalies; and

8c) To examine the risk factors for hospitalisation in the first year after birth among infants with congenital anomalies.

This study aimed to generate new epidemiological findings and build on the current knowledge of infant morbidity and hospitalisation comparing infants with and without congenital anomalies.

The conduct of all the studies in this thesis was based on a predefined protocol written *a priori* to outline the methodology, the details of which was refined after the project was approved by the Secure Anonymised Information Linkage (SAIL) databank and the dataset became available.

Chapter 3: Infant Mortality Associated With Spina Bifida: A Systematic Review and Meta-analysis

3.1 Introduction

Neural tube defects (NTDs) result from failure of the neural tube to close spontaneously between 21 and 28 days post conception (Arth et al. 2015; Blencowe et al. 2010); they constitute the largest subgroup of congenital anomalies of the nervous system. NTDs include anencephaly (i.e. partial or total absence of the scalp, skull and brain tissue), encephalocele (i.e. herniation of the brain and/or meninges through a defect in the skull) and spina bifida (i.e. herniation or exposure of the spinal cord and/ or meninges through an opening defect in the spine). The aetiology of NTDs is multifactorial (Blencowe et al. 2010; Davidoff et al. 2002). Studies have showed that socio-demographic (Shin et al. 2012; Borman et al. 1990), genetic (Davidoff et al. 2002), nutritional and environmental (Baird 1974) factors all play important roles in the development of NTDs.

NTDs pose a significant public health problem. Globally, it is estimated that approximately 300,000 babies are born with an NTD each year, causing approximately 88,000 deaths and leading to 8.6 million disability-adjusted life years (WHO, 2015). In Europe, NTDs affect approximately 1 in 1,000 pregnancies each year according to the EUROCAT data between 2011 and 2017 (EUROCAT 2019b; Khoshnood et al. 2015). In the UK, the prevalence of NTD-affected pregnancies and livebirths were 1.28 and 0.20 per 1,000 total births respectively between the year of 1991 and 2012 (Morris et al. 2016).

The prognosis varies between different NTD subtypes (Table 3.1). Anencephaly is inevitably fatal; the majority of affected fetuses die in utero or shortly after birth. The prognosis and mortality rates for infants with spina bifida and encephalocele has changed over time, mainly due to various factors including advances in prenatal diagnosis and subsequent TOPFA, as well as improving

medical and surgical treatment (Greene and Copp 2014). For example, as discussed in Chapter 1: section 1.2.2, an increasing rate of TOP for an NTD was accompanied by a decreasing IMR, which was mainly due to terminations for severe cases and a reduction in NTDs with the increased consumption of folate, as well as the national implementation of mandatory folic acid food fortification in some countries such as U.S., Canada and Australia over time (Bower et al. 2002; Kalucy et al. 1994; Riley et al. 1998, Wen et al. 1999; Davidoff et al. 2002). In addition, advances in neonatal intensive care have improved the prognosis of infants with spina bifida and encephalocele over time (Bol et al. 2006; Charney et al. 1991). Although studies have shown that fetal surgery for spina bifida improves the prognostic outcomes of the affected fetuses, its impact at population level is limited as the surgical treatment is available only in a few specialised centres and for selected fetuses who meet strict clinical criteria (Adzick et al. 2011).

Table 3.1: Neural tube defects (NTDs) subtypes, clinical features and usual prognoses. (NORD 2020)

NTD subtype	Aetiology	Clinical features	Prognosis
Anencephaly	Anterior cranial neural arch fails to close.	Absence of variable amount of scalp, skull, brain tissue, spinal cord and nerve roots and meninges.	Inevitably stillbirth or death shortly after birth.
Encephalocele	Anterior cranial neural arch fails to close at a later stage of embryogenesis than anencephaly.	Herniation of sac-containing brain tissue through skull defect across midline, usually in the occipital region.	Variable from normal function or mild disabilities to severe multi-system impairment or death.
Spina bifida	Posterior caudal vertebrae arch fails to close.	Herniation of the meninges (i.e. meningocele) or dysplastic spinal cord (i.e. myelomeningocele – a more severe form) through a spinal defect. Often associated with hydrocephalus leading to blockage of the cerebrospinal fluid and raised intracranial pressure.	Majority of patients survive with variable degree of neurological, cognitive, functional, renal and orthopaedic sequelae.

As NTDs are a leading cause of paediatric mortality, morbidity and long-term disability (Yi et al. 2011), estimates of infant mortality rates (IMRs) associated with NTDs are important to inform planning of health and social interventions aimed at reducing infant mortality. Despite this,

current evidence about the impact of spina bifida and encephalocele, and the contribution they make to infant mortality is very limited.

In chapters 3 and 4, I present the first systematic reviews to examine the contemporary evidence of infant mortality associated with spina bifida (chapter 3) and encephalocele (chapter 4).

3.2 Background

Spina bifida is the commonest type of NTDs, which results from failure of the closure of the neural tube between 21 and 28 days post conception (Blencowe et al. 2010). The aetiology of spina bifida is multifactorial. Genetic, nutritional and environmental factors all play an important part in the development of spina bifida (Baird 1974; Davidoff et al. 2002).

Globally, infant mortality associated with spina bifida has been changing over time due to various factors including effective implementation of public health preventive interventions such as folic acid food fortification programmes, preconceptional folic acid supplementation, advances in prenatal screening (RCOG 2010; Thompson 2009), improvements in medical and surgical treatment, as well as the capacity of health care systems to ascertain, track and link all cases with death registers (Rosano et al. 2000). Importantly, folic acid food fortification has not been implemented in many parts of Europe including the UK, although this has proved a successful preventative intervention in other countries including the US, Australia and New Zealand where mandatory folic acid fortification of wheat flour has been implemented (Morris et al. 2016; Zaganjor et al. 2016).

Population-based mortality studies of infants with spina bifida have been previously conducted, mainly restricted to selected geographical regions especially in high-income countries where data were more readily available (Rosano et al. 2000). This chapter presents a systematic review and meta-analysis of population-based studies investigating infant mortality associated with spina bifida.

3.3 Study objectives

The study objectives were to review:

3a) Spina bifida-specific neonatal and infant mortality rates over time;

3b) Spina bifida-specific neonatal and infant case fatality over time; and

3c) Socio-demographic and clinical factors associated with mortality in the first year for infants affected by spina bifida.

3.4 Methods

A systematic review was conducted. The protocol for the systematic reviews was registered in the International Prospective Register of Systematic Reviews (PROSPERO) (NIHR 2019), registration number CRD42018081353.

3.4.1 Search sources and strategy

Comprehensive literature searches of PubMed, Embase, Ovid, Web of Science, CINAHL, Scopus and the Cochrane Library were performed from 1st January, 1990 to 31st August, 2020 in order to identify relatively contemporary evidence. Assistance for the development of the search strategy was provided by a specialist information librarian (NR) from the Bodleian Libraries. Based on the concepts of Population, Exposure(s), Comparison(s) and Outcome (PECO), Medical Education Subject Headings (MeSH) terms and keywords were entered systematically into the databases as follows:

1. neural tube defect* OR congenital brain anomal* OR congenital brain malformation* OR congenital brain abnormal* OR congenital spinal anomal* OR congenital spinal malformation* OR congenital spinal abnormal* OR congenital central nervous system anomal* OR congenital central nervous system malformation* OR congenital central

nervous system abnormal* OR spina bifida* OR myelomeningocele* OR meningomyelocele* OR meningocele* OR encephalocele*

2. newborn* OR neonat* OR infan* OR perinat*
3. mortality OR death* OR survival*
4. 1 AND 2 AND 3

The detailed search terms are shown in Table 3.2, with the exact search methods and strategies depending upon individual databases (Appendix 3.1). No language restrictions were applied; non-English articles were fully translated using online translators. Hand searches of reference lists were performed on all the included publications in order to optimise the search outcome and coverage. All relevant conference and poster abstracts were assessed, and subsequent contacts were made with the authors for further details where necessary (Appendix 3.2). Search results were merged using the reference management software EndNote.

The original literature search of the systematic review was performed from 1st January, 1990 to 13th February, 2017 the date when the search strategy was finalised. This search was updated to 31st August, 2020 when the full draft of this thesis was being reviewed and finalised.

Table 3.2: Detailed search terms (an example from PubMed search).

For systematic reviews: Infant mortality associated with spina bifida (Chapters 3) and encephalocele (Chapter 4).
(((neural tube defect* OR congenital brain anomal* OR congenital brain malformation* OR congenital brain abnormal* OR congenital spinal anomal* OR congenital spinal malformation* OR congenital spinal abnormal* OR congenital central nervous system anomal* OR congenital central nervous system malformation* OR congenital central nervous system abnormal* OR spina bifida* OR myelomeningocele* OR meningomyelocele* OR meningocele* OR encephalocele*[MeSH Terms])) AND (newborn* OR neonat* OR infan* OR perinatal*[MeSH Terms])) AND (mortality OR death* OR survival*[MeSH Terms]) Filters: Publication date from 1990/01/01 to 2020/08/31; Humans

Two assistant reviewers (DT and CB) were trained by PH. Titles and abstracts of all identified studies were screened by PH according to the inclusion criteria. For articles which satisfied the first screen, full articles were then screened independently by two reviewers (PH and DT/ CB) for their eligibility according to the full inclusion and exclusion criteria (i.e. second screen). Any screening issues or discrepancies about eligibility of a given study were discussed by the two

reviewers for a resolution in the first instance. The presence and resolution of disagreements were recorded. If it was not possible to resolve a disagreement about the eligibility of a study (e.g. due to discrepancies in interpretation), this was discussed and reviewed by the full supervision team (PH, MQ and JK) to reach a final decision.

3.4.2 Inclusion criteria

Population-based studies were included if they (1) ascertained all individuals born with spina bifida in a predefined population; (2) provided the number of spina bifida associated neonatal/infant deaths occurring among all livebirths or all spina bifida cases in a given population, or risk factors associated with mortality in the first year for infants affected by spina bifida; and (3) were conducted in high-income countries as defined by the World Bank (The World Bank 2019).

3.4.3 Exclusion criteria

Studies were excluded if: (1) they were conducted solely in tertiary or referral centres (i.e. non-population based studies); and (2) spina bifida-affected individuals were not followed up from birth. In addition, information from eligible studies about spina bifida occulta (i.e. a mild form of spina bifida with no clinical consequence) (Gregerson 1997) and spina bifida related to a syndrome were excluded where possible.

For multiple papers which overlapped in time, study region and/or objectives, only the study (or a combination of studies) with the best quality, largest population size, and covering the longest and most recent periods was included.

3.4.4 Data extraction

Data extraction was performed according to the methods recommended in the Cochrane data collection for systematic review (Higgins et al. 2019). The data extraction form was piloted and standardised (by PH, DT and CB) before usage.

PH conducted the literature searches, screening of abstracts and review of 368 eligible full articles. DT and CB each reviewed half of the eligible full articles. Decisions about the final included articles and extracted data were validated by all three reviewers. Any discrepancies in the extracted data were reviewed, and resolution of disagreements was recorded. Attempts were made to contact the study authors for any relevant unpublished data.

The following data were extracted either directly (i.e. as reported or published by the authors) or indirectly (i.e. where relevant data could be derived from the published data) from the included studies: study population, study design, sample sizes (these included the total number of livebirths, livebirths affected by the anomaly and termination of affected pregnancies), country of study, and descriptive/ mortality data related to maternal age, maternal ethnicity, smoking, maternal education, previous livebirths, prenatal care, mode of delivery, infant sex, gestational age, birthweight, year of birth, plurality, lesion level or position, the presence of multiple defects, hydrocephalus and major cardiac defects and year of implementation of folic acid fortification. Categories of explanatory variables were standardised to ensure comparability between studies.

Spina bifida mortality rates, case fatality and the corresponding 95% CI were extracted at the age of one month and at one year. If the 95% CI of the mortality rates were not reported and sufficient information was reported, they were estimated using 'binomial exact' in Stata software, assuming no cases were censored. A binomial distribution was assumed in this approach and the use of binomial method and was justified as survival outcome is a dichotomous category and statistically independent for each infant (Campbell et al. 2007). In addition, as infant deaths were generally rare, the use of 'exact' method to estimate the CIs for small proportions is

recommended (Campbell et al. 2007). In regard to CI for relative risk, in studies where the 95% CI of RR of a risk factor for infant mortality was not reported, it was estimated using the formula: log RR ± 1.96 × Standard Error, in which the standard error was derived from the observation counts and proportions as reported in that study. The 95% CI for the RR can hence be determined by the antilog of these limits (Bland and Altman 2000).

3.4.5 Main outcomes and measures

The main outcomes were:

(1) Spina bifida neonatal/infant mortality rate, which was defined as:

$$\frac{\text{The number of neonates/infants with spina bifida who died}}{\text{The total number of all livebirths in the population in the relevant time period}}$$

Spina bifida neonatal/infant mortality rate was expressed as the number of neonates/infants died per 100, 000 live births.

(2) Spina bifida neonatal/infant case fatality, which was defined as:

$$\frac{\text{The number of neonates/infants with spina bifida who died}}{\text{The number of all neonates/infants born with spina bifida in the relevant population}}$$

Spina bifida neonatal/infant case fatality was expressed as the proportion (%) of livebirths affected by spina bifida.

(3) Risk factors for death in the first year after birth in infants affected by spina bifida.

3.4.6 Statistical analysis

Pooled estimates of relative risk for risk factors for spina bifida infant case fatality were calculated using random-effects models. Each study was weighted using the inverse of the variance, which aimed to minimise the imprecision of the pooled effect. The precision of the estimation of between-study variance is thought to be greater with greater number of studies with the random-effects model (Borenstein et al. 2007). Random-effects analysis was used to estimate the mean of

a distribution of effects because the true effect size is likely to vary from one study population to another due to different exposures, for example, the survival of infants with spina bifida can be influenced by different policies of mandatory folic acid food fortification and surgical treatment criteria between countries (Kalucy et al. 1994; Shin et al. 2012; Wong et al. 2001). Therefore, the included studies in the meta-analysis were assumed to be a random sample of the distribution of the survival effects, and the pooled estimate represented the mean of a distribution of true effects, rather than assuming one true effect size shared by all the included studies as for the fixed effect model. In addition, random-effects method allows smaller size studies to be given weight more similar to larger size studies so that the assigned weights were more balanced in order to avoid large size studies to dominate the analysis (Higgins and Green 2011; Borenstein et al. 2011). However, as there were only two studies included in the meta-analysis of RR of risk factors contributing to the excess infant mortality, it may not be possible to precisely estimate the between-studies variance (i.e. Tau^2 which represents the absolute value of the true variance), and therefore both random-effects and fixed effects models were used to calculate and compare pooled estimates taking into account of the heterogeneity and small number of the included studies (Cai and Fan 2020; Borenstein et al. 2011). A test of heterogeneity was used to examine time trends. Heterogeneity between studies was assessed using the Cochrane Q test (as chi-square statistics to assess whether the observed differences are compatible with chance alone) and I^2 statistics (i.e. degree of variation expressed as 0-100% as a result of heterogeneity rather than by chance). $P < 0.10$ was considered as statistically significant with $I^2 > 50\%$ indicating a substantial level of heterogeneity (Higgins et al. 2003) (Table 3.3).

Table 3.3: Assessment of heterogeneity. (Higgins et al. 2003)

I^2 statistics	**Between-study heterogeneity**
0-30%	Non-significant
30-50%	Moderate
50-75%	Substantial
75-100%	Considerable
P < 0.10 is considered as a cut-off for statistical significance	

Random-effects meta-regression was used to assess the effect of year of birth, with the mid year of the birth cohort used as an explanatory variable. Results of meta-regressions are presented in bubble plots, where the size of the bubble is proportional to the study weight and therefore the precision of mortality or fatality estimate. The slopes of the meta-regression lines were calculated to examine any changes and directions of mortality rates, with $p < 0.05$ considered as statistically significant.

All data analyses were performed using Stata 13 statistical software (StataCorp. 2013). The reporting of results was in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram and Meta-analysis of Observation Studies in Epidemiology (MOOSE) checklist (Appendix 3.3) (Moher et al. 2015; Stroup et al. 2000).

3.4.7 Quality appraisal

Risk of bias (RoB) assessment was conducted using a refined quality tool based on the Quality in Prognostic Studies (QUIP) (The Cochrane Library 2018), which is recommended for use in evaluating validity and potential bias in prognostic studies, for the following five domains: study participation, measurement of outcome(s), study attrition, measurement of exposure or prognostic factor(s), and statistical analysis and reporting. The RoB assessment form was piloted and standardised (by PH in consultation with the supervision team) prior to usage to ensure that criteria could be applied consistently and consensus could be reached.

Each domain was rated either as 'high', 'moderate' or 'low' RoB by two independent reviewers (PH and DT/CB). The overall RoB for each included study was assessed using the method described by Hayden et al. 2013 in line with the Cochrane Risk of Bias tool (Higgins et al. 2008) (Table 3.4). A study was considered as having an overall low RoB if all of domains assessed were rated as 'low' RoB, and vice versa for high. A study was considered as having an overall low to

moderate RoB if there were no more than 2 domains rated as ‘moderate’ RoB. A study was considered as having an overall high RoB if there were any of the domains rated as ‘high’ RoB.

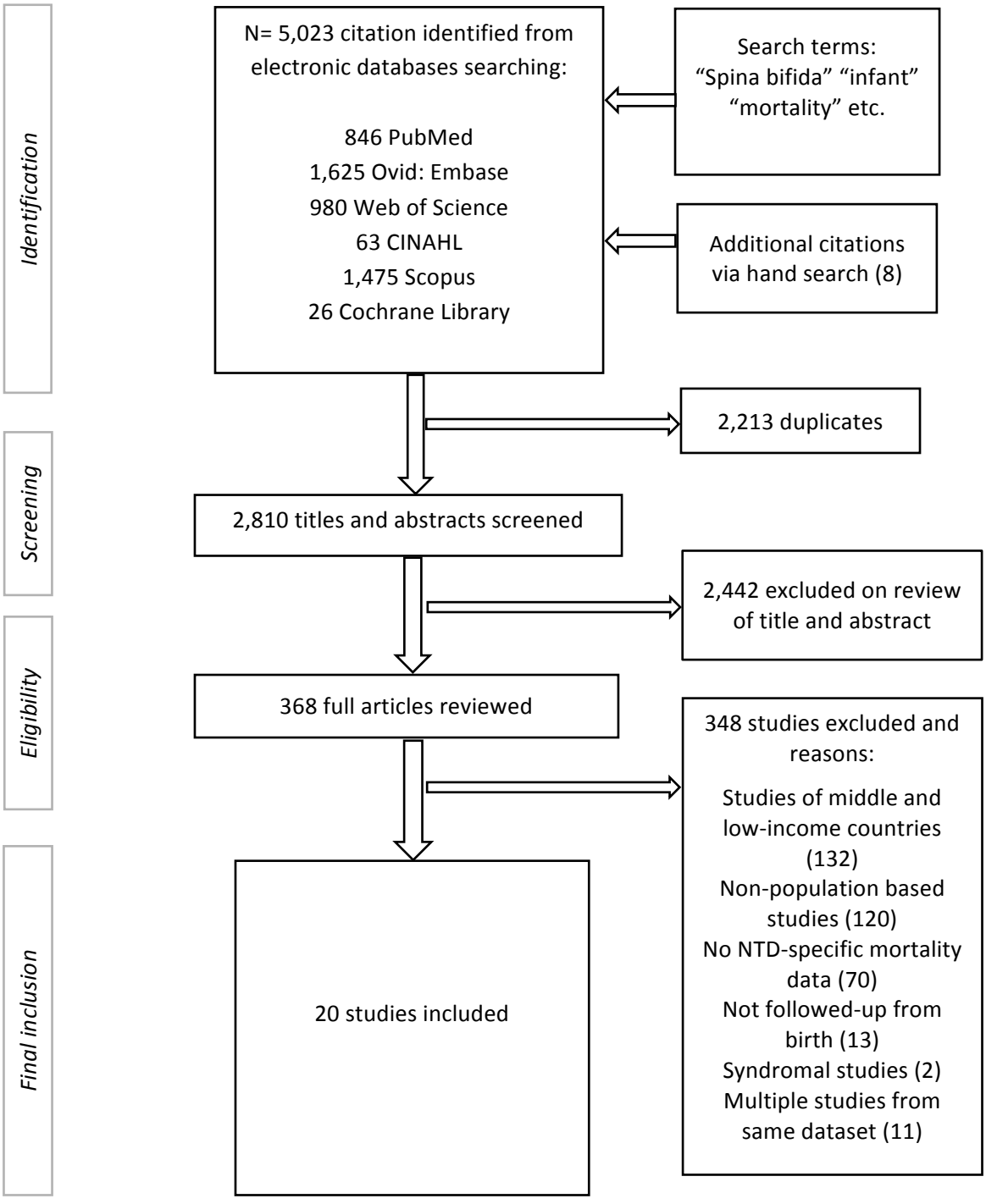
Table 3.4: Risk of Bias (RoB) assessment using a refined version of the Quality in Prognosis Studies (QUIPS) tool. (Hayden et al. 2013)

Potential Bias	Items considered for potential RoB	High RoB (*Very likely)*	Moderate RoB (*Maybe)*	Low RoB (*Unlikely)*
Domain 1: **Study population**	Adequate descriptions and selections of: • The source population/ population of interest; • The baseline study sample; • The place and period of recruitment; • Inclusion and exclusion criteria.	The association between exposure/ prognostic factor and outcome (is) _ _ _ _ _ (to be) different for eligible participants and eligible non-participants.		
Domain 2: **Measurement of outcomes**	Adequate descriptions of: • Outcome measure(s); • A reliable and valid method of outcome measurement used for all study participants.	The measurement of the outcome of interest (is) _ _ _ _ _ (to be) different between participants/ related to the baseline level of exposure or prognostic factor.		
Domain 3: **Study Attrition**	Adequate method and completeness of follow-up. If significant loss to follow up (≥5%), adequate descriptions of: • Participants lost to follow-up; • Reasons or attempts to search the reasons for lost to follow-up. Note: If the proportion of traced cases was unknown, consider if cases were traced and linked using data from national/states registry and vital statistics.	The association between exposure/ prognostic factor and outcome (is) _ _ _ _ _ (to be) different for completing and non-completing participants in the study.		
Domain 4: **Exposure/ Prognostic factor(s) measurement**	The settings and methods of exposure/ prognostic factors measurement are: • Adequate described; • Adequately valid and well categorised where appropriate; • Same for all participants.	The measurements of exposure/ setting/ prognostic factors (are) _ _ _ _ _ (to be) different for different participants in the study population(s).		
Domain 5: **Statistical data, analysis and reporting**	Appropriate and adequate: • Descriptions/ definitions of variables and data source(s). • Statistical model for the study design; • Analytical strategy (e.g. model building); • Confidential intervals were provided. No selective results reporting.	The reported results (are) _ _ _ _ _ (to be) biased or invalid related to analysis or reporting.		

3.5 Results

The flow of literature in this review is summarised in the PRISMA diagram (Figure 3.1). Of 5,023 articles identified, 20 met the inclusion criteria.

Figure 3.1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram for the flow of studies through the systematic review (1.1.1990 to 31.8.2020).



3.5.1 Study characteristics

All 20 included studies were population-based cohort studies conducted in high-income countries (Table 3.5), with six studies in the U.S. where mandatory folic acid food fortification was introduced nationally in 1998 by the U.S. Food and Drug Administration (Davidoff et al. 2002; Waitzman et al. 1994; Wong et al. 2001; Bol et al. 2006; Shin et al. 2012; Wang et al. 2015), four in Canada where mandatory folic acid food fortification was introduced nationally in 1998 (Laishram et al. 1993; Wen et al. 1999; Liu et al. 2001; Wen et al. 2000), four in Australia where mandatory folic acid food fortification was introduced nationally in 2009 (Kalucy et al. 1994; Riley et al. 1998; Algert et al. 2008; Schneuer et al. 2019), two in the Republic of Ireland (Sutton et al. 2008; McDonnell et al. 2015), one in Scotland (Theodorou et al. 2013), one in Sweden (Persson et al. 2005), one in Denmark (Borgstedt-Bakke et al. 2017), and one from the International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR) selected member registries of France, Germany, Italy, Netherlands, Spain, Sweden and UK Wales (Bakkar et al. 2019). These studies included a total study population of more than 30 million liveborn infants (median study sample size: 1,178,452, range: 251,699 – 14 million), in which approximately 12,000 (median: 231 and range: 27-3,903) were affected by spina bifida. All infants included were born at ≥ 20 weeks' gestational age with a birthweight ≥ 500g.

Associated conditions

One study (Persson et al. 2005) reported that 37% of spina bifida cases were associated with hydrocephalus which was analysed separately. Eleven studies (Kalucy et al. 1994; Laishram et al. 1993; Sutton et al. 2008; Waitzman et al. 1994; Wong et al. 2001; Bol et al. 2006; Shin et al. 2012; Theodorou et al. 2013; Bakkar et al. 2019; Wang et al. 2015; McDonnell et al. 2015) reported that between 2.7% and 43.6% of spina bifida cases were associated with multiple anomalies or a syndrome, in which these cases from three studies were excluded from the analysis (Wong et al. 2001; Theodorou et al. 2013; McDonnell et al. 2015).

Whether syndromal spina bifida was included in other included studies was uncertain as this could not be verified with the authors.

Table 3.5: Description of the included studies. *(Note: the included studies are ordered by birth year)*

Author, Included birth years	Study location and no. of liveborn spina bifida	Included NTD subtypes (ICD codes)	Source of cases	Source of death information	Percentage of traced cases	Inclusion of multiple defects	Main limitations
Kalucy (1994) 1966-1990	Western Australia n = 395	Spina bifida ± Hydrocephalus (Coding not specified)	Birth defects registry, inpatient records.	Death certificates, post mortem reports, matched with infants' demographics.	Not stated.	Yes; multiple and chromosomal defects were included but no further details.	1. Variations of cases ascertainment over years. 2. Mortality status was only known for a proportion of cases.
Laishram (1993) 1967-1990	Newfoundland and Labrador, Canada. n = 273	Spina bifida (Coding not specified)	Inpatient records	Death certificate (assumed)	99.6%	Yes; cardiac, gastrointestinal, urological and limbs/skeletal defects, and orofacial cleft. But only those needed operations were reported.	Diagnostic code for classification of disease not described.
Sutton (2008) 1976-1987	Dublin, Ireland n = 475	Spina bifida (Coding not specified)	Four Dublin maternity hospitals medical records.	Medical record and/or parental interview.	92%	Eight cases of encephalocele had an additional spinal lesion.	Diagnostic coding for disease classification not described.
Waitzman (1994) 1983-1986	California, USA n = 226	Spina bifida (ICD-9/BPA[2]: 741, 741.0x, 741.9x)	California Birth Defects Monitoring Programme.	Linked birth and death records.	Not stated.	Yes; but no further details reported.	Confidence interval of estimates not provided.

Table 3.5 (continued): Description of the included studies. *(Note: the included studies are ordered by birth year)*

Author, included birth years	Study location and no. of liveborn spina bifida	Included NTD subtypes (ICD codes)	Source of cases	Source of death information	Percentage of traced cases	Inclusion of multiple defects	Main limitations
Wong (2001) 1979-1994	Atlanta, USA n = 235	Spina bifida (ICD-9: 741)	Metropolitan Atlanta Congenital Defects Programme.	National Death Index and death certificates linked with registry data.	100%	Yes; but cases with anencephaly, and Trisomies 13 or 18 were excluded.	Sizes of birth cohorts limited the statistical power to detect their significance in the trend in one-year survival.
Wen (2000) 1981-83, 1993-95	Canada n = Unspecified	Spina bifida (ICD-9: 740)	Nine Canadian provinces[1], recorded in Statistics Canada's live birth and death databases.	Statistics Canada's livebirth and death databases.	~100%	Not stated.	As described in the study of Wen at al. (1999).
Riley (1998) 1983-1995	Victoria, Australia n = 526	Spina bifida (BPA ICD-9 supplement)	Victorian Birth Defects/ Congenital Malformations Register.	Perinatal death certificates, autopsy reports, maternal and child health nurse notifications, inpatient and outpatient listings; record linkage using Perinatal Morbidity Statistics System.	Up to 86%.	Not stated.	Voluntary notification to congenital malformations register, completeness depended on type of malformation.

Table 3.5 (continued): Description of the included studies. *(Note: the included studies are ordered by birth year)*

Author, Included birth years	Study location and no. of liveborn spina bifida	Included NTD subtypes (ICD codes)	Source of cases	Source of death information	Percentage of traced cases	Inclusion of multiple defects	Main limitations
Liu (2001) 1985-1996	Canada n = Unspecified	Spina bifida (ICD-9: 741)	Canadian stillbirth and infant death registration, and perinatal surveillance system.	Statistics Canada's Mortality Database.	98%	Not stated.	1. Death certificates recorded a single underlying cause of death. 2. Potential errors of assigning and coding the cause of death from death certificates (e.g. minor anomalies being coded as an underlying cause of death).
Borgstedt-Bakke (2017) 1970-2015	Western Demark n = 187	Spina bifida (Coding not specified)	Western Denmark myelo-meningocele database.	Hospital's record linkage (Danish Civil Registration System).	92%	Not stated.	1. Missing data likely underestimate death rate. 2. Unspecified diagnostic code for myelomeningocele.
Wen (1999) 1990-1995	Canada n = Unspecified	Spina bifida (ICD-9: 741)	Nine Canadian provinces, recorded in Statistics Canada's live birth and death databases.	Statistics Canada's livebirth and death databases.	~100%	Not stated.	1. Assumed only lethal anomalies would have been coded as the underlying causes of death. 2. Not possible to assess impact of potential regional differences in maternal exposure and primary prevention. 3. Potential errors of assigning and coding the cause of death from death certificates (<1%).

Table 3.5 (continued): Description of the included studies. *(Note: the included studies are ordered by birth year)*

Author, Included birth years	Study location and no. of liveborn spina bifida	Included NTD subtypes (ICD codes)	Source of cases	Source of death information	Percentage of traced cases	Inclusion of multiple defects	Main limitations
Persson (2005) 1989-1998	Western Sweden n = 84	Myelo-meningocele with hydrocephalus (ICD-9 and -10)	Hospital registers in the region.	Swedish Medical Birth Registration and Statistics of the National Board of Health and Welfare.	Not stated.	The study cohort had hydro-cephalus analysed separately.	Case completeness based on assumption that all cases were referred.
Davidoff (2002) 1996-1998	USA n = Unspecified	Spina bifida (ICD-9: 741.0)	National Centre for Health Statistics.	Period linked birth/infant death data.	Not stated.	Not stated.	Birth certificates can be low in sensitivity in detecting birth defects. Possible miscoding errors for the cause of death.
Bol (2006) 1995-2001	USA n = 2,841	Spina bifida (ICD-9-CM: 741.0)	Birth defects monitoring programmes from 16 states[3].	Death certificates and record linkage with anomaly cases.	95% - 100%	Mixed. 41 (6%) cases with concurrent spina bifida and encephalo-cele were included in both cohorts.	1. Unequal time study periods with different birth defects monitoring programmes. 2. Some participating programmes were unable to submit cases for all birth years. 3. Unequal access to treatment (such as fetal surgery) between participating states. 4. Not differentiate between syndromic and non-syndromic NTDs. Accuracy of diagnosis was not verified by Colorado state.

Table 3.5 (continued): Description of the included studies. *(Note: the included studies are ordered by birth year)*

Author, Included birth years	Study location and no. of liveborn spina bifida	Included NTD subtypes (ICD codes)	Source of cases	Source of death information	Percentage of traced cases	Inclusion of multiple defects	Main limitations
Theodorou (2013) 1990-2009	Southeast Scotland, UK n = 43	Spina bifida (ICD coded)	Audit of congenital anomalies in South East Scotland.	Death certificates/ National Registry Scotland.	43%	Syndromal defects excluded.	High proportion of loss to follow up.
Shin (2012) 1997-2003	USA n = 2,259	Spina bifida (ICD-9-CM: 741.0 and 741.9)	Birth defect monitoring programmes from 10 states[4].	Vital and medical records and the National Death Index, linked with anomaly cases.	Not stated.	2.7-12.7% of spina bifida cases had congenital heart defects, according to different states.	1. High proportions of missing data in lesion level (41%) and maternal education. 2. Regional and periodic variations of maternal and infant characteristics and variation in diagnostic coding.
Bakkar (2019) 2001-2002	ICBDSR[7] selected registry members (France, Germany, Italy, Netherlands, Spain, Sweden, Wales). n = 518	Spina bifida (ICD-9: 741 and ICD-10: Q05)	ICBDSR multi-registries.	Linkage to administrative database and death certificates/ records or other health care databases.	High (used multiple data sources).	14.6-43.6% of spina bifida cases were either part of multiple anomalies or a syndrome.	Heterogeneous methods in data contributions. Data linked to death certificates were not uniform across programmes.

Table 3.5 (continued): Description of the included studies. *(Note: the included studies are ordered by birth year)*

Author, Included birth years	Study location and no. of liveborn spina bifida	Included NTD subtypes (ICD codes)	Source of cases	Source of death information	Percentage of traced cases	Inclusion of multiple defects	Main limitations
Algert (2008) 2001-2003	New South Wales, Australia n = 27	Spina bifida with hydrocephalus (ICD-10)	NSW Admitted Patient Data Collection.	Australian Bureau of Statistics mortality data and record linkage.	Not stated.	Yes; the study cohort had hydrocephalus analysed separately.	1. Infants diagnosed >28 days after birth or who did not have a surgical repair were excluded. 2. Potential diagnostic coding errors. 3. Small sample size and low study power.
Wang (2015) 1999-2007	USA n = 3,903	Spina bifida (ICD-9-CM / CDC[5]/ BPA[2])	Birth defects surveillance programmes from 12 states[6]	Death certificates and National Death Index. Anomaly cases were linked to vital records.	Not stated.	Yes; but no further details reported.	1. Total number of live birth was approximate. 2. Potentially incomplete ascertainment of deaths from missed matches of study cohort to death certificates. 3. Passive cases ascertainment
Schneuer (2019) 2004-2009	New South Wales, Australia n = 56	Spina bifida (ICD-10)	New South Wales Register of Congenital Conditions (RoCC).	Record linkage to New South Wales Perinatal Data Collection, and the Registry of Births, Deaths and Marriages death registration.	High (used multiple data sources).	Yes; but no further details reported.	Unknown loss to follow up due to migration (an estimate of 1.6% of total resident population migrated out during the study period).

Table 3.5 (continued): Description of the included studies. *(Note: the included studies are ordered by birth year)*

Author, Included birth years	Study location and no. of liveborn spina bifida	Included NTD subtypes (ICD codes)	Source of cases	Source of death information	Percentage of traced cases	Inclusion of multiple defects	Main limitations
McDonnell (2015) 2009-2011	East and Southeast of the Republic of Ireland n = 89	Spina bifida (ICD-9)	EUROCAT regional congenital anomaly registers in east, south and southeast of Ireland, all maternity hospital nationally and paediatric hospitals.	Death registrations, post-mortem reports, hospital reports, inpatient enquiry system and National Perinatal Reporting System.	Not stated.	Yes; 11% (n= 21) of the liveborn and stillborn NTD cases had ≥ 1 additional major or minor anomaly. These included T13 or 18, abdominal wall defects and diaphrag-matic hernias.	24% of births from women born outside Ireland, who might have different risk profile for NTDs compared to Irish-born mothers.

[1]Wen (2000): Data from the province of Newfoundland, British Columbia and Ontario were excluded in the original study. [2]BPA = British Paediatric Association Classification of Diseases codes. [3]Bol (2006): 16 states/ regions included Alabama, California, Colorado, Hawaii, Illinois, Iowa, Kentucky, metropolitan Atlanta, Michigan, New York, North Carolina, Oklahoma, Rhode Island, South Carolina, Texas, and West Virginia. [4]Shin (2012): 10 regions included Arkansas, Georgia (5 counties of metropolitan Atlanta), California, Colorado, Iowa, North Carolina, New York (excluding New York City), Oklahoma, Texas and Utah. [5]CDC = Centers for Disease Control and Prevention. [6]Wang (2015): 12 states included Arizona, Colorado, Florida, Georgia (5 counties of metropolitan Atlanta), Illinois, Massachusetts, Michigan, Nebraska, New Jersey, New York (excluded New York City), North Carolina, and Texas. [7]ICBDSR = International Clearinghouse for Birth Defects Surveillance and Research.

3.5.2 Mortality estimates

Decreasing trends in neonatal mortality rates (NMR) and infant mortality rates (IMR), and case fatality from spina bifida were observed over time.

For example, in Australia and the US, the spina bifida NMR decreased ten fold from 17.0 per 100, 000 livebirths in 1983-1995 (pre- mandatory folic acid food fortification), to 1.6 per 100, 000 livebirths in 1999-2007 (post- mandatory folic acid food fortification) (Riley et al. 1998; Wang et al. 2015) (Table 3.6 and Figure 3.2). In Canada and the US, the spina bifida infant IMR also decreased ten fold from 23.0 per 100, 000 livebirths in 1981-1983 to 2.3 per 100, 000 livebirths in 1990-2007 (Wen et al. 2000; Wang et al. 2015) (Table 3.6 and Figure 3.3).

There was considerable heterogeneity between studies for spina bifida NMR (I^2 = 99.6%, $p < 0.001$) and IMR (I^2 = 99.5%, $p < 0.001$) (Table 3.6). The fitted meta-regression shows a decrease over time in NMR and IMR due to spina bifida (slope = 7.14% and 4.76% decrease in death rate per year respectively between 1982 and 2003, $p < 0.001$) (Figures 3.2 and 3.3).

Table 3.6: Neonatal and Infant mortality rates from spina bifida.

Studies (years of birth)	Country of study (Year of introduction of mandatory folic acid fortification)	Mid-year of birth cohort	Population size (total number of livebirths)	Neonatal and infant mortality rate per 100,000 live births *(no. of death) [95%CI]*	
				Neonatal	Infant
Spina bifida					
Wen (1981-83)[1]	Canada (1998)	1982	600,000	-	23.0 (138) [19.3-27.2]
Riley (1983-95)	Victoria, Australia (2009)	1989	825,051	17.0 (140) [14.4-20.0]	-
Liu (1985-87)	Canada (1998)	1986	692,556	-	11.1 (77) [8.7-13.9]
Wen (1993-95)	Canada (1998)	1994	117,8452	-	8.1 (96) [6.6-10.0]
Davidoff (1989-98)	USA (1998)	1993/94	11,713,941	-	1.3 (151) [1.1-1.5]
Theodorou (1990-09)	Southeast Scotland	1999/2000	276,404	2.2 (6) [0.8-4.7]	-
Wang (1999-07)	USA (1998)	2003	14,000,000	1.6 (222) [1.4-1.8]	2.3 (318) [2.0-2.5]
Heterogeneity I^2 and P value				**99.6%, p < 0.001**	**99.5%, p < 0.001**
Spina bifida with hydrocephalus					
Persson (1989-98)	Western Sweden	1993/94	253,378	-	2.0 (5) [0.6-4.6]
Algert (2001-03)	New South Wales, Australia (2009)	2002	251,699	-	1.2 (3) [0.2-3.5]
Heterogeneity I^2 and P value				**-**	**0.0%, p = 0.550**

[1]Data from Wen 1981-83 and 1993-95 were extracted from Wen (2000).

Figure 3.2: Neonatal mortality from spina bifida in Australia, the UK and the U.S. (Birth cohort: 1989-2003). (Riley 1998; Theodorou 2013; Wang 2015).

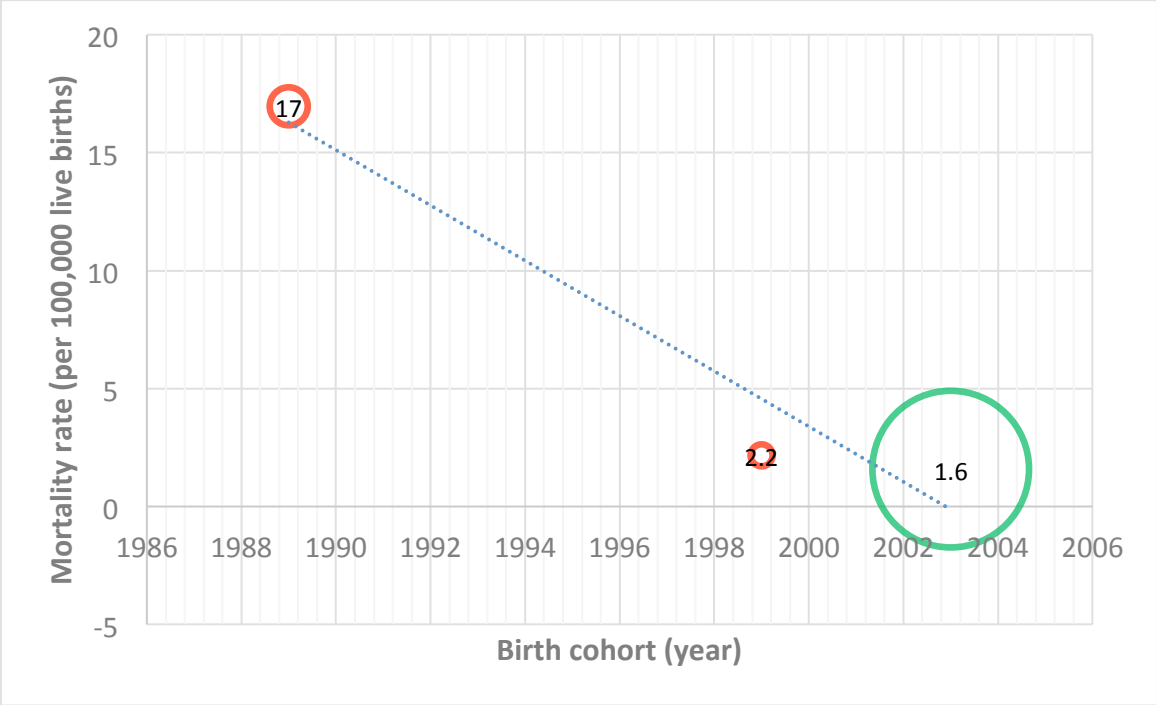
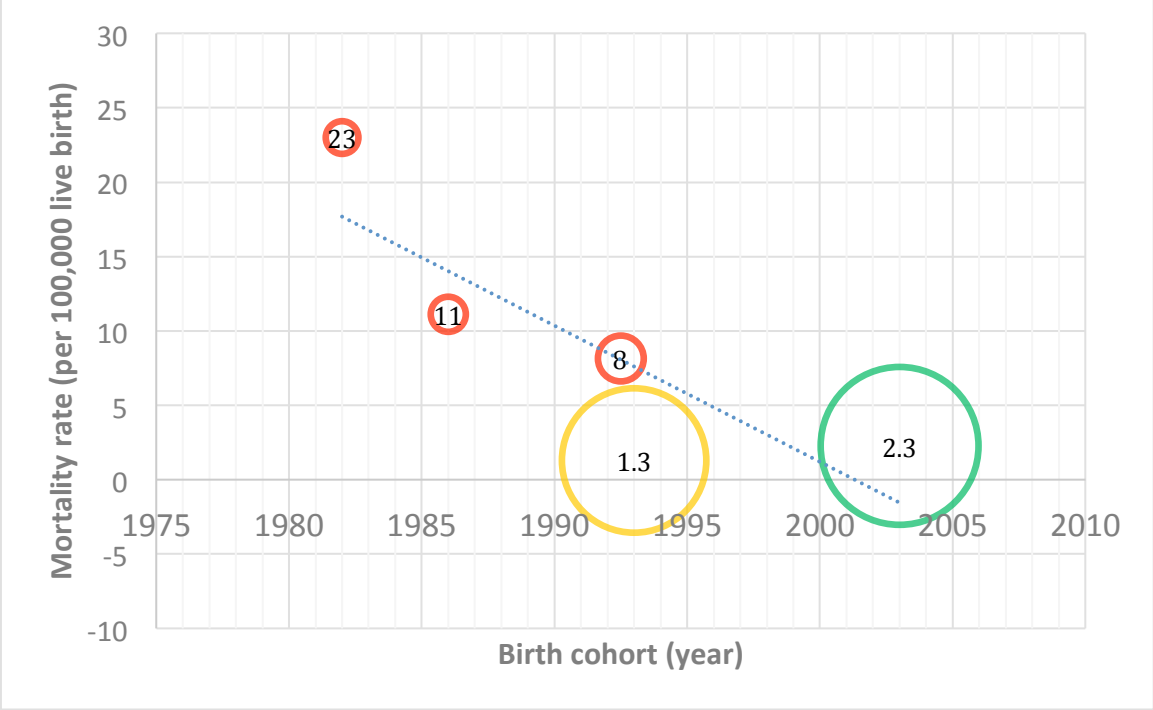


Figure 3.3: Infant mortality from spina bifida in the U.S. and Canada (Birth cohort: 1982-2003). (Wen 2000; Liu 2001; Davidoff 2002; Wang 2015).



Folic acid fortification: Pre- (red), during (orange), post- (green).

3.5.3 Case fatality estimates

Similarly, in Australia, the spina bifida neonatal case fatality decreased from the highest at 63.5% in 1973-1979 to 15.6% in 1986-1990 (pre-mandatory folic acid food fortification) (Kalucy et al. 1994) (Table 3.7 and Figure 3.4); and the spina bifida infant case fatality decreased from the highest at 68.3% in 1973-79 to 19.6% in 2004-09 (pre-mandatory folic acid food fortification) (Kalucy et al. 1994; Schneuer et al. 2019). In Canada, the infant case fatality decreased from 31.4% in 1967-1974 to 9.0% in 1975-1990 (pre- mandatory folic acid food fortification) (Laishram et al. 1993) (Table 3.7 and Figure 3.5).

There was considerable heterogeneity between studies for spina bifida neonatal case fatality (I^2 = 98.7%, $p < 0.001$), and infant case fatality (I^2 = 99.1%, $p < 0.001$) (Table 3.7). The fitted meta-regression shows a decrease over time in neonatal and infant case fatality (slope = 2.44% and 2.70% decrease in death rate per year respectively between 1969 and 2007, $p < 0.001$) (Figures 3.4 and 3.5).

Table 3.7: Neonatal and infant case fatality from spina bifida.

Studies (year of birth cohort)	Country of study (Year of introduction of mandatory folic acid fortification)	Mid-year of birth cohort	No. of liveborn spina bifida	No. of termination	Case Fatality as % of live births affected by spina bifida *(no. of deaths) [95% CI]*	
					Neonatal	Infant
Spina bifida						
Kalucy (1966-72)[1]	Australia (2009)	1969	95	0	16.8 (16) [9.3-24.4]	33.7 (32) [24.2-43.2]
Laishram (1967-74)[1]	Canada (1998)	1970/71	108	Unavailable	-	31.4 (34) [22.6-40.1]
Kalucy (1973-79)[1,2]	Australia (2009)	1976	126	0	63.5 (80) [55.1-71.9]	68.3 (86) [60.1-76.4]
Laishram (1975-90)[1]	Canada (1998)	1982/83	165	Unavailable	-	9.0 (15) [4.6-13.4]
Sutton (1976-87)	Republic of Ireland	1981/82	475	Unavailable	29.6 (141) [25.5-33.7]	54.9 (261) [50.5-59.4]
Wong (1979-94)	USA (1998)	1986/87	235	Unavailable	9.8 (23) [5.9-13.5]	12.8 (30) [8.4-16.9]
Kalucy (1980-85)[1]	Australia (2009)	1982/83	97	7	36.1 (35) [26.5-45.6]	51.5 (50) [41.6-61.5]
Riley (1983-95)	Australia (2009)	1989	526	179	26.6 (140) [22.8-30.4]	-
Waitzman (1983-86)	USA (1998)	1984/85	226	Unavailable	-	19.7 (44) [14.5-24.9]
Kalucy (1986-90)[1]	Australia (2009)	1988	77	17	15.6 (12) [7.5-23.7]	28.6 (22) [18.5-38.7]
Borgstedt-Bakke (1970-2015)	Denmark	1992/93	187	Unavailable	-	7.0 (13) [3.3-10.6]
Theodorou (1990-09)	Scotland, UK	1999/2000	43	Unavailable	14.0 (6) [3.6-24.3]	-
Wang (1999-07)	USA (1998)	2003	3,903	Unavailable	5.7 (222) [5.0-6.5]	8.1 (316) [7.3-9.1]
Schneuer (2004-09)	Australia (2009)	2006	56	Unavailable	19.6 (11) [9.2-30]	19.6 (11) [9.2-30.0]

Table 3.7 (continued): Neonatal and infant case fatality from spina bifida.

Studies (year of birth cohort)	Country of study (Year of introduction of mandatory folic acid fortification)	Mid-year of birth cohort	No. of liveborn spina bifida	No. of termination	Case Fatality as % of live births affected by spina bifida *(no. of deaths) [95% CI]*	
					Neonatal	Infant
Spina bifida (continued)						
Bakkar (2001-12)	ICBDSR registries:					
	Paris, France	2006	34	149	8.7 (3) [0.0-18.4]	-
	Soxony Anhalt, Germany	2006	41	78	0 (0) [0.0-0.0]	0 (0) [0.0-0.0]
	Lombardy, Italy	2007	25	38	0 (0) [0.0-0.0]	0 (0) [0.0-0.0]
	Tuscany, Italy	2006	22	82	4.5 (1) [0.0-13.2]	4.5 (1) [0.0-13.2]
	North, Netherlands	2006	55	41	38.2 (21) [25.3-51.0]	38.2 (21) [25.3-51.0]
	Sweden	2006	263	317	6.1 (16) [3.2-9.0]	7.6 (20) [4.4-10.8]
	Wales, UK	2006	78	216	9.0 (7) [2.6-15.3]	9.0 (7) [2.6-15.3]
McDonnell (2009-11)	Republic of Ireland	2010	89	9	5.6 (5) [0.8-10.4]	-
Heterogeneity I^2 and P value					**98.7%, p < 0.001**	**99.1%, p < 0.001**
Spina bifida with hydrocephalus						
Kalucy (1966-90)	Australia (2009)	1966	Unavailable	Unavailable	-	57.1 [50.8-63.3]
Persson (1989-98)	Western Sweden	1989	84	Unavailable	-	6.0 (5) [2.0-13.3]
Algert (2001-03)	Australia (2009)	2001	27	Unavailable	-	11.1 (3) [2.4-29.2]
Heterogeneity I^2 and P value						**92.7%, p < 0.001**

[1]Data from Kalucy 1966-72, 1973-79, 1980-95 and 1986-90 were extracted from Kalucy (1994). Data from Laishram 1967-74 and 1986-90 were from Laishram (1993).
[2]From 1972 to 1980, selection policy for surgical treatment resulted in a decrease in survival of liveborn infants with spina bifida (Kalucy et al. 1994).

Figure 3.4: Neonatal case fatality from spina bifida in Australia, the U.S., and various European countries (Birth cohort: 1969-2010). (Kalucy 1994; Sutton 2008; Riley 1998; Wong 2001; Theodorou 2013; Wang 2015; Schneuer 2019; Borgstedt-Bakke 2017; Bakkar 2019; McDonnell 2015).

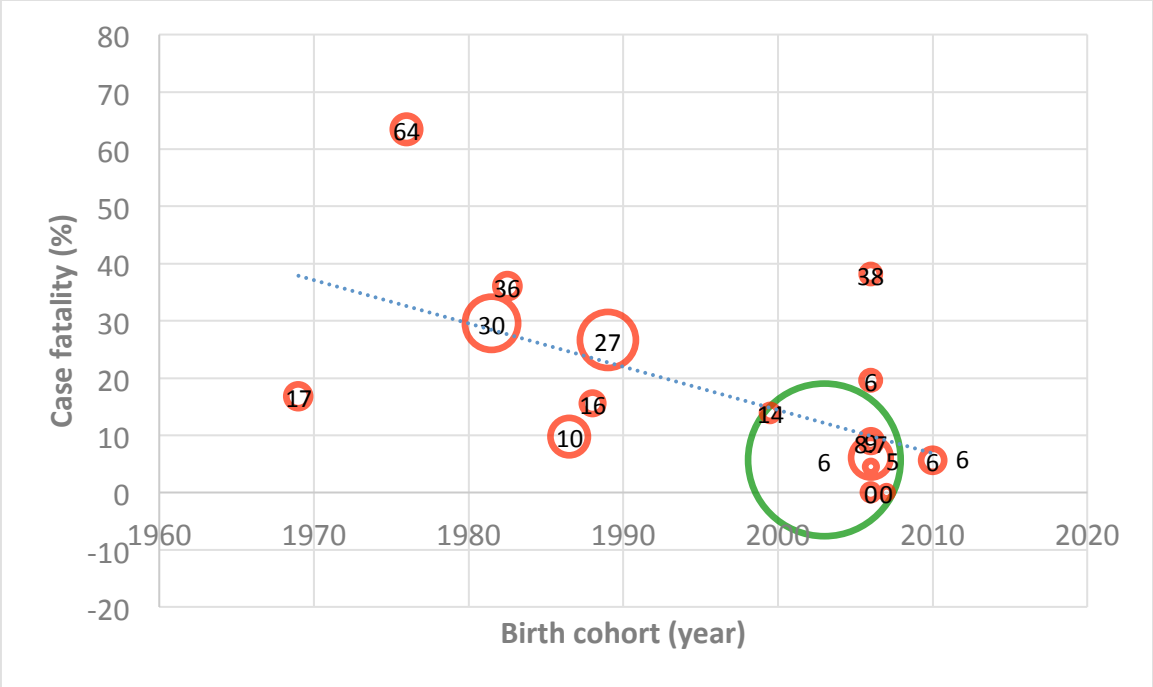
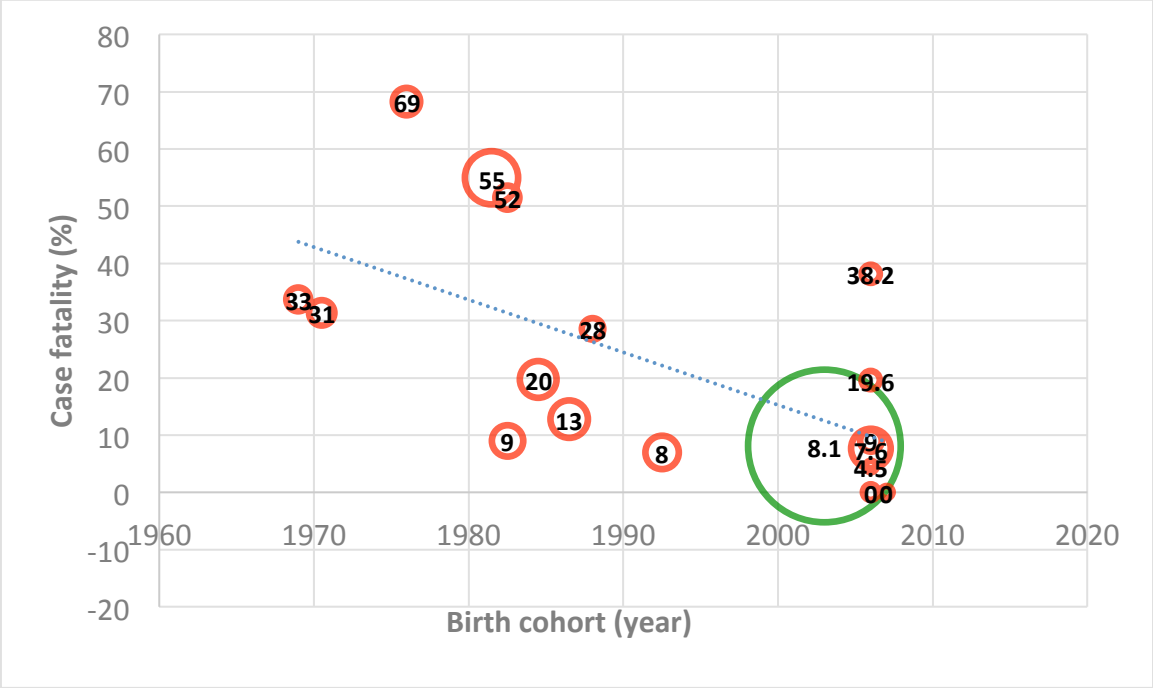


Figure 3.5: Infant case fatality from spina bifida in Australia, the U.S., and various European countries (Birth cohort: 1969-2003). (Kalucy 1994; Laishram 1993; Sutton 2008; Wong 2001; Waitzman 1994; Wang 2015; Schneuer 2019; Borgstedt-Bakke 2017; Bakkar 2019).



Folic acid fortification: Pre- (red), post- (green).

3.5.4 Risk factors for infant case fatality

Meta-analyses showed that the following factors were independently and significantly associated with an increased risk of death among infants with spina bifida: maternal black ethnicity (RR = 2.16, 95% CI: 1.82-2.57), preterm birth (i.e. <37 weeks of gestation) (RR = 4.45, 95% CI: 2.30-8.60), low birthweight (i.e. <2500g) (RR = 4.77, 95% CI: 2.67-8.55), cervico-thoracic lesion level (RR = 3.10, 95% CI: 2.76-3.47) (Wong et al. 2001; Shin et al. 2012), presence of hydrocephalus (RR = 1.67, 95% CI: 1.49-1.87) (Wong et al. 2001; Kalucy et al. 1994), and multiple defects (RR = 2.16, 95% CI: 1.66-2.81) (Wong et al. 2001; Bol et al. 2006) (Table 3.8, Figures 3.6 – 3.11). Heterogeneity of estimates was of substantial to considerable significance for gestational age, birthweight and multiple defects; and was not significant for lesion level, associated hydrocephalus and maternal ethnicity (Table 3.8).

In a multivariable analysis by Bol et al. (2006), mandatory folic acid food fortification was significantly associated with a reduced hazard ratio of spina bifida infant case fatality (adjusted HR = 0.68; 95% CI: 0.50-0.91).

Table 3.8: Risk factors for spina bifida infant case fatality (relative risks estimates).

Risk factors	Studies (Year of birth cohort)	No. of liveborn spina bifida	Unadjusted relative risk of case fatality (95% CI)
Maternal Black vs. White Ethnicity	Wong (1979-1994)	228	2.34 (1.67-3.01)
	Shin (1997-2003)	1,315	2.08 (1.65-2.52)
Pooled estimate (95% CI) by random effects analysis			2.16 (1.82-2.57)
Pooled estimate (95% CI) by fixed effects analysis			*2.16 (1.82-2.57)*
Heterogeneity I^2 and P value			*0.0%, p = 0.534*
Male vs. Female	Wong (1979-1994)	234	1.07 (0.39-1.75)
	Shin (1997-2003)	2,258	0.75 (0.44-1.05)
Pooled estimate (95% CI) by random effects analysis			0.81 (0.56-1.18)
Pooled estimate (95% CI) by fixed effects analysis			*0.81 (0.56-1.18)*
Heterogeneity I^2 and P value			*0.0%, p = 0.419*
Preterm vs. Term Gestation	Wong (1979-1994)	235	3.14 (2.39-3.90)
	Bol (1995-2001)	2,761	6.16 (5.91-6.41)
Pooled estimate (95% CI) by random effects analysis			4.45 (2.30-8.60)
Pooled estimate (95% CI) by fixed effects analysis			*6.05 (5.81-6.30)*
Heterogeneity I^2 and P value			*96.4%, p < 0.001*
Birthweight <2500g vs. ≥2500g	Wong (1979-1994)	235	3.52 (2.88-4.16)
	Shin (1997-2003)	2,255	6.38 (6.09-6.67)
Pooled estimate (95% CI) by random effects analysis			4.77 (2.67-8.55)
Pooled estimate (95% CI) by fixed effects analysis			*6.16 (5.89-6.44)*
Heterogeneity I^2 and P value			*97.4%, p < 0.001*
Cervico-thoracic vs. Lumbosacral level	Wong (1979-1994)	173	3.03 (2.11-3.95)
	Shin (1997-2003)	1,674	3.11 (2.73-3.49)
Pooled estimate (95% CI) by random effects analysis			3.10 (2.76-3.47)
Pooled estimate (95% CI) by fixed effects analysis			*3.10 (2.76-3.47)*
Heterogeneity I^2 and P value			*0.0%, p = 0.887*
Hydrocephalus: Present vs. absent	Kalucy (1966-1990)	-	1.68 (1.52-1.92)
	Wong (1979-1994)	219	1.10 (0.31-1.89)
Pooled estimate (95% CI) by random effects analysis			1.67 (1.49-1.87)
Pooled estimate (95% CI) by fixed effects analysis			*1.67 (1.49-1.87)*
Heterogeneity I^2 and P value			*0.0%, p = 0.364*
Multiple defects: Present vs. absent	Wong (1979-1994)	235	2.55 (1.86-3.24)
	Bol (1995-2001)	2,841	1.93 (1.67-2.20)
Pooled estimate (95% CI) by random effects analysis			2.16 (1.66-2.81)
Pooled estimate (95% CI) by fixed effects analysis			*2.04 (1.81-2.31)*
Heterogeneity I^2 and P value			*67.1%, p = 0.081*

Note: Pooled estimate Relative Risk (RR) was calculated by using random effects analysis. However if there were ≤3 studies, pooled estimate RR was also calculated using fixed effects analysis for comparison, with these results shown in *italics*.

Figures 3.6-3.11: Spina bifida infant case fatality risk factors.

Figure 3.6

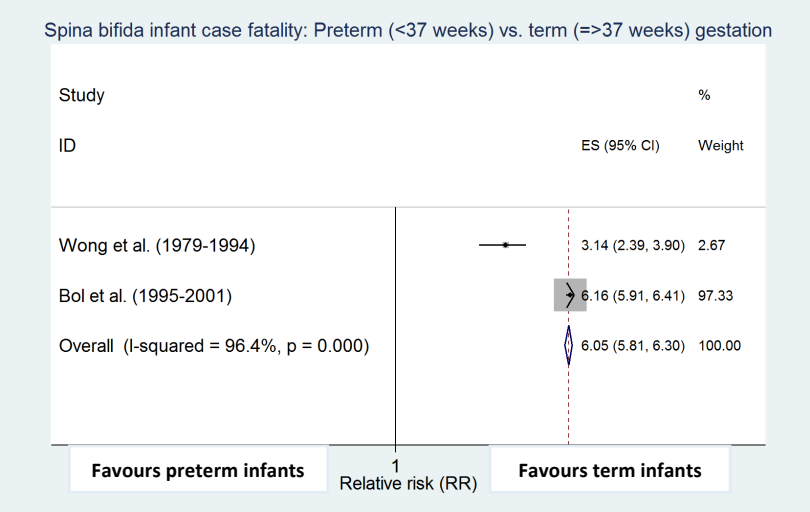


Figure 3.7

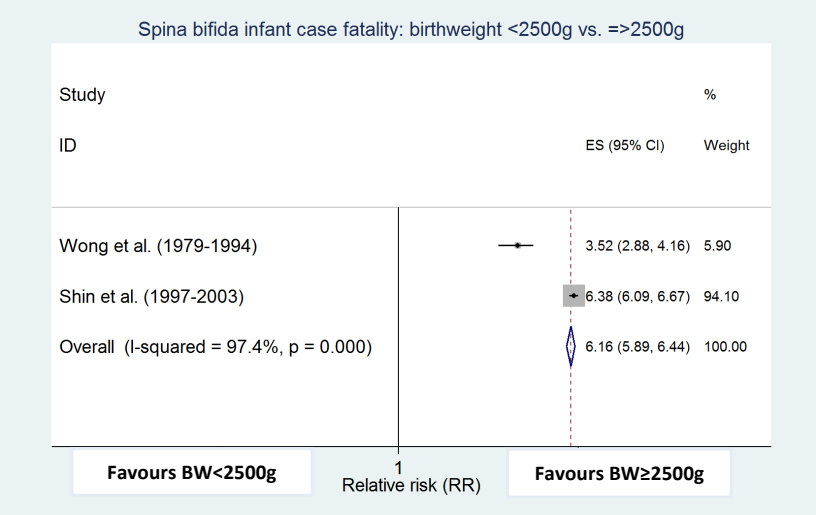


Figure 3.8

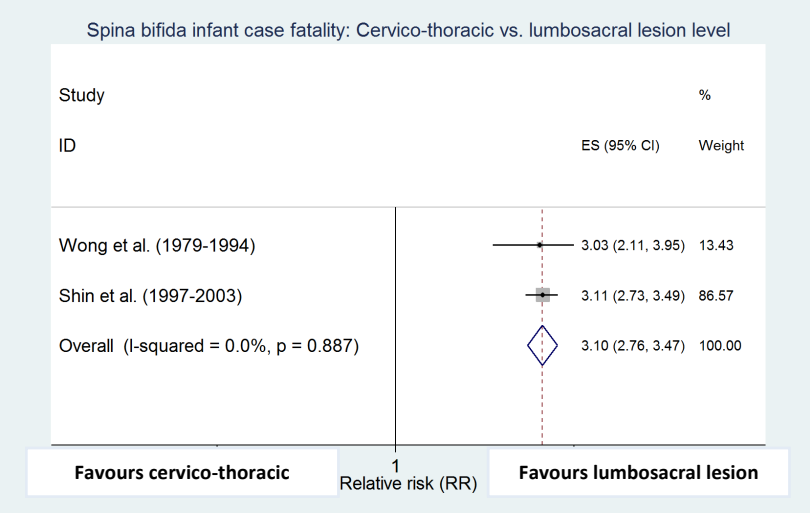


Figure 3.9

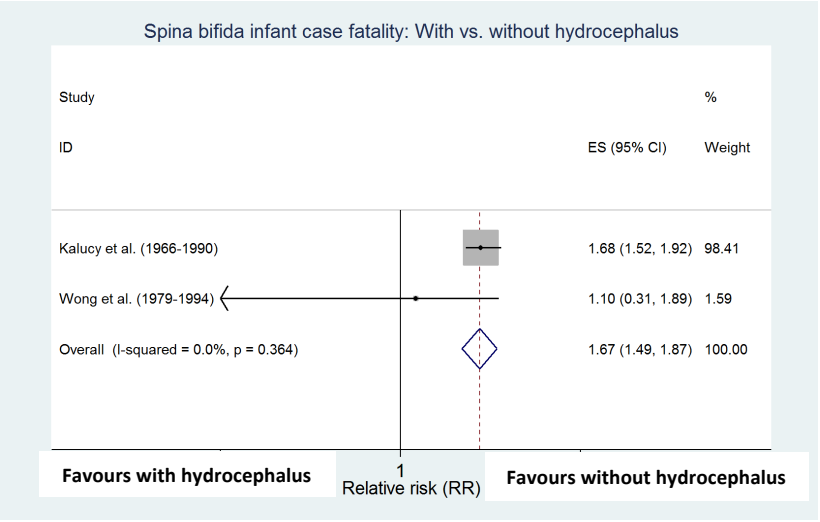


Figure 3.10

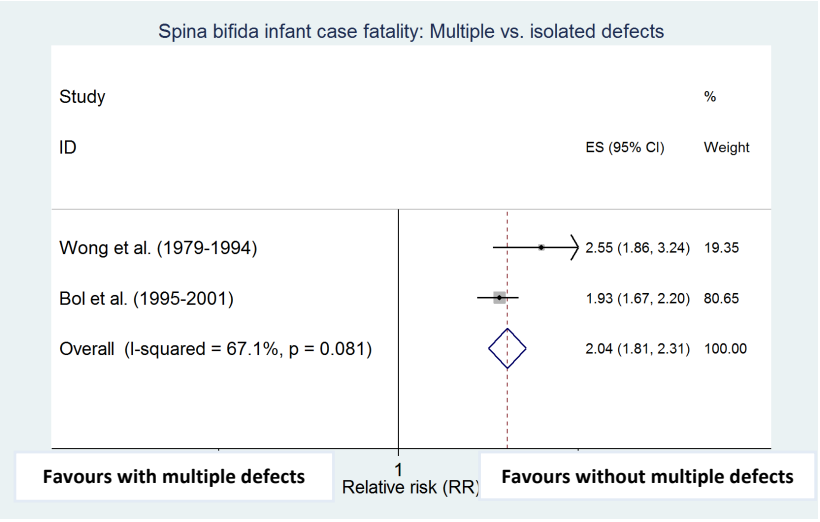
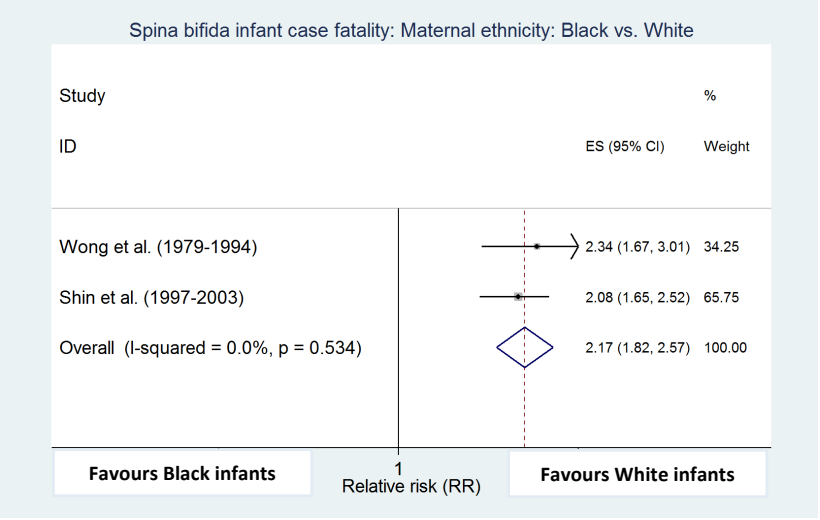


Figure 3.11



Single studies have shown that an increased risk of spina bifida infant case fatality was significantly associated with multiple pregnancy (RR = 2.57; 95% CI: 2.07-3.07) (Shin et al. 2012), single motherhood (RR = 1.31; 95% CI: 1.04-1.57) and inadequate prenatal care (RR = 1.74; 95% CI: 1.36-2.12) (Bol et al. 2006). Caesarean delivery significantly reduced the risk of spina bifida case fatality (RR = 0.50; 95% CI: 0.25-0.76) (Bol et al. 2006).

Infant sex, maternal age, maternal education, maternal smoking and previous livebirths were not significantly associated with mortality for infants born with spina bifida from results either in the meta-analysis or single studies (Bol et al. 2006; Shin et al. 2012; Benjamin et al. 2019) (Table 3.9).

Table 3.9: Other risk factors for spina bifida infant case fatality from single studies (relative risk estimates).

Risk factors	Studies (Year of birth cohort)	No. of liveborn spina bifida	Unadjusted relative risk of infant case fatality (95% CI)
Socio-demographical factors			
Maternal ethnicity: Hispanic vs. White	Shin (1997-2003)	1,986	1.33 (1.00-1.65)
Maternal age: ≥35 vs. <35 years	Shin (1997-2003)	2,258	1.05 (0.61-1.49)
Marital status: Single vs. married	Bol (1995-2001)	2,274	1.31 (1.04-1.57)
Maternal education: High school not completed vs. completed or beyond	Bol (1995-2001)	2,743	1.10 (0.83-1.36)
Prenatal care: Inadequate vs. adequate	Bol (1995-2001)	1,267	1.74 (1.36-2.12)
Maternal factors			
Smoking: Yes vs. No	Bol (1995-2001)	2,752	0.90 (0.53-1.27)
Previous live births: Yes vs. No	Bol (1995-2001)	2,769	1.17 (0.92-1.42)
Infant factors			
Male vs. Female	Bol (1995-2001)	2,701	0.93 (0.69-1.17)
Multiple vs. Singleton	Shin (1997-2003)	2,252	2.57 (2.07-3.07)
Interventional factors			
Mandatory folic acid food fortification vs. pre-fortification	Bol (1995-2001)	2,139	0.81 (0.54-1.09)
Caesarean vs. vaginal delivery	Bol (1995-2001)	2,655	0.50 (0.25-0.76)
Birth delivery in specialised centre with paediatric surgical units vs. others	Algert (2001-2003)	27	0.29 (0.00-2.56)

3.5.5 Quality appraisal

The findings of this systematic review were based on evidence from studies mainly with low to moderate RoB. Results of the quality appraisal of evidence are summarised in Table 3.10 and Figures 3.12-3.14. The majority of the included studies satisfied the study population, measurement of outcomes and study attrition domains with low to moderate RoB. Seventeen out of the 20 included studies were either national or register-based studies, which covered the national or multi-states population and were therefore representative. These studies used data sources from a national or states birth defects registry/ programme in which the methods of record linkage between anomaly cases and vital data by national/ states registry and vital statistics, and the ascertainment of mortality outcome were specified; for example, Liu et al. (2001), Wong et al. (2001), Wen et al. (2000), Borgstedt-Bakke et al. (2017), Wen et al. (1999) and Bol et al. (2006) reported that 92-100% of the anomaly cases were linked to vital statistics or other mortality databases. The exact proportion of the traced cases was not reported in 10 included studies (Kalucy et al. 1994; Waitzman et al. 1994; Persson et al. 2005; Davidoff et al. 2002; Shin et al. 2012; Bakkar et al. 2019; Algert et al. 2008; Wang et al. 2015; Schneuer et al. 2019; McDonnell et al. 2015), however, as these studies used record linkages of multiple data sources (e.g. data from birth defects registry linked to vital statistics or national mortality databases), anomaly cases were generally considered to have been systematically traced. In three studies where the cases were obtained from inpatient medical records, the reported proportion of traced cases varied, for example, Laishram et al. (1993) and Sutton et al. (2008) reported that between 92% and 100% of the anomaly cases were traced in their studies, while only 43% of cases were traced in the study by Theodorou et al. (2013).

For the exposure/ prognostic factors measurement domain, about half of the included studies had a low RoB, and the other half of the included studies had a moderate RoB. These were rated according to advancing medical and surgical treatment, and difference in availability of public health interventions over time and between countries. In addition, there were variations between

studies in reporting multiple defects which are a major prognostic factor. Thirteen out of 20 included studies reported that cases of spina bifida were associated with either multiple anomalies or a syndrome, in which these cases in five studies were either analysed separately or excluded from the analysis. However, the remaining included studies did not state whether cases of spina bifida as multiple anomalies or part of a syndrome were included or excluded in their studies.

For the statistical analysis and reporting domain, all the included studies reporting infant mortality rates and case fatality had a low to moderate RoB, and one study reporting risk factors for case fatality had a high RoB. These were due to a combination of concurrent cases, missing data, unreported 95% CI (Waitzman et al. 1994; Bol et al. 2006; Shin et al. 2012), and the potential for incomplete ascertainment of deaths particularly in early surveillance programmes (Bol et al. 2006; Wang et al. 2015; Riley et al. 1998; Persson et al. 2005). Consequently, infant mortality rates and case fatality could potentially be under- or over- estimated in these studies.

Table 3.10: Risk of bias (RoB) assessment summary table.

Included Studies	Risk of bias domains					Low to moderate risk of bias
	Study population	Measurement of outcome(s)	Study Attrition	Exposure/ Prognostic factor(s) measurement	Statistical analysis and reporting	
Neonatal and infant mortality rates						
Riley (1998)	☺	☺	☺	😐	☺	√
Wen (1999)	☺	☺	☺	😐	😐	√
Wen (2000)	☺	☺	☺	☺	☺	√
Liu (2001)	☺	☺	☺	☺	☺	√
Davidoff (2002)	☺	☺	☺	☺	☺	√
Persson (2005)	😐	☺	☺	😐	☺	√
Algert (2008)	😐	☺	☺	☺	☺	√
Theodorou (2013)	☺	☺	😐	😐	☺	√
Wang (2015)	☺	☺	☺	😐	😐	√
Neonatal and infant case fatality						
Laishram (1993)	☺	☺	☺	☺	☺	√
Kalucy (1994)	☺	😐	☺	☺	☺	√
Waitzman (1994)	☺	☺	☺	☺	😐	√
Riley (1983-95)	☺	☺	☺	😐	☺	√
Wong (2001)	☺	☺	☺	☺	☺	√
Persson (2005)	😐	☺	☺	😐	☺	√
Algert (2008)	😐	☺	☺	☺	☺	√
Sutton (2008)	☺	☺	☺	😐	☺	√
Theodorou (2013)	☺	☺	😐	😐	☺	√
McDonnell (2014)	☺	☺	☺	😐	☺	√
Wang (2015)	☺	☺	☺	😐	😐	√
Borgstedt-Bakke (2019)	☺	😐	☺	😐	☺	√
Schneuer (2019)	☺	☺	😐	☺	☺	√
Bakkar (2019)	☺	😐	☺	☺	☺	√
Risk factors for infant case fatality						
Kalucy (1994)	☺	☺	☺	☺	☹	
Wong (2001)	☺	😐	☺	☺	☺	√
Bol (2006)	☺	☺	☺	😐	😐	√
Algert (2008)	😐	☺	☺	☺	😐	√
Shin (2012)	☺	☺	☺	😐	😐	√
Wang (2015)	☺	☺	☺	☺	😐	√
☺ Low risk of bias		😐 Moderate risk of bias			☹ High risk of bias	

Figure 3.12: Risk of bias (RoB) graphfor the studies reporting spina bifida neonatal and infant mortality rates.

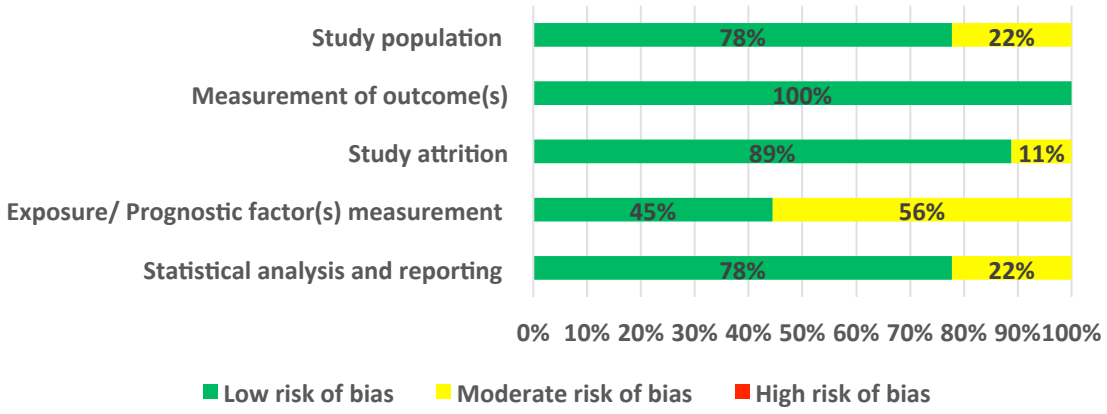


Figure 3.13: Risk of bias (RoB) graph for the studies reporting spina bifida neonatal and infant case fatality.

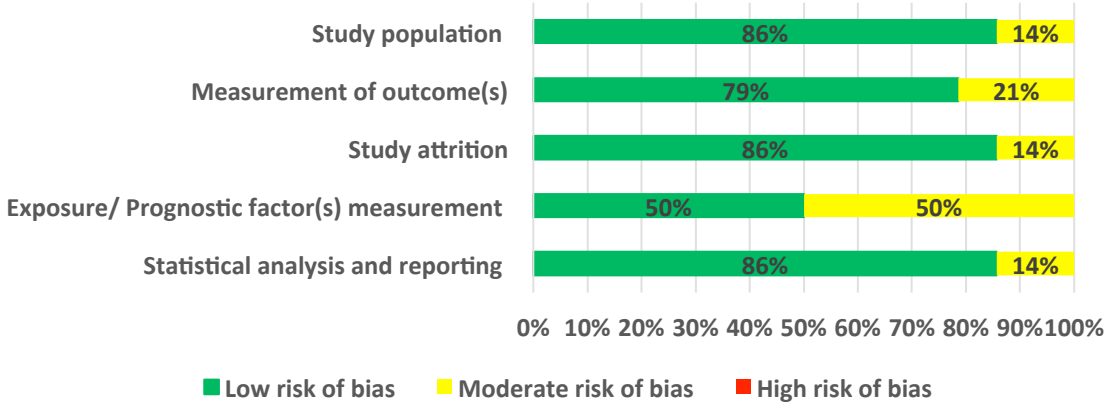
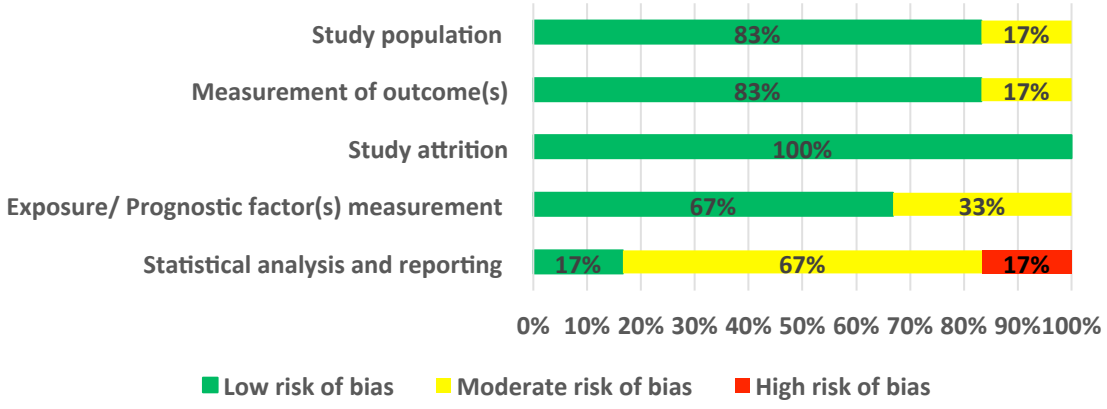


Figure 3.14: Risk of bias (RoB) graph for the studies reporting risk factors for spina bifida infant case fatality.



3.6 Discussion

3.6.1 Summary of findings

This systematic review included 20 population-based cohort studies with a total study population of more than 30 million liveborn infants, in which approximately 12,000 liveborn infants were affected by spina bifida; outcomes were reported based on generally high-quality evidence from studies mainly with a low to moderate risk of bias.

This review aimed to focus on contemporary findings and included studies identified between 1st January, 1990 and 31st August, 2020. This specified review period aimed to capture and investigate changes in the trends of spina bifida associated infant mortality and case fatality during the time that some important public health interventions and developments were implemented. The implementation of national folic acid food fortification began in the 1990's in some high-income countries such as the U.S. and Canada (Wald et al. 2018), important trials such as the MRC trial on folic acid for the prevention of NTDs was published in 1991 (MRC Vitamin Study Research Group 1991), significant advances were made in the prenatal screening of congenital anomalies in 1990's as well as changes in management in pregnancy (RCOG 2010).

This review spanned 49 years with births from 1966 to 2015. Variation in study periods between studies was perhaps the main source of heterogeneity for the mortality estimates. The effect of study period is likely to be largely due to changing and different public health interventions, clinical and interventional exposures to which the patient populations were subject to over time. For example, the implementation of folic acid food fortification occurred at different levels (i.e. none/voluntary/mandatory) and at different times for different countries (e.g. mandatory folic acid food fortification was implemented in 1998 in the U.S. and Canada, and was implemented in 2009 in Australia); while the health care systems and treatment options also varied significantly with time (e.g. as a result of advances in medical and surgical treatment) and between countries.

This review found that, overall, NMR and IMR due to spina bifida have significantly declined over time. In addition, the neonatal and infant case fatalities have significantly declined over time. Results from the meta-analysis has shown that maternal ethnicity, gestational age at birth, birthweight, lesion level, the presence of hydrocephalus and multiple defects were factors significantly associated with an increase or decrease in the risk of infant mortality due to spina bifida.

3.6.2 Spina bifida infant mortality and case fatality

Spina bifida infant mortality and case fatality encompasses both the chance of being born with spina bifida as well as dying from the condition during infancy, both of which have drastically decreased over time. This review estimated that, overall, the NMR due to spina bifida significantly declined by 7.14% per year (from 17.0 to 1.6 deaths per 10,000 livebirths) between 1989 and 2003; and IMR due to spina bifida significantly declined by 4.76% per year (from 23.0 to 2.3 deaths per 10,000 livebirths) between 1982 and 2003. In addition, overall, neonatal case fatality significantly declined by 2.44% per year (from 16.8% to 5.6%) between 1969 and 2010; and infant case fatality significantly declined by 2.70% per year (33.7% to 9.0%) between 1969 and 2006.

Several factors have likely contributed to these significant decreases in spina bifida infant mortality and case fatality.

First, folic acid food fortification plays an important role in reducing spina bifida infant mortality. Large population-based U.S. cohort studies in this review have consistently shown significant decreases over time in spina bifida infant mortality and case fatality since mandatory folic acid fortification of U.S. grain supply was implemented nationally in September 1998 (Davidoff et al. 2002; Wang et al. 2015; Liu et al. 2001; Wen et al. 2000; Wang et al. 2011). Previous systematic reviews (Blencowe et al. 2018; Castillo-Lancellotti et al. 2013) and long-term surveillance data have shown that the birth prevalence of NTDs significantly reduced in countries such as the U.S.,

Canada, Argentina, Chile, Costa Rica, Jordan and South Africa, when mandatory folic acid food fortification was successfully implemented (Atta et al. 2016; Christianson et al. 2006; Kancherla et al. 2018; Murphy et al. 2020; EUROCAT 2003; Crider et al. 2011). Thus, it is clear that folic acid food fortification reduces spina bifida infant mortality and case fatality by reducing the birth prevalence and/or severity of the condition.

Second, the studies by Kalucy et al. (1994), Riley et al. (1998), Wen et al. (1999) and Davidoff et al. (2002) have shown that spina bifida infant mortality and case fatality declined over time prior to national implementation of folic acid food fortification in Australia and the U.S.. These findings suggest that the decreases resulted from some other factors. Importantly, improved technology in and access to prenatal screening over time in high-income countries have led to early prenatal diagnosis, and consequently, significant decreases in both late fetal death and birth prevalence largely as a result of termination of many affected pregnancies (Kalucy et al. 1994; Riley et al. 1998). Indeed, a report from the Oxford Women's centre has shown that the birth prevalence of congenital anomalies in general reduced by 23% as a result of prenatal diagnosis and subsequent termination of pregnancies (Boyd et al. 1988). Similarly, the studies by Tennant et al. (2010), Liu et al. (2002) and Farrant et al. (2016) have shown an association between increased termination of pregnancy for fetal anomaly and consequent reductions in livebirth prevalence of congenital anomalies and infant mortality. Moreover, early prenatal diagnosis of spina bifida enables advanced planning of appropriate care and transfer for delivery in a specialised centre to optimise the chance of survival of affected liveborn babies (Riley et al. 1998).

Third, the declines in spina bifida associated infant mortality and case fatality over time can be further explained by advances in medical and surgical interventions (Laurence 1974). For example, improved ventilatory support in neonatal intensive care, multi-disciplinary team management approach and prophylactic antibiotics guidelines for infections of the central nervous system have been developed to provide better care and treatment for infants affected by spina bifida and associated co-morbidities such as prematurity and low birthweight which are significant

determinants for infant deaths (Bol et al. 2006; Shin et al. 2012; Charney et al. 1991). In addition, advances in surgical treatment for spina bifida and associated hydrocephalus and cardiac defects may also have improved the outcomes for the affected infants over time (Laishram et al. 1993; Mitchell et al. 2004; Grivell et al. 2014; Morris et al. 1991; Date et al. 1993; Adzick et al. 2011; Ames and Shut 1972; Adams et al. 1985). It is also important to note that the case fatality estimates reported by Kalucy et al. (1994) during the period 1973-1979 was extremely high, which was likely due to strict selection criteria for surgical treatment of infants with spina bifida during that period. Although there were no treatment data available from the included studies to objectively assess the effect of treatment on spina bifida associated infant mortality, data from other population-based studies have shown that spina bifida associated mortality is higher where resources and access to healthcare systems are more limited (Christianson et al. 2006; Zaganjor et al. 2016; Blencowe et al. 2015), suggesting an important role of advancing healthcare in reducing spina bifida mortality and case fatality.

3.6.3 Risk factors

This review has shown that maternal ethnicity, plurality, lesion level, multiple defects, folic acid food fortification and supplementation, gestational age at birth and birthweight were factors significantly associated with increasing or decreasing the risk of infant mortality due to spina bifida.

Maternal ethnicity

Infants with spina bifida born to mothers of Black ethnicity in the U.S. had a two-fold increased risk of death compared to infants with a spina bifida born to mothers of White/Others infants (Bol et al. 2006; Shin et al. 2012). Mortality among Black and Hispanic infants with spina bifida has declined with time but remained consistently higher when compared to White infants (Shin et al. 2012). There are several possible explanations for ethnic disparities in case fatality. First, social

barriers and inequality of access to healthcare: previous research has established that Black and minority ethnic groups are more likely to experience reduced access to healthcare resources and adverse birth outcomes (Weightman et al. 2012; Evandrou et al. 2016; Gray et al. 2009; Dominguez et al. 2008; Shin et al. 2012). Second, genetic and other environmental factors: previous studies have shown that Hispanic infants have 50% higher NTD-related infant mortality compared to non-Hispanic White infants (Davidoff et al. 2002). While this may be attributable to cultural and dietary preferences, and reduced access to health services and folic acid fortified food products (Canfield et al. 1996; Botto and Yang 2000), studies have shown that Hispanic populations have a high incidence of C677T methylenetetrahydrofolate reductase homozygous genotype mutations (Botto and Yang 2000; Chowdary et al. 2003) which are associated with a more severe type (i.e. cervio-thoracic level) of spina bifida (Volcik et al. 2000).

Plurality

The study by Bol et al. (2006) has shown that infants with a spina bifida being born as multiples had more than a two-fold increased risk of infant death compared to singleton infants with spina bifida. Previous studies have shown that multiple pregnancies are generally associated with a greater risk of adverse obstetric and neonatal outcomes such as preterm birth, twin-twin transfusion syndrome and intrauterine growth restriction (Kilby et al. 2006; Kilby et al. 2006a; Edwards et al. 1995).

Lesion level

This review has shown that a high (cervico-thoracic) lesion level was associated with more than a three-fold increase in case fatality compared with a low (lumbosacral) lesion level. Upper-level spina bifida is often associated with more severe anomalous brain development and system wide complications compared with lower-level spina bifida (Fletcher et al. 2005; Borgstedt-Bakke et al. 2017).

Associated or multiple defects

Infants with spina bifida and hydrocephalus had a 60% increased risk of infant case fatality compared with infants with spina bifida without a hydrocephalus. Infants with spina bifida as multiple anomalies had more than a two-fold increased risk in infant case fatality compared to infants with an isolated spina bifida. Multiple anomalies are an indicator of disease complications and severity, and hence tend to be associated with poorer prognosis when major systems are involved, compared to isolated anomalies (Wu et al. 2013; Bakker et al. 2019).

Mode of birth

Bol et al. (2006) have shown that infants with spina bifida born via caesarean delivery had a 50% reduced risk of infant death compared to birth by vaginal delivery. Previous studies have shown that caesarean birth can reduce complications during labour and birth in some specific clinical circumstances, for example breech pregnancies (Su et al. 2004) including babies with NTDs presenting by breech (Anteby and Yagel 2003), or when an aseptic environment is needed for immediate postnatal surgical repair (Chervenak et al. 1984). However, there is no conclusive evidence that caesarean birth improves outcomes for infants with spina bifida presenting vertex (Anteby and Yagel 2003; Bensen et al. 1988). However, the indication for caesarean birth may be an indicator of NTDs severity, as infants who are prenatally diagnosed with a more extensive defect would be more likely to be born by caesarean section.

Folic acid food fortification and supplementation

Infants with a spina bifida who were born during the period of mandatory fortification were significantly less likely to die in infancy, compared to infants with a spina bifida who were born with a spina bifida during pre-fortification period. For example, Bol et al. (2006) have shown that infants with spina bifida born during the period of mandatory fortification had a 34% (aHR = 0.66, 95% CI: 0.48-0.89) statistically significant decreased risk of infant mortality, compared to those

who were born during the period of prefortification. In the same study period 1995 to 2001, the estimated infant survival with spina bifida increased from 90.3% (prefortification) to 90.5% (optional fortification) and 92.1% (mandatory fortification); although it is important to note that the estimates may be confounded by variations in maternal consumption of the fortified food which was not measured and adjusted for in the study (Bol et al. 2006). It has been suggested that folic acid reduces the risk of severe types of spina bifida by moving the lesion caudally along the developing spine (Bol et al. 2006; Mitchell et al. 2004; Oakeshott et al. 2010; Bowman et al 2001); however, the effect of folic acid food fortification on infant mortality rate could not be fully assessed without the availability of TOP data. With regard to folic acid supplementation, Berry et al. (1999) have shown that preconceptional intake of folic acid supplementation (400 µg daily) significantly reduced the risk of the development of NTDs in fetuses and infants by 41% (95% CI: 3-64%) in a large population-based cohort study conducted in China. In addition, a randomised controlled trial by MRC Vitamin Study Research Group (1991) also showed that periconceptional intake of folic acid (4mg daily) significantly reduced the recurrence of NTDs by 72% (RR = 0.28, 95% CI: 0.12-0.71). Therefore, the findings of these studies have established the specific role of folic acid in reducing the frequency and severity of spina bifida, as well as contributing to the decrease in spina bifida related infant mortality and case fatality over time.

Preterm birth and birthweight

Finally, this review has shown that infants with a spina bifida who were born preterm (i.e. $<37^{+0}$ weeks' gestation) or with a low birthweight (<2500g) were associated with about four-fold increased odds of infant death, compared to infants with spina bifida who were born at term (i.e. $\geq 37^{+0}$ weeks' gestation) or with a birthweight ≥2500g. Preterm birth and low birthweight are considered as correlated outcomes along with other developmental problems resulting from the anomaly, as fetuses with an anomaly may have other developmental effects during gestation

which may lead to preterm birth (Behrman and Butler 2007; Institute of Medical Staff 1985). Preterm birth and congenital anomalies are likely to have a synergistic effect on infant mortality.

3.6.4 Strengths and limitations

This is the first systematic review conducted to investigate spina bifida-specific neonatal and infant mortality rates over time in high-income countries; and the first meta-analysis to investigate socio-demographic and clinical factors associated with mortality in the first year for infants affected by spina bifida. The main strengths of this systematic review include its comprehensive search strategy with no language restriction and complete coverage of population-based studies according to the robust inclusion criteria. All the extracted data were validated by two independent reviewers to ensure accuracy and minimise subjectivity. Unpublished relevant data were obtained from study authors and included in the analyses where possible. A further strength is the general high quality of the included studies with the majority of studies rated as having low to moderate risk of bias according to the refined QUIP and Cochrane RoB tool (Higgins et al. 2008; The Cochrane Library 2018).

There are several limitations. First, reported mortality in infants with spina bifida depends on various factors including health care systems, treatment, access to termination of pregnancy, women's intake of folic acid supplements, and registries' ability to track all the spina bifida cases and link them with death registers. As the availability and completeness of these data varied between the included studies, this review was not able to assess the extent to which these individual factors contributed to the changes in trends of infant mortality rates and case fatality during the study periods. Consequently, these are likely to be the main cause of high variability and heterogeneity in the mortality estimates. Second, wide confidence intervals of the effect sizes e.g. birth location (specialised centres with paediatric surgical units vs. others) are attributable to small sample sizes. Modest effect sizes or associations that are not statistically significant should therefore be interpreted with caution. Finally, syndromal spina bifida or multiple defects could

not be completely excluded or analysed separately in this review, as they could not be reliably identified in some of the included studies; hence their significance on the overall results could not be accurately determined.

3.7 Conclusions

This systematic review summarised the evidence about the contributions of spina bifida to infant mortality, and has shown that significant declines in spina bifida associated neonatal and infant mortality, and case fatality were consistently observed over time. However, NTDs continue to contribute the second highest number of anomaly-related infant deaths in Europe in the past decade.

Access to prenatal diagnosis, effective medical and surgical interventions, as well as mandatory folic acid food fortification can significantly reduce both the birth prevalence and infant case fatality of spina bifida. This has important implications for public health interventions aiming to reduce infant mortality due to spina bifida. This review has shown that preterm birth and low birthweight are the strongest risk factors associated with excess spina bifida infant mortality, which has significant implications for the care of these vulnerable babies.

Chapter 4: Infant Mortality Associated With Encephalocele: A Systematic Review

4.1 Background

Encephalocele (also known as cranium bifidum) is a major and serious type of NTDs, which results from failure of spontaneous closure of neural tube between 21 and 28 days post conception, leading to sac-like protrusions of the brain and the meninges through openings in the skull (Blencowe et al. 2010). The exact aetiology of encephalocele is unknown, but is most likely due to a combination of genetic, nutritional and environmental factors (Davidoff et al. 2002; Baird 1974).

Previous studies have shown that infant mortality rates (IMRs) associated with encephalocele have been changing over time (Liu et al. 2001; Siffel et al. 2003; Wang et al. 2015). These changes are attributed to various factors including effective public health interventions, advancing prenatal care, improvements in medical and surgical treatment, as well as the capacity of health care systems to track and link all cases with death registers (Rosano et al. 2000).

Encephalocele is associated with a high risk of death, about one third of the affected babies die in infancy in high-income countries (Kalucy et al 1994; Siffel et al. 2003; Wang et al. 2015). Previous studies have examined the impact of certain clinical factors on the risk of infant deaths from encephalocele (Mealey et al. 1970). For example, case series have shown that large meningoencephaloceles containing cerebral tissues were associated with a poor prognosis (Simpson et al. 1984), whereas multidisciplinary team approaches would optimise outcomes (Chervenak et al. 1984).

In order to examine the contemporary evidence of infant mortality associated with encephalocele, a systematic review was conducted.

4.2 Study objectives

The objectives of the review were to investigate and estimate:

4a) Encephalocele-specific neonatal and infant mortality rates over time;

4b) Encephalocele-specific neonatal and infant case fatality over time; and

4c) Socio-demographic and clinical factors associated with mortality in the first year for infants affected by encephalocele.

4.3 Methods

4.3.1 Search sources and strategy

Comprehensive literature searches of PubMed, Embase, Ovid, Web of Science, CINAHL, Scopus and the Cochrane Library were performed from 1st January, 1990 to 31st August, 2020 in order to review evidence in a relatively contemporary setting. The searches were constructed with the assistance of a specialist information librarian (NR).

The detailed search terms are shown in Chapter 3, Table 3.2 and Appendix 3.1.

The equivalent search strategy for this review is described in Chapter 3: Section 3.4.1 (Search sources and strategy).

The literature search of the systematic review was originally conducted from 1st January, 1990 to 13th February, 2017 the date when the search strategy was finalised. This search was later updated to 31st August, 2020 when the full draft of this thesis was being reviewed and finalised.

4.3.2 Inclusion criteria

Population-based studies were included if they (1) ascertained all individuals born with encephalocele in a predefined population; (2) provided the number of encephalocele associated neonatal/infant deaths occurring among all livebirths or all encephalocele cases in a given population, or risk factors associated with mortality in the first year for infants affected by encephalocele; and (3) were conducted in high-income countries as defined by the World Bank (The World Bank 2019).

4.3.3 Exclusion criteria

Studies were excluded if: (1) they were conducted solely in tertiary or referral centres (i.e. non-population based studies); (2) encephalocele-affected individuals were not followed up from birth; and (3) the encephalocele was related to a syndrome.

4.3.4 Data extraction

Data extraction followed the equivalent methods described in Chapter 3: Sections 3.4.4 (Data extraction).

4.3.5 Main outcomes and measures

The main outcomes were:

(1) Encephalocele neonatal/infant mortality rate, which was defined as:

$$\frac{\text{The number of neonates/infants with encephalocele who died}}{\text{The total number of all livebirths in a population in the relevant time period}}$$

Encephalocele neonatal/infant mortality rate was expressed as the number of neonates/infants died per 100, 000 live births.

(2) Encephalocele neonatal/infant case fatality, which was defined as:

$$\frac{\text{The number of neonates/infants with encephalocele who died}}{\text{The number of all neonates/infants born with encephalocele in the relevant population}}$$

Encephalocele neonatal/infant case fatality was expressed as the proportion (%) of livebirths affected by encephalocele.

(3) Risk factors for death in the first year after birth in infants affected by encephalocele.

4.3.6 Statistical analysis

Statistical analysis followed the equivalent methods described in Chapter 3: Sections 3.4.6 (Statistical analysis).

4.3.7 Quality appraisal

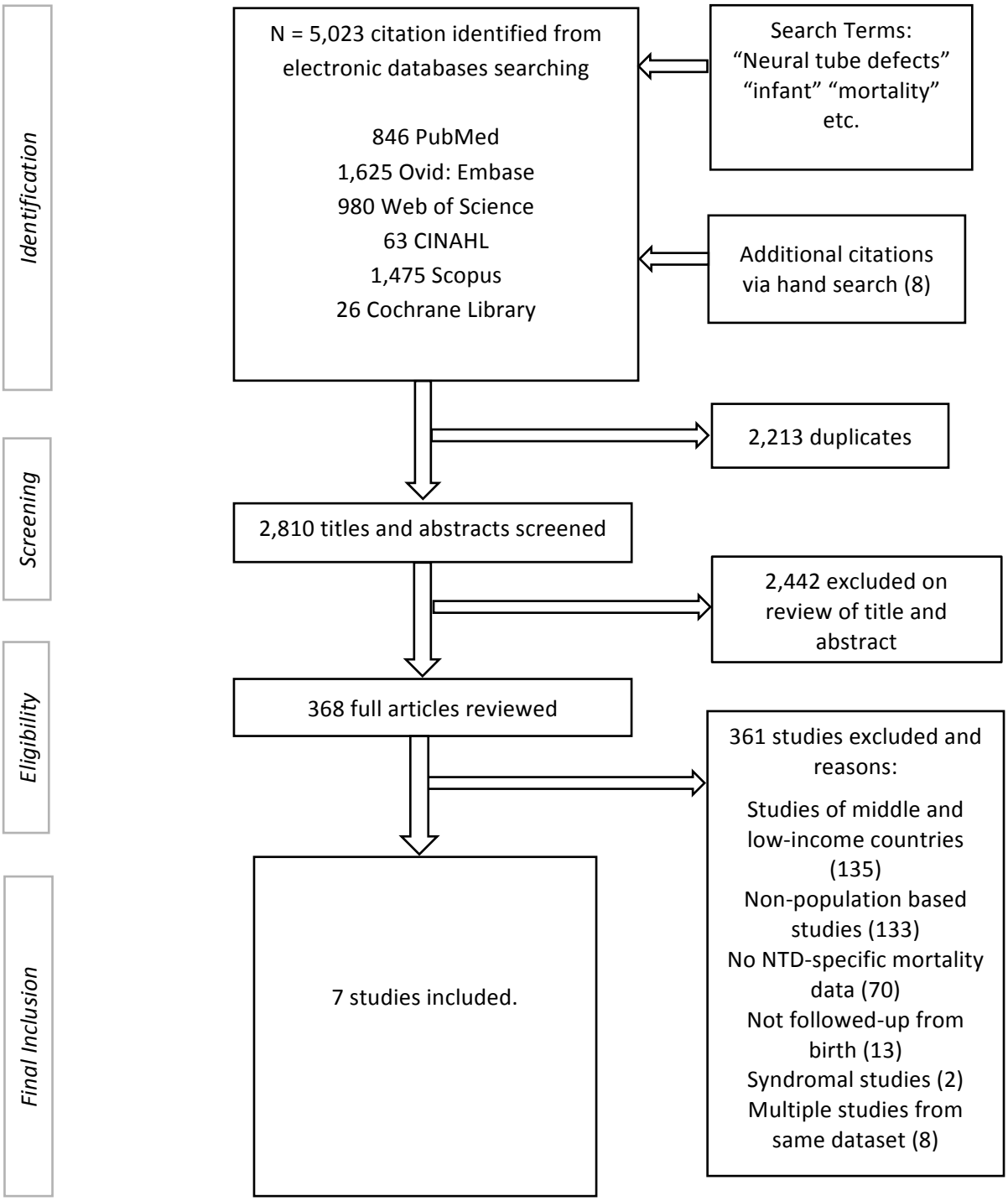
Quality appraisal followed the equivalent methods described in Chapter 3: Sections 3.4.7 (Quality appraisal).

The reporting of results followed the PRISMA flow diagram and MOOSE checklist (Appendix 4.1) (Moher et al. 2015; Stroup et al. 2000).

4.4 Results

Following screening of 5,023 articles identified in the literature search, 368 articles were examined in full text. Seven studies met all inclusion criteria and hence were included in this systematic review. The flow of literature in this review is summarised in the PRISMA diagram (Figure 4.1).

Figure 4.1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram for the flow of studies through the systematic review (1.1.1990 to 31.8.2020).



4.4.1 Study characteristics

Of the seven included population-based cohort studies, three studies were conducted in the U.S. before and after implementation of mandatory folic acid food fortification nationally in 1998 (Siffel et al. 2003; Bol et al. 2006; Wang et al. 2015); two studies were conducted in Australia prior to national mandatory folic acid food fortification in 2009 (Kalucy et al. 1994; Riley et al 1998); one study was conducted in Canada prior to national mandatory folic acid food fortification in 1998 (Liu et al. 2001); and one study was conducted in the UK where there has not been any policy of mandatory folic acid food fortification (Sutton et al. 2008) (Table 4.1). Together, these seven studies included a total study population of over 17 million liveborn infants (median sample size: 701,458, range: 395,000 – 14 million), in which approximately 1,900 liveborn infants (median: 101, range: 50 - 909) were affected by encephalocele. All infants included were born at ≥ 20 weeks' gestational age with a birthweight ≥ 500g.

Associated conditions

Bol et al. (2006) and Sutton et al. (2008) reported 41 (6%) and 8 (13%) infants of encephalocele respectively had an additional spina bifida or lesion. Siffel et al. (2003) reported a total of 17 (20.5%) infants born with encephalocele had at least one major structural defect. Kalucy et al. (1994) and Wang et al. (2015) reported infants with encephalocele as part of multiple anomalies or a chromosomal defect were included, however no further details were reported. Whether there were any syndromal encephaloceles in other included studies was uncertain as this could not be verified with the authors.

Table 4.1: Description of the included studies. *(Note: the included studies are ordered by birth year)*

Author, Included birth years	Study location and no. of liveborn encephalocele	Included NTD subtypes (ICD codes)	Source of cases	Source of death information	Percentage of traced cases	Inclusion of multiple defects	Main limitations
Kalucy (1994) 1966-1990	Western Australia n = 50	Encephalocele (Coding not specified)	Birth defects registry, inpatient records.	Death certificates, post mortem reports, matched with infants' demographics.	Not stated.	Yes; multiple and chromosomal defects were included but no further details.	1. Variations of cases ascertainment over years. 2. Mortality status was only known for a proportion of cases.
Sutton (2008) 1976-1987	Dublin, Ireland n = 64	Encephalocele (Coding not specified)	Four Dublin maternity units medical records.	Medical record and/or parental interview.	92%	Yes; 8 (13%) cases had an additional spinal lesion.	Diagnostic coding for disease classification not described.
Siffel (2003) 1979-1998	USA n = 83	Encephalocele (ICD-9-CM: 742.0)	Metropolitan Atlanta Congenital Defects Programme.	National Death Index and death certificates, and record linkage to anomaly cases.	Not stated.	Yes; 17 (20.5%) of total cases had multiple defects.	Limited in study sample sizes and power decreased the precision on survival estimates.
Riley (1998) 1983-1995	Victoria, Australia n = 120	Encephalocele (BPA[3] ICD-9 supplement)	Victorian Birth Defects/ Congenital Malfor-mations Register.	Death certificates, autopsy reports, maternal/child health nurse notifications, and record linkage to inpatient and outpatient listings.	Up to 86%.	Not stated.	Voluntary notification to congenital malformations register, completeness depended on type of malformation.

Table 4.1 (continued): Description of the included studies. *(Note: the included studies are ordered by birth year)*

Author, Included birth years	Study location and no. of liveborn encephalocele	Included NTD subtypes (ICD codes)	Source of cases	Source of death information	Percentage of traced cases	Inclusion of multiple defects	Main limitations
Liu (2001) 1985-1996	Canada n = Unspecified	Encephalocele (ICD-9: 742.0)	Canadian stillbirth and infant death registration, and perinatal surveillance system.	Statistics Canada's Mortality Database.	98%	Not stated.	1. Death certificates recorded a single underlying cause of death. 2. Potential errors of assigning and coding the cause of death from death certificates (e.g. minor anomalies being coded as an underlying cause of death).
Bol (2006) 1995-2001	USA n = 638	Encephalocele (ICD-9-CM: 742.0)	Birth defects monitoring programmes from 16 states[1].	Death certificates and record linkage with anomaly cases.	95% - 100%	Mixed. 41 (6%) cases had concurrent spina bifida and encephalocele were included in both cohorts.	1. Unequal time study periods with different birth defects monitoring programmes in different states. 2. Some participating programmes were unable to submit cases for all birth years. 3. No differentiation between syndromic and non-syndromic NTDs. Accuracy of diagnosis was not verified in Colorado. 4. Unequal access to treatment between participating states.

Table 4.1 (continued): Description of the included studies. *(Note: the included studies are ordered by birth year)*

Author, Included birth years	Study location and no. of liveborn encephalocele	Included NTD subtypes (ICD codes)	Source of cases	Source of death information	Percentage of traced cases	Inclusion of multiple defects	Main limitations
Wang (2015) 1999-2007	USA n = 909	Encephalocele (ICD-9-CM/ CDC[4]/BPA[3])	Birth defects surveillance programmes from 12 states[2].	Death certificates and National Death Index. Anomaly cases were linked to vital records.	Not stated.	Yes; but no further details reported.	1. Total number of livebirths was approximate. 2. Potentially incomplete ascertainment of deaths from missed matches of study cohort to death certificates. 3. Passive cases ascertainment.

[1]Bol (2006): 16 sates/ regions included Alabama, California, Colorado, Hawaii, Illinois, Iowa, Kentucky, metropolitan Atlanta, Michigan, New York, North Carolina, Oklahoma, Rhode Island, South Carolina, Texas, and West Virginia. [2]Wang (2015): 12 states included Arizona, Colorado, Florida, Georgia (5 counties of metropolitan Atlanta), Illinois, Massachusetts, Michigan, Nebraska, New Jersey, New York (excluded New York City), North Carolina, and Texas. [3]BPA = British Paediatric Association Classification of Diseases codes. [4]CDC = Centers for Disease Control and Prevention.

4.4.2 Mortality estimates

Neonatal and infant mortality rates, and case fatality from encephalocele have decreased over time. For example, in the U.S., encephalocele neonatal mortality rate (NMR) halved from 2.9 per 100, 000 livebirths in 1979-1998 (pre-mandatory folic acid food fortification) to 1.4 per 100, 000 livebirths in 1999-2007 (post- mandatory folic acid food fortification) (Siffel et al. 2003; Wang et al. 2015) (Table 4.2 and Figure 4.2). In Canada, the encephalocele infant mortality rate (IMR) reduced from 2.6 per 100, 000 livebirths in 1985-1987 to 1.7 per 100, 000 livebirths in 1994-1996 (pre-mandatory folic acid food fortification) (Liu et al. 2001) (Table 4.2 and Figure 4.3).

Considerable heterogeneity was evident between studies of encephalocele NMR (I^2 = 91.5%, $p < 0.001$) and IMR (I^2 = 64.0%, $p = 0.039$) (Table 4.2). The fitted meta-regression shows a statistically significant 6.90% and 5.88% decrease in death rate per year for encephalocele NMR and IMR respectively between 1986 and 2003 ($p < 0.001$) (Figures 4.2 and 4.3).

Table 4.2: Neonatal and infant mortality rates from encephalocele.

Studies (years of birth cohort)	Country of study (Year of introduction of mandatory folic acid fortification)	Mid-year of birth cohort	Population size (no. of total livebirths)	Neonatal and infant mortality rate per 100,000 live births *(no. of death) [95% CI]*	
				Neonate	Infant
Encephalocele					
Liu (1985-87)	Canada (1998)	1986	692,556		2.6 *(18) [1.5-4.1]*
Siffel (1979-98)	USA (1998)	1988/89	701,458	2.9 *(20) [1.6-4.1]*	3.3 *(23) [2.1-4.9]*
Riley (1983-95)	Victoria, Australia (2009)	1989	825,051	3.5 *(29) [2.4-5.1]*	
Liu (1994-96)	Canada (1998)	1995	699,571		1.7 *(11) [0.8-2.8]*
Wang (1999-07)	USA (1998)	2003	14,000,000	1.4 *(202) [1.3-1.7]*	1.8 *(254) [1.6-2.1]*
Heterogeneity I^2 and P value				**91.5%, p < 0.001**	**64.0%, p = 0.039**

Figure 4.2: Neonatal mortality from encephalocele in Australia and the U.S. (Birth cohort: 1987-2003). (Riley 1998; Siffel 2003; Wang 2015)

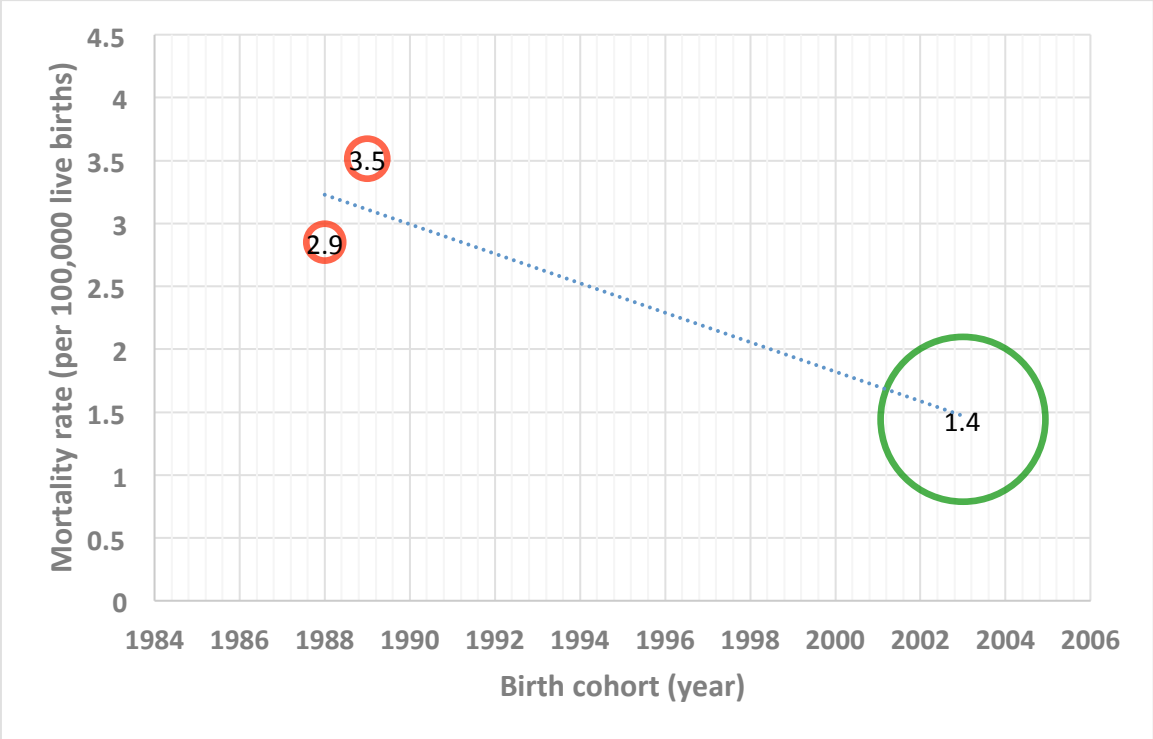
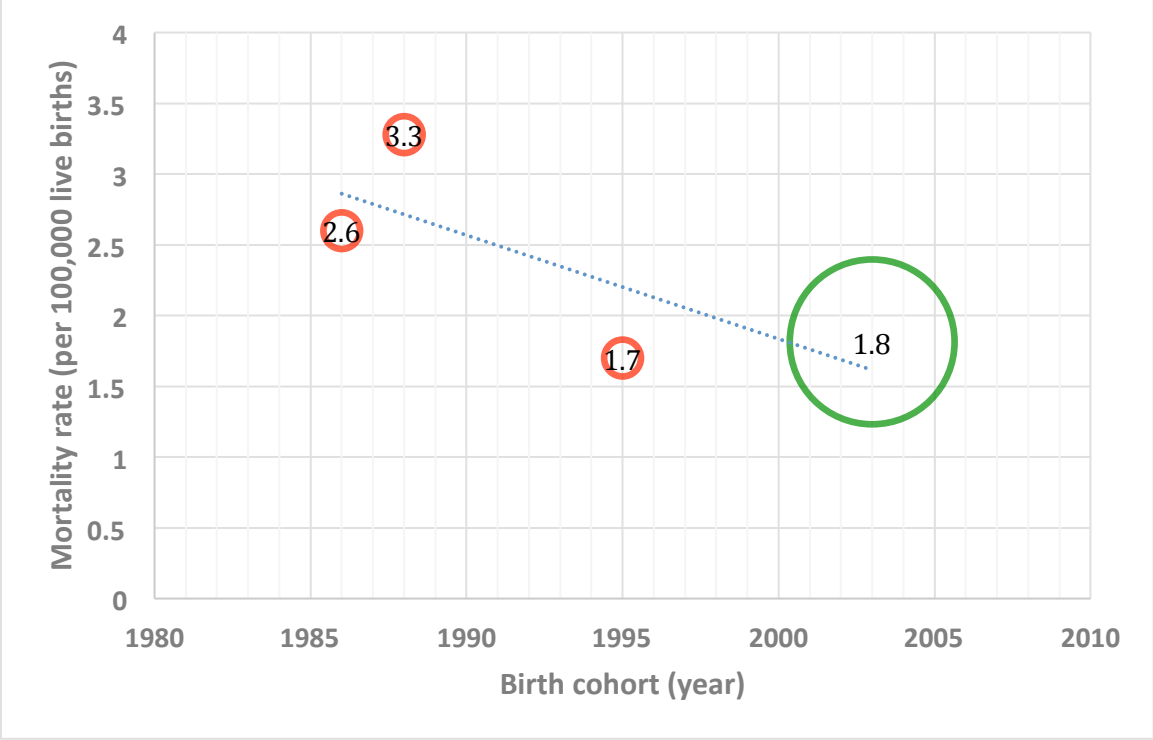


Figure 4.3: Infant mortality from encephalocele in the U.S. and Canada (Birth cohort: 1986-2003). (Liu 2001; Siffel 2003; Wang 2015)



Folic acid fortification: Pre- (red), post- (green).

4.4.3 Case fatality estimates

In Australia, encephalocele neonatal case fatality decreased from 34.0% in 1966-1990 to 24.2% in the 1983-1995 (pre- mandatory folic acid food fortification) (Kalucy et al. 1994; Riley et al. 1998) (Table 4.3 and Figure 4.4).

Considerable heterogeneity was evident between studies of encephalocele neonatal case fatality (I^2 = 93.8%, p < 0.001) and infant case fatality (I^2 = 95.9%, p < 0.001) (Table 4.3). The fitted meta-regression shows a statistically significant 4.00% decrease in both neonatal and infant case fatality per year between 1978 and 2003 (p < 0.001) (Figures 4.4 and 4.5).

Table 4.3: Neonatal and infant case fatality from encephalocele.

Studies (year of birth cohort)	Country of study (Year of introduction of mandatory folic acid fortification)	Mid year of birth cohort	No. of liveborn encephalocele	No. of termination	Case Fatality as % of live birth *(no. of deaths) [95% CI]*	
					Neonate	Infant
Encephalocele						
Kalucy (1966-90)[1]	Australia (2009)	1978	50	6	34.0 *(17) [20.9-47.1]*	40.0 *(20) [26.4-53.5]*
Sutton (1976-87)[2]	Ireland, UK	1981/82	64	Unavailable	58.7 *(37) [46.6-70.8]*	67.1 *(43) [55.6-78.6]*
Siffel (1979-98)	USA (1998)	1988/89	83	6	24.1 *(20) [14.9-33.3]*	27.7 *(23) [18.1-37.3]*
Riley (1983-95)	Australia (2009)	1989	120	35	24.2 *(29) [16.5-31.8]*	
Wang (1999-07)	USA (1998)	2003	909	Unavailable	22.3 *(202) [19.8-25.2]*	27.9 *(253) [25.1-31.0]*
Heterogeneity I^2 and P value					**93.8%, p < 0.001**	**95.9%, p < 0.001**

[1]Data from Kalucy 1966-72, 1973-79, 1980-95 and 1986-90 were extracted from Kalucy (1994). [2]Sutton (1976-87): eight out of 63 (13%) cases of encephalocele had an additional spinal lesion and hence the study was excluded in the meta-regression.

Figure 4.4: Neonatal case fatality from encephalocele in Australia, the UK and the U.S. (Birth cohort: 1978-2003). (Kalucy 1994; Riley 1998; Siffel 2003; Sutton 2008; Wang 2015)

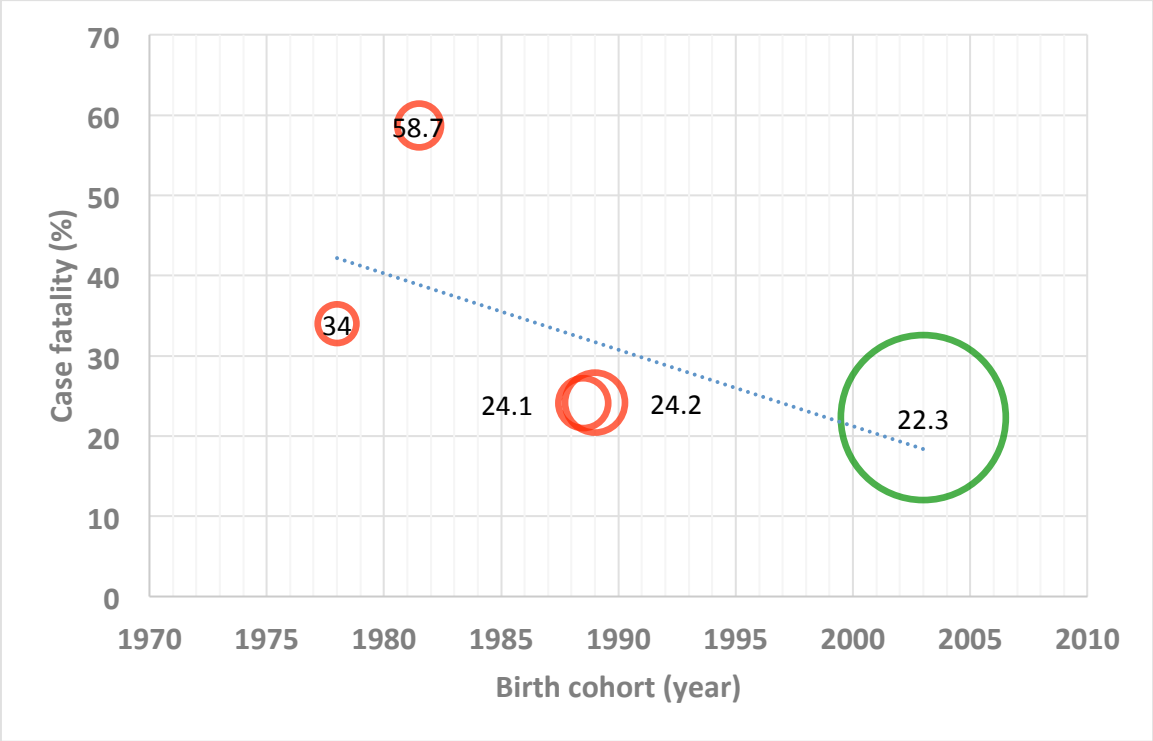
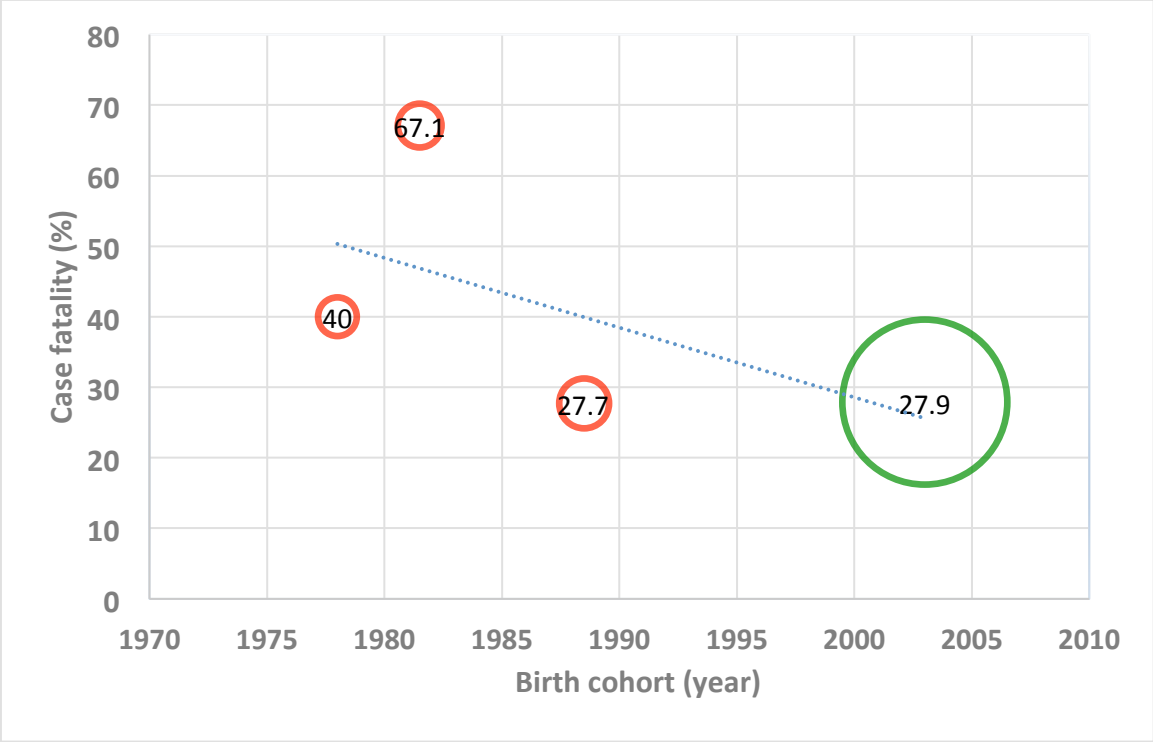


Figure 4.5: Infant case fatality from encephalocele in Australia, the UK and the U.S. (Birth cohort: 1978-2003). (Kalucy 1994; Siffel 2003; Sutton 2008; Wang 2015)



Folic acid fortification: Pre- (red), post- (green).

4.4.4 Risk factors for infant case fatality

As there was a limited number of studies which have examined potential risk factors for encephalocele infant case fatality, it was not possible to conduct a meta-analysis. However, reviews of single studies have found that maternal Black and Hispanic ethnicity, single motherhood, inadequate prenatal care, preterm birth, low birthweight, the presence of multiple defects and a posterior encephalic lesion were significantly associated with an increased risk of infant death due to encephalocele, compared with their respective reference categories (Siffel et al. 2003; Bol et al. 2006) (Table 4.4).

Maternal age, maternal education, maternal smoking, previous livebirths, infant sex, induction of labour and mode of birth have not shown to be significantly associated with infant deaths due to encephalocele (Bol et al. 2006) (Table 4.4).

Table 4.4: Risk factors for encephalocele infant case fatality in single studies (relative risks estimates).

Risk factors	Studies (Year of birth cohort)	No. of liveborn encephalocele	Unadjusted relative risk for infant death (95% CI)
Socio-demographical factors			
Maternal ethnicity: Black vs. White (excluding Hispanic)	Bol (1995-2001)	447	1.12 (0.71-1.53)
Maternal ethnicity: Hispanic vs. White	Bol (1995-2001)	455	1.65 (1.30-1.99)
Maternal ethnicity: Black vs. Other	Siffel (1979-1998)	83	2.39 (1.63-3.15)
Maternal age: ≥35 vs. <35 years	Bol (1995-2001)	636	0.89 (0.44-1.34)
Marital status: Single vs. married	Bol (1995-2001)	456	1.38 (1.04-1.71)
Maternal education: High school not completed vs. completed or beyond	Bol (1995-2001)	602	1.10 (0.77-1.42)
Prenatal care: Inadequate vs. adequate	Bol (1995-2001)	279	1.58 (1.09-2.07)
Maternal factors			
Smoking: Yes vs. no	Bol (1995-2001)	607	0.69 (0.22-1.15)
Previous live births: Yes vs. no	Bol (1995-2001)	628	0.97 (0.67-1.27)
Infant factors			
Preterm (<37 weeks) vs. Term (≥37 weeks) birth	Bol (1995-2001)	177	1.63 (3.32-3.94)
Birthweight: <2500g vs. ≥2500g	Bol (1995-2001)	608	3.46 (3.15-3.76)
Male vs. female	Bol (1995-2001)	605	1.08 (0.77-1.39)
Presence of multiple defects: Yes vs. No	Bol (1995-2001)	638	1.86 (1.55-2.17)
Posterior vs. anterior encephalocele	Siffel (1979-1998)	70	2.40 (1.00-3.80)
Interventional factors			
Mandatory folic acid food fortification vs. pre-fortification	Bol (1995-2001)	487	0.86 (0.53-1.19)
Induction of labour: Yes vs. No	Bol (1995-2001)	627	1.20 (0.80-1.61)
Caesarean vs. vaginal birth	Bol (1995-2001)	605	0.89 (0.59-1.20)

4.4.5 Quality appraisal

The majority of the included studies had a low RoB for study population, measurement of outcomes and study attrition domains (Tables 4.5, Figures 4.6-4.8). Six out of the seven included studies were either national or register-based studies which covered the national or states population; these studies used data sources from the national or states birth defects registry/ programme in which the methods of record linkage between anomaly cases and vital data by national/ states registry and vital statistics, and the ascertainment of mortality outcome were specified (Kalucy et al. 1994; Siffel et al. 2003; Riley et al. 1998; Bol et al. 2006; Wang et al. 2015; Liu et al. 2001). For example, Bol et al. (2006) and Liu et al. (2001) reported that 95-100% of the anomaly cases were linked to vital statistics. The exact proportion of the traced cases was not reported in three included studies (Kalucy et al. 1994; Siffel et al. 2008; Wang et al. 2015), however, as these studies used record linkages of multiple data sources, cases were generally considered to be systematically traced. In the study of Sutton et al. (2008) where cases were identified from medical records, the reported proportion of traced cases was also high (92%).

For the exposure/ prognostic factors measurement domain, the majority of the included studies had a moderate RoB, and one study had a high RoB; these were rated according to the changes in the available treatment and public health interventions over time and differences between countries. In addition, some studies were better than the others at reporting multiple and chromosomal defects which are a major prognostic factor. For example, Bol et al. (2006) and Siffel et al. (2003) reported and included 6-20.5% of the encephalocele cases with an additional spina lesion or as part of a multiple defects in the risk factor analysis for mortality; Kalucy et al. (1994) and Wang et al. (2015) reported infants with encephalocele as part of multiple or chromosomal defects were included in their studies, however no further details were available; whereas Riley et al. (1998) and Liu et al. (2001) did not state whether multiple and syndromal defects were included or excluded in their studies.

For the statistical analysis and reporting domain, some included studies had a moderate RoB due to a combination of concurrent cases (Siffel et al. 2003; Wang et al. 2015; Bol et al. 2006), missing information in data collection and failure to estimate or report 95% CI (Wang et al. 2015; Bol et al. 2006; Riley et al. 1998; Liu et al. 2001), and the potential for incomplete ascertainment of deaths especially in early surveillance programmes (Kalucy et al. 1994; Wang et al. 2015; Bol et al. 2006). IMR and case fatality could have been under- or over- estimated in these studies.

Table 4.5: Risk of bias (RoB) assessment summary table.

Included Studies	Risk of bias domains					Low to moderate risk of bias
	Study population	Measurement of outcome(s)	Study Attrition	Exposure/ Prognostic factor(s) measurement	Statistical analysis and reporting	
Neonatal and infant mortality rates						
Riley (1998)	☺	☺	☺	😐	☺	√
Liu (2001)	☺	☺	☺	☺	☺	√
Siffel (2003)	☺	☺	☺	😐	☺	√
Wang (2015)	☺	☺	☺	😐	😐	√
Neonatal and infant case fatality						
Kalucy (1994)	☺	😐	☺	☺	☺	√
Sutton (2008)	☺	☺	☺	☹	☺	
Riley (1983-95)	☺	☺	☺	😐	☺	√
Siffel (2003)	☺	☺	☺	😐	☺	√
Wang (2015)	☺	☺	☺	😐	😐	√
Risk factors for infant case fatality						
Bol (2006)	☺	☺	☺	😐	😐	√
Siffel (2003)	☺	☺	☺	😐	☺	√
☺ Low risk of bias	😐 Moderate risk of bias			☹ High risk of bias		

Figure 4.6: Risk of bias (RoB) graph for the studies reporting encephalocele neonatal and infant mortality rates.

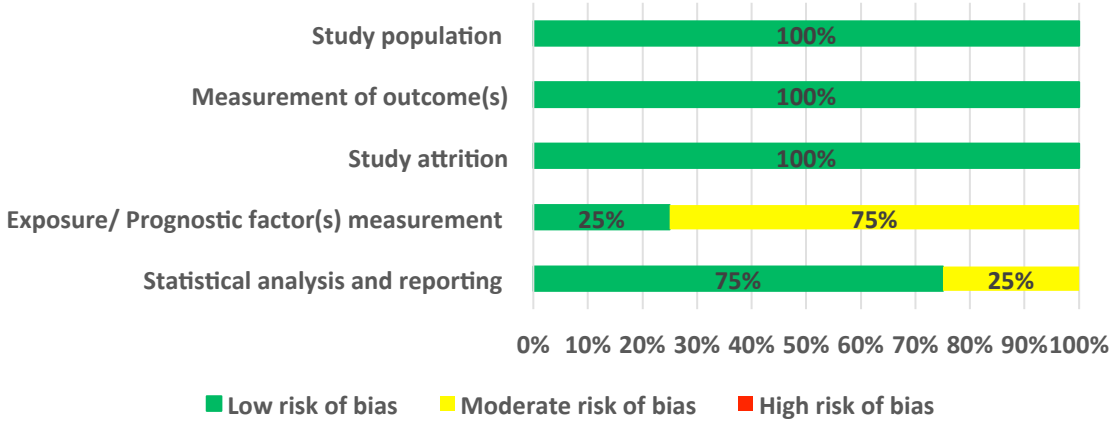


Figure 4.7: Risk of bias (RoB) graph for the studies reporting encephalocele neonatal and infant case fatality.

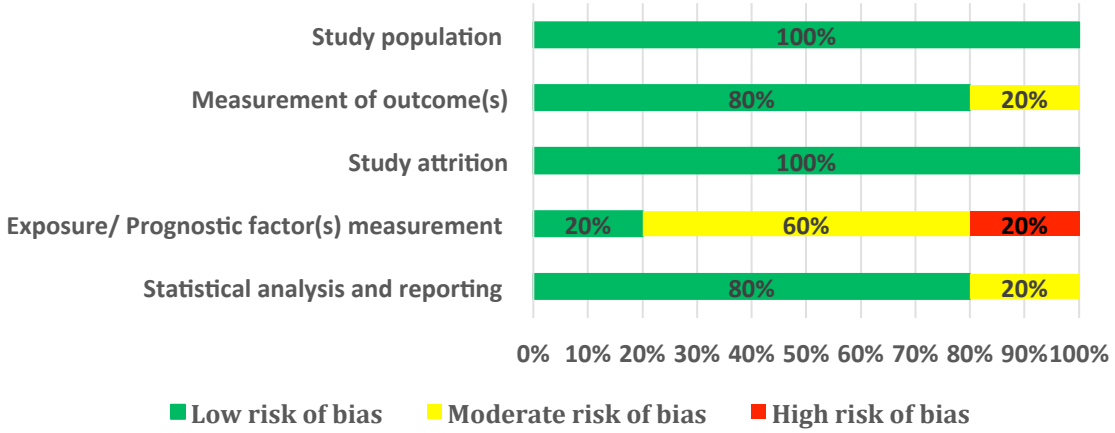
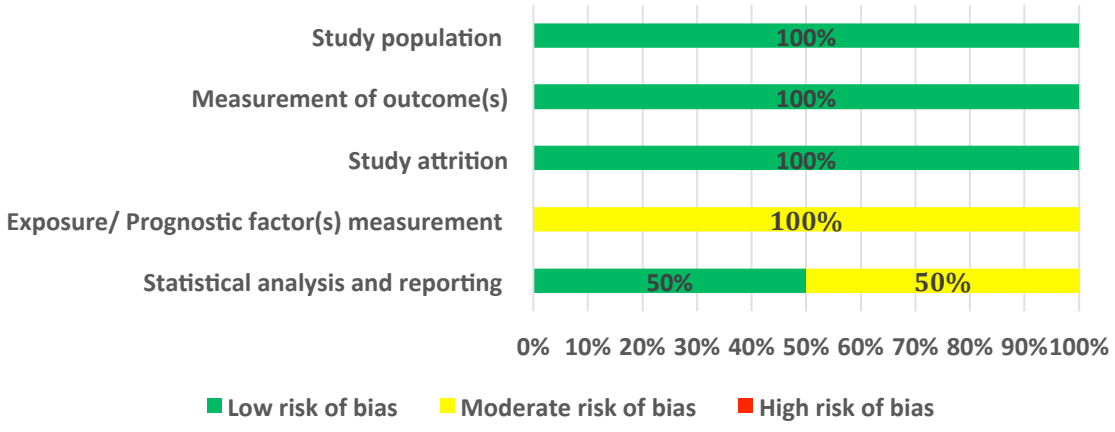


Figure 4.8: Risk of bias (RoB) graph for the studies reporting risk factors for encephalocele infant case fatality.



4.5 Discussion

4.5.1 Summary of findings

This systematic review included seven population-based cohort studies identified between 1st January, 1990 and 31st August, 2020, with a total study population of over 17 million liveborn infants, in which approximately 1,500 liveborn infants were affected by an encephalocele.

This review spanned 45 years with births from 1966 to 2011, and therefore was able to examine changes in the trend of encephalocele associated infant mortality and case fatality during the period of important public health interventions (e.g. the implementation of mandatory folic acid food fortification in the U.S., Canada and Australia) and clinical developments (e.g. advances in prenatal screening and changes in management in pregnancy). Consequently, variation in the year of birth of the cohorts between studies was likely to be the main cause for heterogeneity for the mortality estimates.

This review estimated that the, overall, NMR due to encephalocele significantly declined by 6.90% per year (from 2.9 to 1.4 deaths per 10,000 livebirths) between 1988 and 2003; and IMR due to encephalocele significantly declined by 5.88% per year (from 2.6 to 1.8 deaths per 10,000 livebirths) between 1986 and 2003. In addition, overall, neonatal case fatality significantly declined by 4.00% per year (from 34.0% to 22.3%); and infant case fatality significantly declined by 4.00% (from 40.0% to 27.9%) between 1978 and 2003.

Maternal ethnicity, marital status, prenatal care, lesion site, multiple defects, folic acid food fortification, gestational age at birth and birthweight were factors significantly associated with an increase or decrease in the risk of infant mortality due to encephalocele.

4.5.2 Encephalocele infant mortality and case fatality

Similar factors that contributed for the declines in spina bifida infant mortality and case fatality have likely contributed to the significant declines in encephalocele infant mortality and case fatality.

First, the U.S. population-based cohort studies by Siffel et al. (2003) and Wang et al. (2015) demonstrated significant declines in encephalocele neonatal and infant mortality and case fatality over time between 1979 and 2007, in the middle of U.S. national mandatory folic acid fortification which was implemented in 1998. The most likely explanation is that folic acid food fortification significantly reduces encephalocele infant mortality and case fatality by effectively reducing the risk of intrauterine development and/or severity of the condition, and hence prevents infants dying from the condition (Atta et al. 2016; Christianson et al. 2006; Kancherla et al. 2017; Murphy et al. 2020; EUROCAT 2003; Crider et al. 2011).

Second, improved technology in and access to prenatal screening over time have led to early prenatal diagnosis of encephalocele, and consequently, significant declines in late fetal death and birth prevalence as a result of termination of many affected pregnancies. This is likely to be the main cause of the declines in encephalocele infant mortality and case fatality (Kalucy et al. 1994; Liu et al. 2001; Riley et al. 1998; Boyle et al. 2018). In addition, early diagnosis of encephalocele while these affected babies are in utero enables advanced planning of specialist care and transfer for delivery in a specialised centre, and therefore the chance of survival of the affected infants can be optimised (Riley et al. 1998).

Third, improvements in medical and surgical care and treatment such as improved ventilatory support in neonatal intensive care, a multi-disciplinary clinical management approach and antibiotics guideline for infections of the central nervous system have provided a better prognosis for infants affected by encephalocele and associated complications, which may also explain the declines in encephalocele associated infant mortality and case fatality over time.

4.5.3 Risk factors

Maternal ethnicity

Among infants with an encephalocele, those born to Hispanic mothers had a 65% increased risk of infant case fatality, compared to those born to White mothers (Bol et al. 2006). The likely explanations, as discussed in Chapter 3, include differences in genetics, access to and the use of folic acid fortified food products between Hispanic and non-Hispanic mothers (Bol et al. 2006; Davidoff et al. 2002; Feuchtbaum et al. 1999; Kirby et al. 2000; Canfield et al. 1996; Botto et al. 2000).

In addition, infants with an encephalocele born to Black mothers had a two-fold increased risk of infant case fatality, compared to infants with an encephalocele born to mothers of other ethnicity (Siffel et al. 2003). Previous studies have suggested that this likely resulted from social inequalities between ethnic groups in access to healthcare (Shin et al. 2012).

Ethnic disparities in infant mortality have been shown in previous studies of other congenital anomalies (Petrini et al. 1997; Malcoe et al. 1999).

Marital status

This review has shown that among infants with an encephalocele, those born to single mothers had a 38% increased risk of case fatality during infancy, compared to those born to married mothers (Bol et al. 2006).

Single motherhood has previously been shown to be associated with an increased risk of infant mortality (Bennett et al. 1994). While single motherhood is generally associated with a low socio-economic status (McAdoo 1980), the effect of marital status on infant mortality is often confounded by other circumstances such as maternal age, ethnicity, education level, income and employment status (Furstenberg 1981; McLaughlin et al. 1986). Therefore, the effect of single motherhood on infant mortality should be interpreted with care. Further research is needed to

investigate the social circumstances of single motherhood that contribute to the mortality outcomes of their infants.

Prenatal care

Among infants with an encephalocele, those born to mothers who received inadequate prenatal care had a 58% increased risk of infant case fatality, compared to those born to mothers who received adequate prenatal care (Bol et al. 2006).

Adequate prenatal care is generally considered as an effective method of improving pregnancy and birth outcomes (Fink et al. 1992); inadequate prenatal care can suboptimise prenatal diagnosis and limit the options of potential interventions which may explain the differences in infant case fatality.

However, a previous review by Villar and Bergsjø (1997) has shown that many antenatal care practices have not been robustly evaluated; hence further studies are needed in order to assess the consistency of potential beneficial effect of prenatal care on infant mortality.

Lesion site

This review has shown that infants with a posterior encephalocele had more than a two-fold increased risk of infant case fatality, compared to infants with an anterior encephalocele (Siffel et al. 2003; Bol et al. 2006). This finding is consistent with earlier studies, which showed that case fatality among infants with encephaloceles was largely confined to those infants with posterior defects (Brown and Sheridan-Pereira 1992; Lorber and Schofield 1979).

Posterior encephaloceles tend to be larger in size, containing a greater amount of cerebral tissue, and associated with other significant brain abnormalities and complications (Kim et al. 2014). Therefore, posterior encephaloceles tend to have a poorer prognosis compared to anterior encephaloceles (Kiymaz et al. 2010).

Multiple defects

Infants with an encephalocele as a part of multiple anomalies had a 1.86 times increased risk of infant case fatality, compared to infants with an isolated encephalocele (Bol et al. 2006). As discussed in Chapter 3, multiple anomalies are a proxy for disease complications and severity, and hence tend to be associated with a poorer prognosis, compared to isolated anomalies (Springett et al. 2013).

Folic acid food fortification

Infants who were born with an encephalocele during the period of mandatory folic acid food fortification were less likely to die in infancy, compared to infants who were born with an encephalocele during the pre- folic acid fortification period in the U.S.. For example, although not statistically significant, Bol et al. (2006) has shown that infants with encephalocele born during the periods of optional and mandatory fortification were associated with 32% (aHR = 0.68, 95% CI: 0.41-1.12) and 30% (aHR = 0.70, 95% CI: 0.45-1.07) decreased risks of mortality respectively, compared to those who were born during the period of prefortification. In addition, the estimated survival rates for infants with encephalocele increased from 75.7% (prefortification) to 79.5% (optional fortification) and 79.1% (mandatory fortification) during the study period between 1995 and 2001 although the differences were not statistically significant, and the estimates may have been confounded by variations in maternal consumption of the fortified food which was not measured and adjusted for in the study; and hence the periods of fortification does not necessarily indicate the actual maternal intake of folic acid (Bol et al. 2006). Therefore, the effect of folic acid food fortification on infant mortality rate would also be difficult to be fully assessed without the availability of TOP data. With regard to folic acid supplementation, as discussed in Chapter 3, Berry et al. (1999) showed that preconceptional intake of folic acid supplementation significantly reduced the risk of the development of NTDs in fetuses and infants; and the randomised controlled trial by MRC Vitamin Study Research Group (1991) demonstrated

the benefit of periconceptional intake of folic acid supplementation in reducing the recurrence of NTDs. Therefore, the findings of these studies have established the specific role of folic acid in reducing the frequency and severity of encephalocele, as well as contributing to the decrease in encephalocele infant mortality and case fatality over time. Previous studies have suggested that the mechanism by which folic acid reduces the severity of encephalocele is by moving the location of the defect (Bol et al. 2006).

Preterm birth and birthweight

Finally, this review has shown that infants with an encephalocele who were born preterm or with a low birthweight had a 1.63 and 3.46 fold increased odds respectively of infant death, compared to those who were born at term or with a birthweight ≥2500g (Bol et al. 2006). As discussed in Chapter 3, preterm birth and low birthweight can be considered as correlated outcomes resulting from congenital anomaly, as fetuses with an anomaly in general often have other developmental effects during pregnancy which may lead to preterm birth (Behrman and Butler 2007; Institute of Medical Staff 1985). Therefore, the effects of preterm birth and congenital anomalies on infant mortality are likely to be synergistic.

4.5.4 Strengths and limitations

Strengths

This is the first systematic review conducted to investigate encephalocele-specific neonatal and infant mortality rates over time in high-income countries. The main strengths of this systematic review include its comprehensive search strategy with no language restriction, robust inclusion criteria and complete coverage of population-based studies. A further strength of this review relates to the study evidence, which was obtained from generally high quality population-based cohort studies mainly with low to moderate risk of bias (Higgins et al. 2008; The Cochrane Library 2018).

Limitations

The limitations of this review include incomplete data in the included studies relating to treatment, termination of pregnancy, women's intake of folic acid supplements, and the registries' ability to track and link all encephalocele cases with death registers. Hence, this has prevented an assessment of these specific factors attributed to the changes in infant mortality rates and case fatality. Consequently, these could cause high variability and heterogeneity in the mortality estimates. In addition, as there were only single studies reporting risk factors for encephalocele-associated infant case fatality, it was not possible to carry out a meta-analysis. Therefore, results of risk factors and associations reported from single studies should be interpreted with caution. Finally, three out of the seven included studies did not state whether the encephalocele cases were part of multiple or syndromal defects, therefore it was not possible to precisely assess the extent to which infant death was due to the encephalocele as opposed to co-occurring abnormalities.

4.6 Conclusions

The current review has updated the evidence about the contributions of encephalocele to infant mortality in a contemporary setting. Significant declines in encephalocele neonatal and infant mortality, and case fatalities were consistently observed. Access to prenatal diagnosis, effective treatment and their improvement over time as well as mandatory folic acid food fortification are likely to be the main contributory factors for these changes. Preterm birth, low birthweight and maternal Black ethnicity were the strongest risk factors associated with excess infant mortality due to encephalocele found in single studies. This review has identified research gaps, in which future studies should focus on investigating risk factors contributing to excess infant mortality due to encephalocele.

Table 4.6: What these systematic reviews from Chapters 3 and 4 add.

- These are the first systematic reviews conducted to investigate spina bifida- and encephalocele- specific neonatal and infant mortality rates over time in high-income countries; and the first meta-analysis to investigate socio-demographic and clinical factors associated with excess mortality in the first year for infants affected by spina bifida.

- Infant mortality rates and case fatality of infants with spina bifida and encephalocele have significantly declined over time in high-income countries including the U.S., Canada, UK, Republic of Ireland, and Australia. This can be attributed to folic acid food fortification, improved technology in and access to prenatal screening and diagnosis, and advances in medical and surgical interventions.

- Preterm birth and low birthweight are the strongest risk factors associated with an increased spina bifida/encephalocele associated infant case fatality.

- Maternal ethnicity, prenatal care, lesion location, multiple defects, plurality, and folic acid supplementation are significant determinants of excess infant mortality due to spina bifida or encephalocele.

- The interplay of factors contributing to spina bifida/encephalocele associated infant mortality is complex and geographically dependent.

Chapter 5: Overview Of Data Sources For Population-based Cohort Studies

This chapter presents an overview and background relating to the data sources, case ascertainment and quality of data for the data analyses of the study aim 1 (Chapter 6: Mortality study) and study aim 2 (Chapter 8: Hospitalisation study). The study design, methods and statistical analyses are described in the respective chapters.

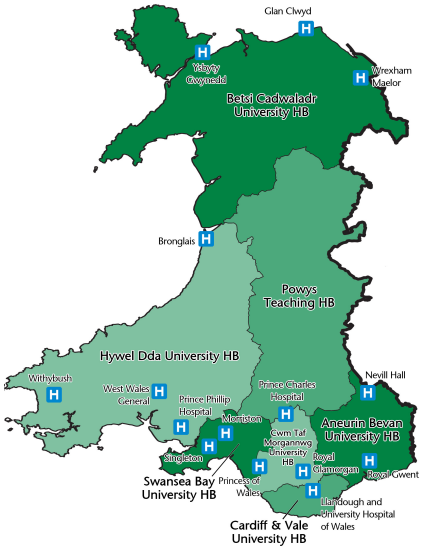
Data sources for the data analysis for study aim 1

5.1 Congenital Anomaly Register and Information Service (CARIS) for Wales

The data analysis for the main study aim 1 used linked de-identified registry data from the Congenital Anomaly Register and Information Service (CARIS) for Wales, and births and deaths registration data from the Office for National Statistics (ONS).

CARIS is a high-quality population-based congenital anomaly register, which was established in 1998 to identify congenital anomalies in all regions of Wales (Figure 5.1). All fetuses and babies with an anomaly who were born from 1st January, 1998 onwards to mothers who are normally residents in Wales at the time of birth/ end of the pregnancy are recorded (CARIS 2020a).

Figure 5.1: Map of health board boundaries and main hospitals in Wales. (NHS Wales 2020)



CARIS collects data about anomalies involving structural, metabolic, endocrine or genetic defects, as well as rare diseases of genetic or hereditary origin (CARIS 2020b). All anomalies which are detected during pregnancy, at birth or within one year after birth (except for chromosomal anomalies and syndromes which can be diagnosed later) are recorded. There is no lower gestational age limit for registration of cases (CARIS 2020c). CARIS is known to have high reporting rates due to its robust surveillance and multiple sources reporting system (CARIS 2020a).

CARIS collaborates with the British Isles Network of Congenital Anomaly Registers (BINOCAR), the European Surveillance of Congenital Anomalies (EUROCAT) and the International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR) to allow research and surveillance of congenital anomalies within UK, Europe and the wider world (CARIS 2020d).

5.1.1 Welsh background and coverage

An average of 35,000 pregnancies occur in Wales each year. Of these pregnancies, about 75% are registered as live- or still- births, and 25% either end with spontaneous losses (i.e. miscarriages) before 24 weeks of gestation, or terminations of pregnancy (CARIS 2020e). The incidence and birth prevalence of congenital anomalies in Wales have remained stable since 1998 at around 5.1% and 4.4% respectively. The great majority (about 97%) of babies born with an anomaly survive to their first birthday (CARIS 2020f).

The majority of births take place in hospital and about 3% of births take place at home (CARIS 2020e). Wales currently has 16 consultant obstetric units and 10 midwifery/ general practitioner led units (CARIS 2020c). For mothers residing close to the English border and babies requiring specialised care which is not available in their local health providers, birth may take place in England or a nearby specialised centre. For example, babies in Mid or North Wales needing surgery for cardiac anomalies or gastroschisis are often referred to Alder Hey Children's Hospital in Liverpool or Birmingham Children's Hospital for the specialist care (EUROCAT 2020). CARIS

maintains good links with the Congenital Anomalies Registers near these areas, for example Mersey and West Midlands (CARIS 2020c).

5.1.2 Case sources and data quality of CARIS

CARIS uses a multiple sources reporting system to optimise case finding and ascertainment (Table 5.1). These sources include information from the NHS Health Boards, cytogenetic laboratories, pathology department, neonatal units and other child health services. Data are captured as close to the first point of activity as possible, i.e. from clinicians who are involved with the care (CARIS 2020a).

Table 5.1: Multiple data sources and reporting system to CARIS. (CARIS 2020a)

Clinical reporting
• Obstetricians • Paediatricians • Midwives • Special Care Baby Unit (SCBU) and Neonatal Intensive Care Unit (NICU) • Patient Episode Database for Wales (PEDW)
Diagnostic services
• Ultrasonography • Welsh neonatal screening • Paediatric pathology • Serum screening
Regional services
• Regional paediatric cardiology • Community (Paediatrics) services • Regional paediatric surgery and maxillo-facial surgery • Health visiting service • Paediatric orthopaedics • Audiology • Ophthalmology
Medical Genetics
• Molecular genetics • Welsh cytogenetic unit
Others
• All Wales perinatal survey (until 2012) • National Community Child Health Database (NCCHD) • Mersey congenital anomaly registry (until 2007) • South West congenital anomaly registry • West Midlands congenital anomaly registry • Protos, Cardiff (an early maternity database system – historic)

Clinical reporting is the primary source of information for CARIS, especially for those affected babies who die without a post mortem, and those babies who survive but have anomalies which do no need immediate or urgent specialist care. Clinical reporting is undertaken by healthcare professionals (e.g. clinicians, midwives etc.), who complete a paper notification cards and data collection forms which are available on wards, clinics, delivery suites, special care baby units, and online (e.g. E-alert, RadIS systems) (Appendix 5.1). Each hospital has a nominated coordinator and champion to ensure good reporting locally. In addition, CARIS collects information from other NHS databases such as diagnostic service (e.g. ultrasound and pathology), regional service (e.g. cytogenetics and specialist clinical service such as paediatric cardiology), medical genetics and the Patient Episode Database Wales (PEDW) to ensure accurate diagnoses especially for complex cases and multiple anomalies. Chromosomal anomalies such as Down syndrome are reported directly from the national cytogenetics service (CARIS 2020c).

Better reporting has been considered as the main reason for the relatively higher rates of congenital anomalies in Wales compared to other parts in the UK and many parts of Europe; fewer cases were missed from 1998 compared to previous years in Wales. This was attributed to the replacement of the Health Authority based paper-form reporting system by the CARIS electronic reporting system in 1998. This is illustrated from analyses of reports made to ONS prior to 1998. Using the new electronic reporting system, CARIS was able to back-report any cases for the previous years between 1995 and 1997 and found that under-reporting had occurred using the Health Authority system (Appendix 5.2); this suggested that the development of the electronic system has led to improvements in data reporting and collection, which may account for higher rates of anomalies reported by CARIS compared to other English Congenital Anomaly Registers and many other EUROCAT registers, although ongoing monitoring is also being conducted to observe any true difference in the prevalence rates (CARIS 2020a).

In addition, case details and prevalence data are checked and compared against the Welsh Demographic System, Orphanet and ICBDSR to ensure validity and consistency (CARIS 2020b;

CARIS 2020g). CARIS undertakes data quality checks every year to assess and remove double counting of cases from multiple sources. Duplication of cases is rare (duplication rate <1%; identified using dates of birth, address, NHS numbers etc.) in the CARIS dataset (CARIS 2020a).

5.1.3 Data completeness

While having a multiple sources reporting system and every effort is made to ensure data are complete, there are circumstances where missing data can occur. For example, when clinical priority is given to care delivery rather than record keeping, and diagnoses that are made some time after birth. There can also be cross-border issues with care delivered by health care providers in England (CARIS 2020b).

Nonetheless, CARIS actively follows up missing data, for example, by liaising with the local facilitators or traveling to the health board to retrieve missing data from medical note etc. in order to optimise data completeness where possible (CARIS 2020b).

5.1.4 Case ascertainment and coding

Each anomaly case is assigned a status once it is registered, depending on the data source and the strength of evidence for the diagnosis (Table 5.2) (CARIS 2020g).

Table 5.2: Status of cases of congenital anomalies. (CARIS 2020g)

Data source	Status assigned by CARIS
Clinical reports of livebirths	Confirmed
Cytogenetics and post-mortem	Confirmed
Prenatal ultrasound	Suspected
Inpatient data and NCCHD[1] with specific codes[2]	Probable
Inpatient data and NCCHD with non-specific codes[2]	Suspected
[1]The National Community Child Health Database. [2]All cases are followed up and verified with paediatric case notes.	

All clinically reported cases of anomalies from livebirths, post-mortems and cytogenetic reports are classed as confirmed cases. Inpatient data about anomalies are classed as probable cases when specific codes are used, and as suspected cases when non-specific codes are used. Prenatal ultrasound findings of structural abnormalities and soft markers are classed as suspected cases, which are regularly followed up and confirmed at the end of pregnancy. Each probable and suspected case is reviewed regularly and resolved into being either a confirmed, normal (i.e. no anomaly, e.g. an antenatal finding is resolved) or unknown case (i.e. if no further information is available) (CARIS 2020g). In addition, all anomalies reported to CARIS are coded by trained coders using the International Classification of Diseases, 10th Revision (ICD-10) with the Royal College of Paediatrics and Child Health (RCPCH) extension. CARIS aims to code every anomaly identified, with the principle of using the minimum number of codes necessary to accurately describe the conditions (or clinical picture) to the greatest specificity in the disease classification (CARIS 2018; CARIS 2020g).

5.2 The Office for National Statistics (ONS)

The Office for National Statistics (ONS) is the national statistical institute of the UK, which has been responsible for collecting and publishing statistics related to the population, society and economy at national, regional and local levels in England and Wales since 1996 (ONS 2020). Denominator data of births and deaths for the analyses for study aims 1 (Chapter 6) and 2 (Chapter 8) were obtained from the ONS.

5.2.1 Mortality case ascertainment, validation and data quality

In the UK, the registration of births and deaths is a statutory requirement. The Births and Deaths Registration Act 1836 made it a legal requirement for all births and deaths to be registered. These data are the most complete data source of births and deaths available (ONS 2020).

ONS collects data on the causes of death from civil registration records including the death certificate which is completed by a doctor or a coroner. Death registration details for each file are passed through a series of routine checks and validation processes for completeness, consistencies and duplications prior to coding. After data extraction is completed, further quality checks are carried out before the data become usable for analysis (Appendix 5.3) (ONS 2020b).

5.2.2 Mortality data coding

Mortality data are coded using the ICD coding system (ONS 2020c; Dattani and Rowan 2002; ONS 2011). See Chapter 1: Section 1.2.3 (Infant mortality).

Data sources for the data analysis for study aim 2

The data analysis for the study aim 2 used linked de-identified anomaly registry data from CARIS, hospital episodes data from the Patient Episode Database for Wales (PEDW), and births and deaths data from the ONS in order to investigate the hospitalisation trajectories of infants with congenital anomalies.

5.3 Patient Episode Database for Wales (PEDW)

5.3.1 Background

Established in 1991, the PEDW database contains routinely collected hospital episodes administrative data. These include clinical and demographic data for all inpatient, outpatient and day case activities within NHS Wales hospitals, and for some Welsh residents who are treated in the other UK home countries. These records include elective and emergency admissions, minor and major operations, and the hospital stay for giving births (NHS Wales Information Service 2020). Therefore, PEDW is representative of the secondary healthcare received by the whole

population of Wales. Data from PEDW have been used extensively for research (NHS Wales Information Service 2020).

5.3.2 Hospital admission data

Each admission record includes a wealth of fields. For example, details of date of admission and discharge, methods of admission (e.g. emergency or elective), patients classification (e.g. inpatient or day case), information about episodes and spells (e.g. diagnoses, hospital length of stay and outcomes), specialty code, discharge destination (e.g. home, transfer to other hospital etc.) and other patient demographic information (e.g. infant sex, gestational week of birth and health care provider etc.) are recorded for each hospital admission within PEDW.

Details of the conduct of record linkage, inclusion and exclusion criteria of the study cohort for the data analysis are described in Chapter 8: Section 8.4 (Methods).

5.4 Research ethics and information governance

Since this project involved analyses using retrospective routinely collected anonymised health data, individual consent was not required. All data were accessed via the Secure Anonymised Information Linkage (SAIL) database. However, as per the SAIL data governance, this project (including amendments) was reviewed and approved by the SAIL information Governance Review Panel (IGRP) (SAIL project number: 0754).

Prior to usage of the data, I completed the Safe User of Research data Environments (SURE) training by the ONS and the Good Research Practice course by the Medical Research Council (MRC 2020) and passed the required assessments.

To ensure anonymisation standards were met, data encryption and the anonymisation process were conducted by trained health analysts at SAIL. Data for rare outcomes were checked by an experienced reviewer from SAIL information governance before it was released to the secure area

(i.e. the SAIL Gateway) for viewing and analysis by me (CARIS 2020b). All analyses were conducted in the SAIL analytical environment.

All statistical disclosure control and checks were strictly followed according to the SAIL Databank and ONS guidelines, for example to ensure that patients are not identifiable through small numbers. No individual data records were downloaded and all analytical outputs were checked prior to release to the researcher (CARIS 2020b).

5.5 Challenges and adjustments of the original plan

The original plan for the main data analyses components of this thesis was to conduct the studies using a larger combined dataset from several regional English congenital anomalies registries linked to the Hospital Episode Statistics (HES) in England, and births and deaths registration from ONS. These would have covered more than 50% of births in England.

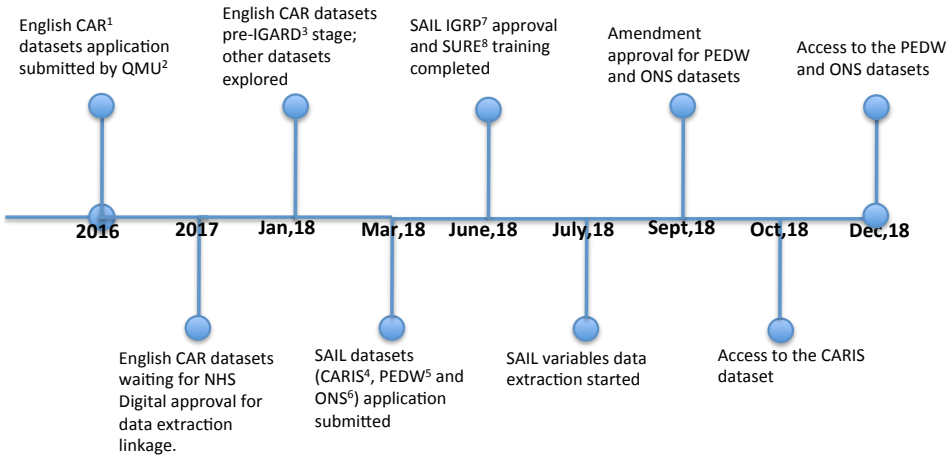
However, in early 2018, it became clear that the English BINOCAR data that we hoped to access was unlikely to become available until after the end of my DPhil. This was due to the complex process of gaining permission to extract and link data via the NHS Digital, which were completely beyond our control. As a consequence, I explored with my supervisors the potential of using various other UK and international datasets to best address the study objectives. Having evaluated various options, the conclusion reached was that using CARIS (a high-quality BINOCAR register), linked to PEDW and ONS would not fundamentally alter what I was planning to investigate.

The initial review for IGRP approval for the CARIS dataset took 80 days from submission. In addition, the SAIL team requested further clarifications and amendments to IGRP regarding the inclusion period required for the PEDW data, which took an additional 25 days for approval (Figure 5.2). The period pending the approval of the datasets was effectively spent on conducting the systematic and literature reviews (this included training the second reviewers for article

screening, data extraction and RoB assessment), drafting the pre-analytical protocol for the main data analyses, and attending relevant training courses (e.g. Introduction to Hospital Episode Statistics at UCL Great Ormond Street Institute of Child Health) (Appendix 5.4).

Although the full datasets from CARIS, PEDW and ONS required for the analysis became accessible to me in December 2018, further delays occurred due to errors associated with some variables generating the study cohort from the CARIS dataset, as well as linkage errors with the PEDW dataset. I worked closely with SAIL data scientists to resolve the issues prior to starting the analyses.

Figure 5.2: Timeline of datasets



[1]CAR = Congenital Anomaly Registries; [2]QMU = Queen Mary University of London; [3]IGARD = Independent Group Advising on Release of Data as part of NHS Digital Data Access Service (DARS); [4]CARIS = Congenital Anomaly Register and Information Service for Wales; [5]PEDW = Patient Episode Database for Wales; [6]ONS = Office for National Statistics; [7]SAIL IGRP = the Secure Anonymised Information Linkage Information Governance Review Panel; [8]SURE = Safe User of Research data Environments.

Chapter 6: An Investigation Into The Nature And Clinical Features Of Congenital Anomalies Leading To Infant Mortality.

6.1 Introduction

The UK has one of the highest infant mortality rates (IMR) in Europe (Wolfe et al. 2014). Between 2014 and 2018, the IMR has increased by 5.5% from 3.6 deaths per 1,000 livebirths to 3.8 deaths per 1,000 livebirths in the UK (ONS 2020). This increase has been shown to be mainly due to changes in neonatal practice of extremely preterm babies at less than 23 gestation weeks, and reporting and registration of extremely preterm births over time (Nath et al. 2020; Davis et al. 2018), which have consequently affected the overall IMR (ONS 2019c). However, it remains unclear how particular causes of death have contributed to a high IMR in the UK.

Congenital anomalies are a leading cause of infant mortality in the UK, however, population-based mortality studies of infants with congenital anomalies are limited to inform clinical and public health practices. In particular, study evidence is inadequate to understand what are the causes that babies with congenital anomalies die of and the contributing risk factors. Estimates of infant mortality associated with congenital anomalies have the potential to inform public health prevention programmes, as well as healthcare and social interventions aimed at reducing infant mortality.

In addition, the systematic reviews in Chapters 3 and 4 have shown that the risks of spina bifida- and encephalocele- associated infant mortality can be significantly influenced by various socio-demographic, maternal, infant and interventional characteristics. Therefore, the nature and clinical characteristics of wider congenital anomalies leading to excess mortality warrant further investigations in order to inform the healthcare professionals caring for the affected babies.

6.2 Aim

The aim of this chapter was to investigate the nature and clinical features of congenital anomalies associated with the risk of infant death versus survival.

6.2.1 Specific objectives

The specific objectives were:

6a) To estimate infant mortality rates by anomaly;

6b) To describe the cause of death of infants with an anomaly;

6c) To describe and compare the characteristics of infants with congenital anomalies who survived and those who died;

6d) To examine the risk factors contributing to death versus survival of infants with an anomaly.

6.3 Methods

6.3.1 Definition of congenital anomalies

The European Surveillance of Congenital Anomalies (EUROCAT) defines congenital anomalies as structural defects (including congenital malformations, deformations, disruptions and dysplasias) and chromosomal abnormalities (i.e. ICD10 'Q', 'P35' and 'P37" codes only) (EUROCAT 2013a).

Congenital anomalies, as included in the data analyses presented in this thesis (i.e. Chapters 6 and 8), are defined by CARIS as involving structural, metabolic, endocrine, or genetic defects, as well as rare diseases of genetic and hereditary origin present in the child or fetus at the end of pregnancy, even if not detected until after birth (CARIS 2018). Therefore, the analyses presented in Chapters 6 and 8 comprehensively included all those anomalies defined by EUROCAT (i.e. ICD10

'Q', 'P35' and 'P37" codes), as well as other rare diseases of congenital origin (i.e. other non 'Q' ICD 10 codes).

6.3.2 Inclusion and exclusion criteria

Inclusion criteria

1. All livebirths between 1st January, 1998 and 31st December, 2016 (birth cohort) with a known diagnosis of a congenital anomaly and rare disease as defined by and reported to CARIS. These included all confirmed cases by diagnostic tests or investigations (e.g. cases diagnosed by karyotyping, genetic tests or post-mortem); clinically confirmed cases after review by a geneticist or clinician; and probable cases (e.g. structural anomalies diagnosed antenatally but no further information was available at the time of registration).

Exclusion criteria

1. Infants with gestational age at birth < 22 completed weeks or birthweight < 500g were excluded from the analysis.

These exclusions were identified because these thresholds of gestational age and birthweight are the lowest limits for mortality registration in most European countries (including UK), USA, Canada, Australia and New Zealand (OECD Health Statistics 2019; Smith et al. 2018). In addition, the risk of death of infants who are born < 22 completed weeks' gestation and/or with a birthweight < 500g is significantly higher per se, compared to that of infants who are born at an older gestational age or with a higher birthweight.

6.3.3 Data Sources

The data sources for this study were described in Chapter 5: Sections 5.1 (CARIS) and 5.2 (ONS).

6.3.4 Coding and classifications of congenital anomalies

Coding of anomalies

In line with other BINOCAR and EUROCAT registers, all congenital anomalies and their related conditions and complications reported to CARIS were coded using the Royal College of Paediatrics and Child Health adaptation of the 10th revision of the International Classification of Diseases and Related Health Problems (ICD-10 RCPCH). As part of internal checks and data cleaning, CARIS reviewed all the ICD10 diagnostic codes. Furthermore, additional checks were performed on diagnostic coding by the researcher (PH). Syndromic infants who had more than one diagnostic code recorded in the CARIS dataset were reviewed and checked for potential duplication of entry (e.g. same condition was recorded using different codes). For example, a small proportion of infants diagnosed with DiGeorge syndrome (coded D82.1) were found to have an additional code for a 22q11.2 microdeletion (coded Q93.5) which represented the same condition in the CARIS dataset. Such duplications were discussed with the CARIS manager and removed from the analysis where appropriate in order to prevent those infants from being incorrectly classified as having multiple conditions.

Classifications of anomalies

Congenital anomalies were categorised according to the EUROCAT subgroup classification 2013 (Appendix 1.1) (EUROCAT 2013a); other rare diseases (i.e. not in the EUROCAT subgroup classification) were categorised according to the ICD chapter headings (Appendix 6.2) (WHO 2004). Infants were considered as having an isolated congenital anomaly (or disease) if a single anomaly (or disease) occurred and was reported to CARIS. Infants were considered as having multiple anomalies (or diseases) if more than one anomaly (or diseases) occurred, either within the same body system or involving different body systems, and were reported to CARIS. Infants

who were diagnosed with a syndrome involving more than one anomaly (or disease) were considered as having multiple anomalies (or diseases).

6.3.5 Explanatory variables identified in the dataset

Explanatory variables were selected *a priori* based on evidence from the systematic reviews (Chapters 3 and 4), the availability of variables within the datasets, as well as extent of missing values. Details about the explanatory variables were collected from the Congenital Anomaly Register Notification form (Appendix 5.1). Each form contains questions about maternal demographics, current and past pregnancy, labour and delivery, infant birth history and outcomes, prenatal screening and investigations, and postnatal details of the anomaly (CARIS 2020). Answers to the questions were extracted and made available in the CARIS dataset from inception in 1998, except data for 'infant surgery status' which has been collected more systematically by CARIS from 2005.

Data cleaning

All quantitative data were checked to ensure that they were within plausible ranges, and their prevalence was consistent with current evidence in the literature. For example, a literature check was performed showing that the vast majority (>95%) of the Welsh population is of White ethnicity (ONS 2019a), hence <5% non-White maternal ethnicity in the CARIS dataset was plausible and consistent with the ONS data. Any implausible data or outliers were discussed with the full supervision team (PH, MQ and JK) as well as the CARIS manager before deciding how they would be best dealt with, for example, by dropping, treating them as missing or performing a sensitivity analysis where appropriate.

Categorisation of explanatory variables

Explanatory variables were categorised according to: (1) Sample size such that the number of events in each category of a variable was optimised to ensure stable estimates and statistical power; and (2) Clinical relevance based on the literature. The complete list of the explanatory variables included and their categorisations is shown in Table 6.1.

Table 6.1: Description of explanatory variables and their categorisations included in the analyses.

Variable	Data source	Description note	Evidence for which variable is associated with infant mortality in the literature.
Socio-demographic factors			
Townsend (as area-based deprivation)	CARIS/ LSOA[1]	Categorised into 1 (least deprived)[2], 2, 3, 4, 5 (most deprived), and Not known/missing[3].	Some
Maternal ethnicity	CARIS	Categorised into White[2], Other (Chinese, Indian, Bangladeshi, Pakistani, Other Asian, Black Caribbean, Black African, Other Black, Mixed, Other), and Not known/missing.	Strong
Maternal age at birth	CARIS	Categorised into ≤24, 25-29[2], 30-34, ≥35 years, and Not known/missing[4].	Some
Maternal factors			
Parity[3]	CARIS	Categorised into Nulliparous[2], ≥1, and Not known/missing.	Some
Multiple fetus	CARIS	Categorised into Yes, No[2], and Not known/missing[4].	Some
Maternal smoking	CARIS	Categorised into Smoker, Non/ Ex-smoker[2], and Not known/missing.	Some
Anomaly in previous pregnancies	CARIS	Categorised into Yes, No[2], and Not known/missing.	Some
Infant factors			
Infant sex[5]	CARIS	Categorised into Male[2], Female and Not known/missing[4].	Strong
Infant's birthweight	CARIS	Categorised into <2500 (low birthweight), ≥2500[2] g and Not known/missing[4].	Strong
Infant's gestational age at birth	CARIS	Significant departure of linearity was shown in the effect of gestational age in weeks on infant mortality (outcome), hence gestational age (in weeks) was categorised into $<37^{+0}$ (preterm), $\geq 37^{+0\,(2)}$, and Not known/missing (note: further preterm subgroups were categorised where appropriate, Tables 6.10 and 6.14). The distributions of the gestational age at birth for the congenital anomalies were negatively skewed for both 'deaths' and 'alive one year' groups (Table 6.12).	Strong

Table 6.1 (continued): Description of explanatory variables and their categorisations included in the analyses.

Variable	Data source	Description note	Evidence for which variable is associated with infant mortality in the literature.
Disease severity (for congenital heart defects only)	CARIS	Categorised into Less severity[2,6], Moderate severity, Most severity, PDA[8] and other unclassified CHDs[7] and Not known/missing.	Strong
Interventional factor			
Surgery	CARIS	Categorised into surgery performed in the first year after birth, surgery not performed in the first year after birth[2] (this included a minority of conditions which were too severe for surgery) and Not known/missing.	Some

[1]Lower Layer Super Output Area (LSOA). [2]Reference group. [3]Parity was generated from two available variables in the dataset: number of stillbirths (defined as babies born at 24 weeks and did not take a breath) + number of livebirths. [4]Not known/ missing category were not included in complete case analysis or if missing proportion < 5%. [5]Indeterminate sex was not included in the analyses due to small number n < 5 (i.e. risk of statistical disclosure). [6]Congenital heart defects (CHDs) severity category was based on criteria used by Khoshnood et al. (2012): CHD less severe = Ventricular septal defect (VSD) (Q21.0), Atrial septal defect (ASD) (Q21.1), Pulmonary valve stenosis (Q22.1). CHD moderate severe = Common arterial truncus (Q20.0), Transposition of great vessels (Q20.3), Atrioventricular septal defect (AVSD) (Q21.1), Tetralogy of Fallot (Q21.3), Pulmonary valve atresia (Q22.0), Aortic valve atresia/ stenosis (Q23.0), Coarctation of aorta (Q25.1), total anomalous pulmonary venous return (Q26.2). CHD most severe = Single ventricle (Q20.4), Tricuspid atresia and stenosis (Q22.4), Ebstein's anomaly (Q22.5), Hypoplastic left heart (Q23.4) and Hypoplastic right heart (Q22.6). [7]Other CHD, circulatory or peripheral diseases = Double outlet right ventricle (Q20.1), discordant AV connection (Q20.5), atrial appendage (Q20.6), aortopulmonary defects, other malformation of aortic and mitral valves (Q23) other malformation of cardiac chamber and septa and arteries (Q24, Q25), other malformation of great veins (Q26), other malformations/ diseases of circulatory system (I31.3, I42, I45, I67, I78) (mostly dilated cardiomyopathy, pre-excitation syndrome and other conduction disorders). [8]PDA = Patent ductus arteriosus.

Sample size and power

The associated risk factors identified in this study underwent post hoc estimations of power. The study power to detect given odds ratios varied according to the risk factor being explored and the study population, for example 'all anomalies' had the largest sample size, whereas the particular anomaly subgroups such as 'cardiovascular anomalies' had the smallest sample size. Study power of each variable was estimated retrospectively and assured by using total sample size (n), sample size ratio (nratio), prevalence of the outcome in the baseline group, and the estimated odds ratio (oratio) at the 5% level of significance. The total sample size was based on all of the available data. As an example, for the analysis of preterm birth and infant mortality, the study had >99% power at the 5% level of significance to detect a true significant odds ratio of 4.53 in the analysis of 'all anomalies', and >99% power at the 5% level of significance to detect a true significant odds ratio of 2.76 in the analysis of 'cardiovascular anomalies' (Table 6.2).

Table 6.2: Study sample size and power for objectives 6c and 6d.

	All anomalies	All isolated anomalies	All multiple anomalies	Cardiovascular anomalies
Sample size[1]	29,487	19,265	10,180	3,084
Sample size ratio[1]	4.90	5.73	3.80	4.47
Prevalence of outcome in the baseline group (%)[1]	81.1	82.4	79.6	80.5
OR estimate[1]	4.53	4.72	3.84	2.76
Estimated study power (%)[1]	>99	>99	>99	>99
[1]Estimate based on the analysis of preterm birth and infant mortality.				

6.3.6 Reshaping and linkage of datasets

The CARIS dataset provided to the researcher (PH) consisted of five Structured Query Language (SQL) tables, which included:

1. CARIS Mothers' Townsend Deprivation Quintile (n = 33,793);

2. CARIS Mother (n = 34,147);

3. CARIS Pregnancy (n = 33,620);

4. CARIS Baby/ Fetus (n = 35,240); and

5. CARIS Anomaly (n = 60,648).

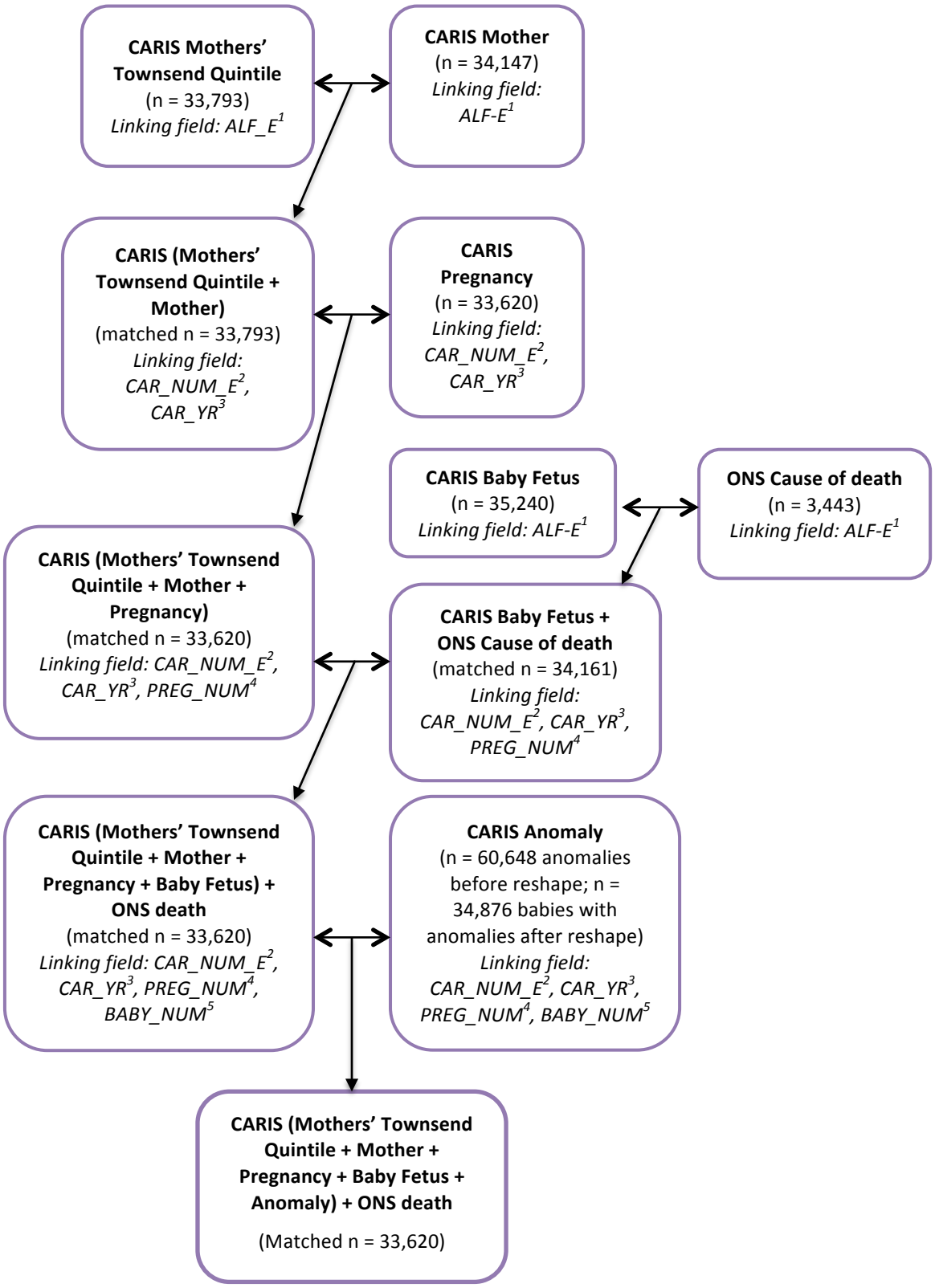
The descriptions and contents of these tables are summarised in Table 6.3.

A liveborn infant with an anomaly was taken as the unit of analysis for specific objectives 6a-6d outlined in this Chapter (Section 6.2.1). Therefore, the CARIS Anomaly table, which had anomalies as the unit of entry in its original form, was reshaped wide prior to linkage resulting in one record per baby. The data linkage between CARIS and ONS datasets was carried out by the researcher (PH). Details of the reshaping and linkage of datasets are summarised in Figure 6.1.

Table 6.3: Tables received from CARIS and ONS (1998-2016 Birth cohort).

Table	Observations (n)	Descriptions	Key data items
CARIS Mothers' Townsend Deprivation Quintile	33,793	Socio-demographic details of the mother from Lower Layer Super Output Area (LSOA) statistical classification.	Townsend deprivation score quintiles.
CARIS Mother	34,147	Maternal details of the babies with anomalies.	Maternal ethnicity and GP practice codes.
CARIS Pregnancy	33,620	Pregnancy and labour details.	Number of fetus, a history of anomaly in previous pregnancy, family history of anomalies, total number of previous pregnancies (livebirths, stillbirths etc.), maternal age, body mass index (BMI), smoking, alcohol consumption, folic acid intake, history of diabetes and epilepsy.
CARIS Baby/ Fetus	35,240	Information about the baby/ fetus who is diagnosed or suspected of having a congenital anomaly.	Delivery hospital, pregnancy outcomes, week of birth, infant sex, gestational age at birth, birthweight, syndrome ICD codes, aetiology of the anomaly, surgery, date of death and cause of death.
CARIS Anomaly	Before reshape: 60,648 After reshape: 34,876 (i.e. 60,648 anomalies in 34,876 babies)	Details about the anomaly when it was first suspected.	Anomaly ICD codes, status of anomaly (e.g. confirmed, probable, geneticist's review etc.).
ONS Births and Causes of death	Livebirths, n = 632,945; Infant deaths, n = 3,443.	Information about births and causes of infant deaths	ICD coded causes of death.

Figure 6.1: Flow diagram of the linkage between CARIS tables and the ONS dataset.



[1]ALF_E = Encrypted anonymised linking field; [2]CAR_NUM_E = Encrypted CARIS number; [3]CAR_YR = CARIS year; [4]PREG_NUM = Pregnancy number; [5]BABY_NUM = Baby number.

6.3.7 Statistical analysis

All analyses were performed separately for the following groups unless otherwise stated:

1. All anomalies (i.e. all isolated and multiple anomalies);

2. All isolated anomalies;

3. All multiple anomalies;

4. Various isolated anomaly subgroups where sample size allowed. For example, all major anomaly groups were included in the investigations of anomaly-specific IMR, case fatality (objective 6a) and cause of death (objective 6b). CHDs and vascular anomaly subgroups were included in the investigation of potential risk factors contributing to infant mortality (objective 6c and 6d).

Descriptive statistics

For objective 6a: To estimate the infant mortality rates by anomaly.

Infant mortality rate (IMR) is defined as the number of infant deaths per 10,000 livebirths. Denominator data for IMR included the total number of livebirths in Wales between 1998 and 2016, which was obtained from ONS.

Infant case fatality related to an anomaly was defined as the proportion of deaths of infants with an anomaly among total number of liveborn cases with that anomaly (as a percentage). Denominator data for infant case fatality for anomalies included the total number of livebirths with an anomaly in Wales between 1998 and 2016, which was obtained from CARIS.

Confirmed and probable cases of congenital anomalies were included in the estimates for IMR and infant case fatality, in line with the EUROCAT and the ICBDSR criteria (CARIS 2018).

For objective 6b: To describe the cause of death of infants with an anomaly.

As discussed in Chapter 1, a neonatal death certificate has been used to record neonatal deaths in England and Wales since 1986, this certificate does not require a single underlying cause of neonatal death to be recorded (ONS 2019b). Consequently, up to eight causes of neonatal death were recorded for every deceased neonate in the CARIS dataset, where the first coded cause of death recorded in the dataset represents the main condition or disease contributing to death of neonates (i.e. section a in the neonatal death certificate). For post-neonatal deaths, the standard death certificate is used to record a single underlying cause of death, the direct cause of death and contributory conditions (ONS 2019b). Consequently, the underlying cause of post-neonatal death, and up to eight contributory conditions were recorded for every deceased post-neonate in the CARIS dataset, where the first coded cause of death in the dataset represents the underlying cause of death of post-neonates.

The causes of death for neonates and post-neonatal infants were investigated as follows:

The main condition or disease contributing to death of neonates, and the underlying cause of death of post-neonates were used for the analysis of neonatal and post-neonatal causes of death respectively. These (first) recorded codes of cause of death were the most complete cause of death data in the ONS/ CARIS dataset.

All ICD-9 codes for causes of deaths were converted to ICD-10 codes using an online ICD codes converter (http://www.icd10codesearch.com) (Nextgen Healthcare 2019), prior to categorisation into causes of death group for the analysis.

In order to explore what neonates and post-neonatal infants with congenital anomalies were dying from, descriptive statistics were conducted to examine:

a. Distributions of the main condition or disease contributing to death of neonates by ONS cause (of death) group hierarchical classification (Appendix 6.1) (ONS 2020a);

b. Distributions of post-neonatal underlying causes of deaths by ONS classification and ICD9/10 chapter headings (Appendix 6.2) (WHO 2019; WHO 2020a).

In order to explore the pattern of causes of death, and its relationship with specific congenital anomalies subgroups, descriptive statistics were conducted to examine:

a. Distributions of the main condition or disease contributing to death of neonates by the ONS hierarchical classification, stratified by congenital anomalies subgroups;

b. Distributions of the post-neonatal underlying causes of death by the ONS classification and ICD9/10 chapter headings, stratified by congenital anomalies subgroups.

The frequency of postmortem and the recorded causes of death of infants with congenital anomalies who died were examined to assess the robustness of the coding and classification of the recorded causes of death of infants with congenital anomalies who died.

For objective 6c: To describe and compare the characteristics of infants with congenital anomalies who survived and those who died.

Socio-demographic, maternal, infant and intervention characteristics of infants with congenital anomalies who survived (i.e. the comparator group) and those who died were described and compared.

Descriptive analyses were performed for all anomalies (isolated and multiple), all isolated anomalies, all multiple anomalies, and CHDs and vascular anomalies groups. Other isolated anomaly subgroups were not analysed separately due to small number of infant deaths, which would pose a risk of statistical disclosure ($n < 10$) and/or result in imprecise estimates.

Collinearity testing and correlation statistics

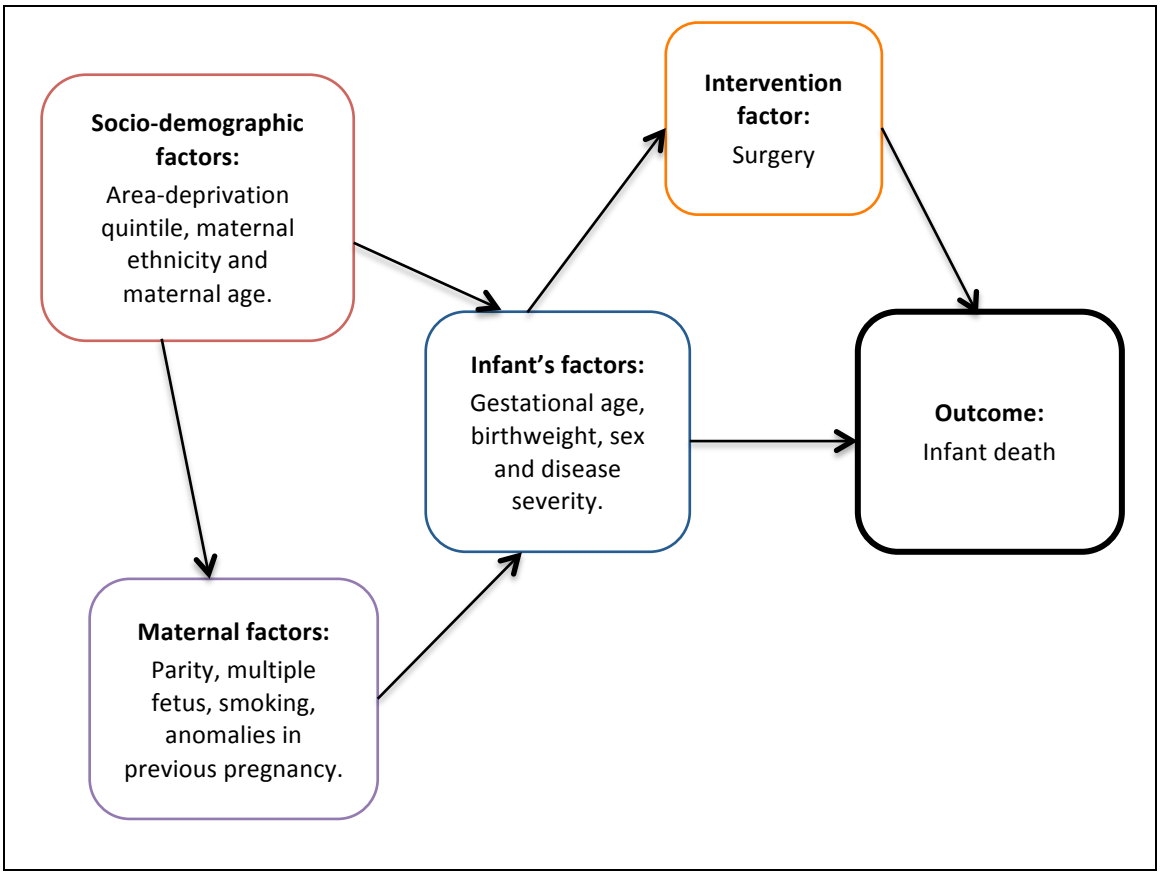
Collinearity testing using Pearson's correlation test and two-way scatterplot were performed for birthweight (in grams) and gestational age at birth (in weeks), which were shown to be strongly correlated with a correlation coefficient (r) > 0.7. Gestational age at birth is regarded as a better measure of fetal growth and development than birthweight, therefore only gestational age at birth was included in the multivariable analysis.

For objective 6d: To examine the risk factors contributing to death versus survival of infants with an anomaly.

Analytical strategy

The conduct of data analysis for objective 6d was based on the hypothesis that the risk of case fatality in an infant diagnosed with a congenital anomaly could be influenced by socio-demographic, maternal, infant and intervention factors (Figure 6.2). Therefore, these factors were explored in the analysis for mortality risk.

Figure 6.2: Chronological pathway between socio-demographic, maternal, infant and intervention factors used in this analysis, in relation to death of an infant born with a congenital anomaly.



Univariable analysis

Univariable logistic regression was performed to obtain the crude odds ratio with corresponding 95% CI and p-values for each explanatory variable comparing infants with congenital anomalies who survived (i.e. the comparator group) and those who died.

Multivariable analysis

Variables were considered to be included in the multivariable analysis if:

- They were variables identified *a priori* to be of interest based on a strong association with infant mortality from the literature (Table 6.1); or

- They were statistically significantly associated with mortality in the univariable analysis (i.e. p < 0.1 from LR test).

Since the number of variables which met these criteria for inclusion in the multivariable analyses in different anomaly subgroups was relatively small (between six and nine variables) and the number of observations for each variable was relatively large (Tables 6.14-6.17), a stepwise logistic regression approach was justified and the chance of finding a statistically significant result by chance was reduced (Mantel 1970). Multivariable analysis was conducted using a backward stepwise regression due to its advantages over forward stepwise regression of reducing the number of predictors, potential problems of multicollinearity and overfitting of variables in a model. In addition, starting with the full model, the backward stepwise approach has an advantage of considering the effects of all eligible variables simultaneously (Neter et al. 1996; Hocking 1976). The analysis was carried out as follows:

First, all *a priori* variables and significant variables from univariable analysis were fitted together in the same (full) model. Using the likelihood ratio test (LRT), variables were removed (or tested for removal) from the full model one at a time (variables with the largest p values i.e. least significant in the univariable analysis were tested first), and the effects of removing each variable were examined one by one. Variables with LRT $p < 0.05$ were retained in the model and carried forward until all variables in the full model had been removed and/or replaced. To check the robustness of the final model, the variables which had been removed (i.e. LRT $p \geq 0.05$) were individually put back to re-check that they remained non-significant in the final model. Finally, the LRT was performed in order to assess the independent effect (i.e. adjusted OR) for each variable in the final model. $P < 0.05$ was considered as statistically significant. All *a priori* variables were included in the final model.

6.3.8 Missing data

Most variables had very little missing data. However, significant proportions of missing data were observed for maternal ethnicity, maternal smoking, history of anomalies in previous pregnancies and surgery; the missing proportion ranged from 19.4% to 41.1% (Table 6.4).

Table 6.4: Variables with a substantial proportion of missing data.

Explanatory variables	Deaths, Frequency (%)	Alive one year, Frequency (%)
Maternal ethnicity	*n = 1,044*	*n = 28,355*
White	715 (68.5)	15,807 (55.7)
Other	89 (8.5)	902 (3.2)
Not known/ missing	240 (23.0)	11,646 (41.1)
Maternal smoking	*n = 1,044*	*n = 28,356*
Smoker	261 (25.0)	4,712 (16.6)
Non/ Ex smoker	541 (51.8)	12,110 (42.7)
Not known / missing	242 (23.2)	11,534 (40.7)
Anomalies in previous pregnancies	*n = 1,044*	*n = 28,356*
Yes	117 (11.2)	2,257 (8.0)
No	724 (69.3)	16,153 (57.0)
Not known / missing	203 (19.4)	9,946 (35.1)
Surgery	*n = 1,044*	*n = 29,380*
Performed (or expected) in the first year after birth	216 (20.7)	6,405 (21.8)
Not performed or required in the first year after birth	465 (44.5)	11,833 (40.3)
Not known/ missing	363 (34.8)	11,142 (37.9)

Statistical associations with missing data

In order to investigate the reason and pattern of missingness in maternal ethnicity, maternal smoking, history of anomalies in previous pregnancies and surgery variables, it was necessary to examine which variables (if any) were associated with (or predictive of) such missingness, regardless of the direction of their association. Therefore, logistic regression models were fitted, where the outcome variable was a binary indicator of whether data for maternal ethnicity, maternal smoking, history of anomalies in previous pregnancies and surgery were observed or missing.

The patterns of missingness are summarised in Appendix 6.1-6.4. The results suggest that the Townsend (socio-demographic) quintile, maternal age, gestational age, parity and year of CARIS registration were significantly associated with missingness of maternal ethnicity, maternal smoking and history of anomalies in previous pregnancies. In addition, year of CARIS registration was associated with missingness of information about surgery.

Since the missingness could be explained from other observed variables, there was strong evidence that the missing values in maternal ethnicity, maternal smoking, history of anomalies in previous pregnancies and surgery were not missing completely at random (MCAR). Therefore, the missingness could either be missing at random (MAR) or missing not at random (MNAR). As it is not possible to differentiate between MAR and MNAR using observed data or by statistical tests, it would be reasonable to assume that the missing data could be MAR (Sterne et al. 2009). In this case, analysis based on complete cases may be biased, which can be overcome by multiple imputation.

Other reasons for missing data

It was highly likely that poor record keeping at pregnancy booking e.g. due to lack of staff, and poor access to maternal medical notes e.g. when notes taken for outpatient clinics or other purposes were the main reasons for the missing data (having had a discussion with the CARIS manager). Increasing pressure on resources and prioritising clinical services within the NHS might explain the increasing missing proportions for all variables over the years between 1998 and 2016. In addition, the missing proportions of all variables were consistently lower among infants with a congenital anomaly who died, compared to those who survived. A likely explanation is that average surviving infants had relatively less severe types of anomalies, and might not require regular hospital admissions or outpatient follow-ups. Therefore, there were fewer opportunities to obtain socio-demographic and other maternal data for these babies with a mild form of anomalies.

With this information, the missing data were dealt with using the following strategies:

1. Variables with more than 50% of missing data were excluded from the analysis. For example, maternal body mass index (BMI) was poorly recorded in the CARIS dataset, nearly 70% missing data were observed because pregnant women were not often weighed in the past. Consanguinity and family history of congenital anomalies had more than 50% missing data, thought likely by the CARIS manager to be due to a combination of missing medical notes and pressure on prioritising clinical service. In addition, this information was not always voluntarily given by mothers at booking. This amount of missing data was too great to be addressed statistically.
2. For variables with a missing proportion of between 5% and 49%, the missing data were included in the main analysis with 'missing' as one of the categories for the variable (see also multiple imputation).
3. Complete case analysis was performed in the final model as a sensitivity analysis.
4. Multiple imputation (MI) was suitably performed for variables with high proportions of missing data (e.g. missing proportion between 15% and 50%), these included maternal smoking, history of anomalies in previous pregnancies, maternal ethnicity and infant surgery status where the missing data of these variables could be explained by some other observed variables. Analysis using imputed data was performed in the final model as a further sensitivity analysis.

Robustness and methods of using multiple imputation

Previous studies have shown that the proportion of missing data provides limited evidence about the bias and efficiency gain that can be achieved from MI, and hence should not solely be used to inform decisions as whether or not to perform MI (Clavel et al. 2014; Mishra and Khare 2014; Lee and Huber 2011). The robustness of using MI for large proportion of missing data (i.e. up to <50%) in this study objective was justified as previous simulation studies have shown that MI can reduce

bias and optimise efficiency of effect estimate even with large proportion of missing data, provided that the imputation model was appropriately specified and included all the observed variables which were significantly associated with the missingness, and the data were MAR (Madlet-Dowd et al. 2019).

Hence, MI was performed using chained equations (MICE) with fully conditional specification appropriate for the distributions of the affected variables to account for missing data simultaneously (Lee and Carlin 2010; Rezvan et al. 2015). In this analysis, Townsend quintile, maternal age, parity, gestational age, birthweight and year of CARIS registration were included in the logistic multivariable MICE as these explanatory variables were associated with missingness of at least one of the variables: maternal smoking, history of anomalies in previous pregnancies, maternal ethnicity and infant surgery status ($p < 0.05$) (Appendix 6.3-6.6).

The full conditional models and their outputs are shown in Appendix 6.7.

In order to assess the quality and validity of the imputed data derived from the MI model, the fraction of missing information (FMI) which is a parameter-specific measure to quantify the loss of information due to missing data and has been shown to be a better guide to the efficiency gain from MI than the proportion of missing data was estimated (Madlet-Dowd et al. 2019; White et al. 2011; Wagner 2010). The required number of imputations was therefore determined by the rule that the number of imputation ≥ 100 x FMI, which would provide an adequate reproducibility of MI analysis (StataCorp. 2013). It was estimated that the largest FMI was 0.292, and therefore the required number of imputations was 29 (= 100 x 0.292); and the relative increase in variance (RVI = 0.116) was non-significant. The number of imputations performed was 35, which exceeded the requirement described.

6.3.9 Further exploratory analyses

Two further exploratory analyses were performed with the following hypotheses:

Hypothesis 1:

That, there was an overall protective effect for death associated with 'Surgery performed in infancy, compared with 'Surgery not performed (included a minority of conditions which were too severe for surgery) in infancy'. However, it was hypothesised that this odds ratio was different between anomalies. Therefore, the odds ratio for surgery with 95% CI were estimated separately for each anomaly subgroup.

Hypothesis 2:

Although congenital anomalies were more prevalent in liveborn boys (58%) compared to girls (40%) in the CARIS cohort between 1998 and 2016, girls were shown to have an increased infant case fatality overall, compared to boys (See Results: Section 6.4.5 and Table 6.16). It was hypothesised that there was significant sex disparity in infant case fatality for certain subtypes of congenital anomalies. Therefore, the association between infant sex and infant case fatality was examined across different anomaly subgroups. The birth prevalence and mortality odds ratio for sex with 95% CI were estimated for different anomaly subgroups and subtypes particularly in lower and upper gastrointestinal (GI) anomalies, blood disorders and syndromes which have shown a significant sex disparity in the infant case fatality.

6.3.10 Interactions and sensitivity analyses

The models fitted assumed that there were no interactions between the risk factors explored. There was no strong evidence of plausible interactions in the literature, and the study had relatively low power to detect interactions. Therefore, the analysis focused on estimating main effects rather than interactions.

Three sensitivity analyses were performed as follows.

1. Probable cases excluded

The CARIS dataset includes confirmed and probable cases of congenital anomalies as discussed in Chapter 5: Overview of data source, Section 5.1.4. A sensitivity analysis was performed to exclude the probable cases, so that only confirmed cases were included in the analysis.

2. Complete case analysis

As discussed in Section 6.3.8, a sensitivity analysis was conducted to repeat the regression analyses for objective 6d using a complete case analysis in order to check the robustness of results.

3. Multiple imputation

Similarly, a further sensitivity analysis was performed for objective 6d using multiple imputation in order to check the robustness of results.

6.3.11 Statistical software

All statistical analyses were performed using Stata 13 statistical software (StataCorp. 2013).

6.4 Results

For study objective 6a:

6.4.1 Livebirth prevalence of congenital anomalies

A total of 632,945 livebirths were identified in Wales between 1998 and 2016, of which 30,424 were affected by one or more congenital anomalies; this represented a prevalence of 480 per 10,000 livebirths (Table 6.5). Among those affected, isolated anomalies were more prevalent (n = 20,008) occurring in 320 per 10,000 livebirths compared to multiple anomalies (n = 10,374) occurring in 160 per 10,000 livebirths. Overall, 83% (n = 16,510) of the livebirths with isolated anomalies were confirmed cases, and 73% (n = 7,583) of the livebirths with multiple anomalies were confirmed cases (Figure 6.3).

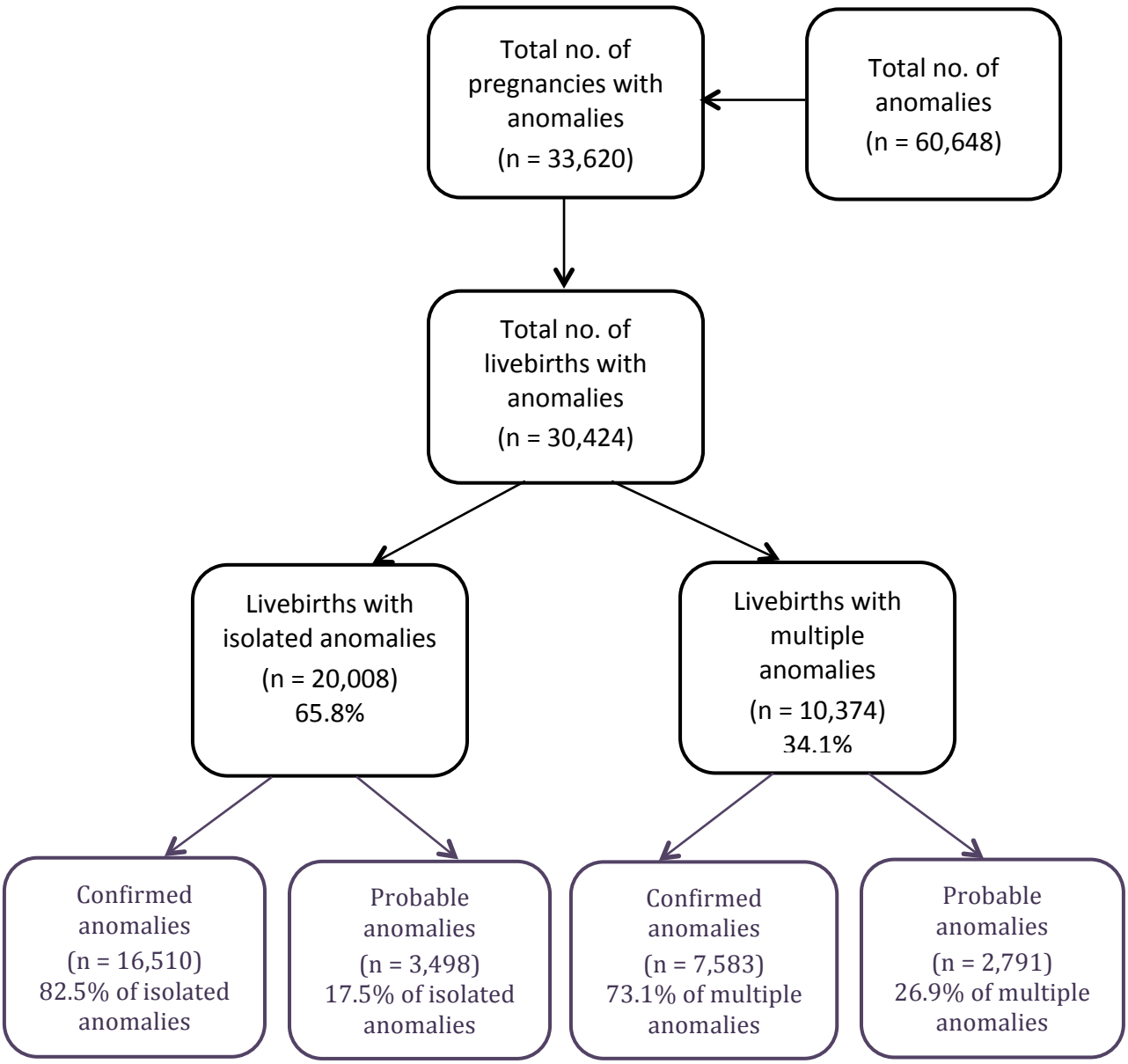
Among all the liveborn infants affected by isolated anomalies, anomalies of the genitourinary system has the highest prevalence of 70 per 10,000 livebirths, this was followed by anomalies of the cardiovascular system (50 per 10,000 livebirths), and anomalies of limbs and skeletal system (50 per 10,000 livebirths) (Table 6.5).

Table 6.5: Infant mortality rate by congenital anomaly subgroup in Wales (1998-2016 birth cohort)[1].

Anomaly subgroup[2]	Livebirths N = 632,945[3], (%)	Deaths (%) N = 3,443[4] (%)	Case fatality	IMR (per 10,000 livebirths)
Without an anomaly	60,2521 (95.2)	2,399 (69.7)	0.40%	37.9
All isolated and multiple anomalies	30,424 (4.8)	1,044 (30.3)	3.4%	16.5
All isolated anomalies	20,008 (3.2)	327 (9.5)	1.6%	5.17
All multiple anomalies	10,374 (1.6)	714 (20.7)	6.9%	11.28
Isolated anomaly subgroups				
Nervous system	609 (0.1)	38 (1.1)	6.2%	0.60
Eye, ear, face and neck	1,739 (0.3)	12 (0.4)	0.7%	0.19
Cardiovascular system	3,149 (0.5)	84 (2.4)	2.7%	1.33
Respiratory and clefts	1,017 (0.2)	29 (0.9)	2.9%	0.46
Abdominal wall defects and diaphragmatic hernias	353 (0.1)	29 (0.8)	8.2%	0.46
Upper and lower gastrointestinal	1,724 (0.3)	19 (0.6)	1.1%	0.30
Genitourinary	4,264 (0.7)	13 (0.4)	0.3%	0.21
Limb and skeletal	3,018 (0.5)	17 (0.5)	0.6%	0.27
Blood disorders	277 (0.04)	12 (0.4)	4.3%	0.19
Endocrine and Metabolic	947 (0.2)	18 (0.5)	1.9%	0.28
Neoplasm	444 (0.1)	12 (0.4)	2.7%	0.19
Syndromes and congenital malformation syndromes	1,122 (0.2)	19 (0.6)	1.7%	0.30
Maternal Infection leading to malformations	774 (0.1)	18 (0.5)	2.3%	0.28

[1]Confirmed and probable cases were included in the analysis. [2]Observations in the subgroup may not add up to the total as some of the categories are not shown due to small number (n < 5) or risk of statistical disclosure. [3]Total number of livebirths in Wales between 1998 and 2016 (ONS data) as the denominator. [4]Total number of deaths in Wales between 1998 and 2016 (ONS data) as the denominator.

Figure 6.3: Overview of anomaly status and categories in the CARIS dataset.



6.4.2 Infant mortality rates and case fatality

In the 1998-2016 birth cohort in Wales, there were 1,044 deaths of infants who were affected by either an isolated anomaly or multiple anomalies. This represented an IMR of 16.5 deaths per 10,000 livebirths and case fatality of 3.4% for infants with any anomaly (Table 6.5). Among these deaths, 327 infants had isolated anomalies representing an IMR of 5.17 deaths per 10,000 livebirths and case fatality of 1.6%; and 714 infants had multiple anomalies representing an IMR of 11.3 deaths per 10,000 livebirths and case fatality of 6.9%. In relation to the overall infant mortality, infants with an anomaly who died represented just less than one-third (30.3%) of all infant deaths (n = 3,443); about two-thirds (20.7%) of these deaths related to infants with multiple anomalies and one-third (9.5%) of these deaths related to infants with isolated anomalies (Table 6.5).

Among all the isolated anomaly subgroups, structural anomalies contributed the highest infant mortality. For example, cardiovascular anomalies were associated with the largest number of infant deaths (n = 84), representing an IMR of 1.33 deaths per 10,000 livebirths and case fatality of 2.7%. This was followed by nervous system anomalies (n = 38), representing an IMR of 0.60 deaths per 10,000 livebirths and case fatality of 6.2%. Abdominal wall defects (i.e. exomphalos and gastroschisis) and congenital diaphragmatic hernias had the highest case fatality at 8.2% (Table 6.5).

In addition, infants born with an anomaly had a higher fatality in infancy (3.4%) compared to infants without an anomaly (0.4%) (Table 6.5).

For study objective 6b:

6.4.3 Contributing and underlying causes of deaths

Of all the deaths of infants affected by congenital anomalies in the 1998-2016 birth cohort in Wales, 40.7% (n = 425) of deaths occurred within the neonatal period and 59.3% of deaths (n = 619) occurred within the post-neonatal period (Tables 6.6).

Congenital anomalies were the main recorded cause of death for infants with anomalies who died (Table 6.6-6.10), contributing more than half of the main conditions or diseases contributing to death of neonates, and underlying causes of death of post-neonates affected by congenital anomalies (Tables 6.6). In addition, immaturity-related conditions, and asphyxia, anoxia or trauma represented over a quarter of main conditions contributing to deaths of babies affected by congenital anomalies who died in the neonatal period. Late infections contributed 8.6% of the underlying cause of death of babies affected by congenital anomalies who died in the post-neonatal period (Table 6.6).

Subgroup analysis of isolated anomalies demonstrated that the underlying causes of post-neonatal death of babies affected by an isolated anomaly were often related to the anomaly or its complications (Tables 6.8 and 6.10). For example, post-neonatal infants with isolated anomalies of the nervous, cardiovascular, gastrointestinal system or chromosomal defects who died frequently died from the anomalies themselves or their complications.

Table 6.6: Neonatal and post-neonatal causes of death in infants affected by all (isolated and multiple) congenital anomalies.

Causes of death classification	Frequency n[1] (%)	
	Main condition or disease contributing to death of neonates with anomalies[2], n = 425	Underlying cause of death of post-neonatal infants with anomalies[2], n= 619
1. Congenital anomalies	216 (50.8)	346 (55.9)
3. Immaturity related conditions	95 (22.4)	26 (4.2)
4. Asphyxia, anoxia, or trauma	17 (4.0)	5 (0.8)
5. External conditions	19 (4.5)	20 (3.2)
6. Infections	8 (1.9)	53 (8.6)
7. Other specific conditions	10 (2.4)	40 (6.5)
9. Sudden infant deaths	6 (1.4)	32 (5.2)

[1]Observations in categories may not add up to the total, as some of the categories are not shown due to small number or risk of statistical disclosure. [2]The first coded cause of death recorded in the CARIS/ONS dataset was used in this analysis.

Table 6.7: Distribution of the main condition or disease contributing to death of neonates stratified by isolated congenital anomalies subgroups (ONS cause (of death) group hierarchical classification).

Neonatal ONS causes of death *(Main condition or disease contributing to death of neonates)*[1]	**Isolated congenital anomalies subgroups**					
	Nervous system (n = 12)	**Cardiovascular (n = 44)**	**Respiratory and clefts (n = 22)**	**Abdominal wall defects/ congenital diaphragmatic hernias (n = 20)**	**Maternal infections leading to malformations (n = 13)**	**Limb (n = 5)**
Before the onset of labour						
1. Congenital anomalies	1st	1st	2nd	1st		
2. Antepartum infections						
3. Immaturity related conditions	2nd	2nd	1st	2nd	1st	1st
In or shortly after labour						
4. Asphyxia, anoxia, or trauma		3rd				
Postnatal						
5. External conditions						
6. Infections						
7. Other specific conditions						
9. Sudden infant deaths			3rd			
Unclassified						
0. Other conditions		2nd		2nd		

[1]The first coded cause of death recorded in the CARIS/ONS dataset was used in this analysis. Note: Up to the first three commonest causes of death are shown where statistical disclosure allows. 1st = most common cause of death, 2nd = second most common cause of death and so on. Empty cell = No death or small number of death are not shown due to risk of statistical disclosure.

Table 6.8: Distribution of the coded post-neonatal underlying causes of deaths stratified by isolated congenital anomalies subgroups (ONS cause (of death) group hierarchical classification).

Post-neonatal ONS underlying causes of death[1]	Isolated congenital anomalies subgroups						
	Nervous system (n = 26)	Eye, ear, face and neck (n = 11)	Cardio-vascular (n = 40)	Respiratory (n = 7)	Abdominal (n = 9)	Upper and lower GI (n = 13)	Genitourinary (n = 8)
1. Congenital anomalies	1st	1st	1st		1st	1st	
2. Antepartum infections							
3. Immaturity related conditions			2nd				1st
4. Asphyxia, anoxia, or trauma							
5. External conditions		2nd		1st			
6. Infections	3rd		3rd				
7. Other specific conditions							
9. Sudden infant deaths							
0. Other conditions	2nd		2nd			1st	

[1]The first coded cause of death recorded in the CARIS/ONS dataset was used in this analysis. Note: Up to the first three commonest causes of death are shown where statistical disclosure allows. 1st = most common cause of death, 2nd = second most common cause of death and so on. Empty cell = No death or small number of death are not shown due to risk of statistical disclosure.

Table 6.8 (continued): Distribution of the coded post-neonatal underlying causes of deaths stratified by isolated congenital anomalies subgroups (ONS cause (of death) group hierarchical classification).

Post-neonatal ONS underlying causes of death[1]	Isolated congenital anomalies subgroups					
	Limb and skeletal (n = 12)	Blood disorders (n = 10)	Endocrine and metabolic (n = 15)	Neoplasm (n = 11)	Syndromes and congenital malformation syndromes (n = 15)	Maternal infections leading to malformations (n = 5)
1. Congenital anomalies			1st		1st	
2. Antepartum infections						
3. Immaturity related conditions						
4. Asphyxia, anoxia, or trauma						
5. External conditions						
6. Infections			2nd			
7. Other specific conditions	1st	1st		1st		
9. Sudden infant deaths					2nd	
0. Other conditions						1st

[1]The first coded cause of death recorded in the CARIS/ONS dataset was used in this analysis. Note: Up to the first three commonest causes of death are shown where statistical disclosure allows. 1st = most common cause of death, 2nd = second most common cause of death and so on. Empty cell = No death or small number of death are not shown due to risk of statistical disclosure.

Table 6.9: Distribution of the coded post-neonatal underlying causes of deaths of infant affected by all (isolated and multiple) congenital anomalies by ICD9/10 chapter headings.

Post-neonatal underlying cause of death[1], n = 619	Frequency n (%)
Certain infectious and parasitic diseases	22 (3.6)
Neoplasms	38 (6.1)
Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	
Endocrine, nutritional and metabolic diseases	35 (5.7)
Diseases of the nervous system	87 (14.1)
Diseases of the circulatory system	22 (3.6)
Diseases of the respiratory system	50 (8.1)
Diseases of the digestive system	17 (2.8)
Diseases of the skin and subcutaneous system	
Diseases of the musculoskeletal system and connective tissue	
Diseases of the genitourinary system	
Certain conditions originating in the perinatal period	38 (6.1)
Congenital malformations, deformations and chromosomal abnormalities	243 (39.3)
Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	
External causes of morbidity and mortality	20 (3.2)

[1]The first coded cause of death recorded in the CARIS/ONS dataset was used in this analysis. Note: Empty cell = n < 10 or risk of statistical disclosure are not shown.

Table 6.10: Distribution of the coded post-neonatal underlying causes of deaths stratified by isolated congenital anomalies subgroups (Causes of death classification using ICD-10 chapters heading).

Post-neonatal underlying causes of death by ICD chapter headings[1]	Isolated congenital anomalies subgroups					
	Nervous system (n = 26)	Eye, ear, face and neck (n = 11)	Cardiovascular (n = 40)	Respiratory (n = 7)	Abdominal wall defects/ congenital diaphragmatic hernias (n = 9)	Upper and lower GI (n = 13)
Infectious and parasitic diseases						
Neoplasms						
Diseases of blood and immune systems						
Endocrine, nutritional and metabolic diseases						
Diseases of the nervous system	1st	1st				
Diseases of the circulatory system			2nd			
Diseases of the respiratory system						
Diseases of the digestive system						
Diseases of the genitourinary system						
Conditions originating from perinatal period			3rd			1st
Congenital malformations, deformation and chromosomal abnormalities	2nd		1st		1st	1st
Abnormal symptoms, signs or lab findings						
External causes		2nd		1st		

[1]The first coded cause of death recorded in the CARIS/ONS dataset was used in this analysis. Note: Up to the first three commonest causes of death are shown where statistical disclosure allows. 1st = most common cause of death, 2nd = second most common cause of death and so on. Empty cell = No death or small number of death are not shown due to risk of statistical disclosure.

Table 6.10 (continued): Distribution of the coded post-neonatal underlying causes of deaths stratified by isolated congenital anomalies subgroups (Causes of death classification using ICD-10 chapters heading).

Post-neonatal underlying causes of death by ICD chapter headings[1]	Isolated congenital anomalies subgroups						
	Genitourinary (n = 8)	Limb and skeletal (n = 12)	Blood disorders (n = 10)	Endocrine and metabolic (n = 15)	Neoplasm (n = 11)	Syndromes and congenital malformation syndromes (n = 15)	Maternal infections leading to malformation (n = 5)
Infectious and parasitic diseases							
Neoplasms			1st		1st		
Diseases of blood and immune systems							
Endocrine, nutritional and metabolic diseases				1st			
Diseases of the nervous system				2nd			
Diseases of the circulatory system							
Diseases of the respiratory system							
Diseases of the digestive system							1st
Diseases of the genitourinary system							
Conditions originating from perinatal period	1st	1st					
Congenital malformations, deformation and chromosomal abnormalities		1st				1st	
Abnormal symptoms, signs or lab findings						2nd	
External causes							

[1]The first coded cause of death recorded in the CARIS/ONS dataset was used in this analysis. 1st = most common cause of death, 2nd = second most common cause of death and so on. Empty cell = No death or small number of death are not shown due to risk of statistical disclosure.

Postmortem was performed in about one in ten (110/1,044, 10.5%) infants with congenital anomalies who died (Table 6.11). Only eight percent (44/562) of infants with congenital anomalies who died and had 'Congenital anomalies' as the coded cause of death had a post-mortem, 16.5% (20/121) of infants with congenital anomalies who died and had 'Immaturity related conditions' as the coded cause of death had a post-mortem, 30% (15/50) of infants with congenital anomalies who died and had 'Other specific conditions' as the coded cause of death had a post-mortem, and 28.9% (11/38) of infants with congenital anomalies who died and had 'Sudden infant deaths' as coded cause of death had a post-mortem. A relatively small number of postmortem was recorded for infants with congenital anomalies who died and had 'Asphyxia, anoxia, or trauma', 'External conditions' and 'Infections' as the coded causes of death.

Table 6.11: Postmortem of infants with congenital anomalies who died.

Causes of death classification	Frequency n[1]	
	Cause of death of infants with anomalies, n = 1,044	Postmortem, n = 110
1. Congenital anomalies	562	44
3. Immaturity related conditions	121	20
4. Asphyxia, anoxia, or trauma	22	
5. External conditions	39	
6. Infections	61	
7. Other specific conditions	50	15
9. Sudden infant deaths	38	11

[1]Observations in categories may not add up to the total, as some of the categories are not shown due to small number or risk of statistical disclosure. Empty cell = small number are not shown due to risk of statistical disclosure.

For study objectives 6c and 6d

6.4.4 Univariable analysis

The univariable results are shown first for all anomalies, and then for all isolated, all multiple and finally cardiovascular anomalies.

All (isolated and multiple) anomalies

The unadjusted odds ratio (uOR) for infant case fatality generally increased with increasing deprivation; uOR = 1.55 (95% CI: 1.26-1.92) comparing the most to the least deprived (Table 6.12). For maternal ethnicity, the majority of mothers in the study population were White (94.3%) versus non-White (5.7%); infants born to mothers of non-White ethnicity had a significantly increased odds of infant case fatality, compared to infants born to mothers of White ethnicity (uOR = 2.18, 95% CI: 1.73-2.75). In addition, infants had a significantly increased odds of case fatality if their mothers were parous (uOR = 1.24, 95% CI: 1.09-1.41), smokers (uOR = 1.24, 95% CI: 1.07-1.44) and if they were born as multiples (uOR = 2.48, 95% CI: 2.03-3.04). Babies who died were born on average two weeks earlier and with a birthweight 775g lighter than babies who survived in infancy. A statistically significant odds of case fatality was found for infants who were born preterm ($<37^{+0}$ week) (uOR = 4.53, 95% CI: 4.00-5.14) or with a low birthweight (<2500g) (uOR = 5.49, 95% CI: 4.84-6.22). Subgroup analysis of gestational age showed that the odds of case fatality increased as gestational age at birth decreased. Infants who were born extremely preterm ($\geq 22^{+0}$ to $< 28^{+0}$) had a 13 fold increased odds of case fatality (uOR = 13.2, 95% CI: 10.4-16.8) compared to infants who were born at term. Boys had a higher birth prevalence of congenital anomalies overall compared to girls; however, girls with an anomaly had a significantly increased odds of infant case fatality compared with boys (uOR = 1.29, 95% CI: 1.14-1.46). Infants with an anomaly who required surgery before their first birthday had a decreased uOR, compared to infants who did not require surgery (including a minority of conditions which were too severe for surgery) during infancy (uOR = 0.86, 95% CI: 0.73-1.01). Maternal age at birth was

not statistically associated with infant case fatality (p = 0.228), and therefore was not included in the multivariable logistic regression analysis.

Table 6.12: Comparison of maternal and infant variables between babies who died and survivors with any anomaly (isolated or multiple): Univariable analysis.

	Deaths, Frequency (%)	Alive one year, Frequency (%)	Unadjusted OR (95% CI)	P-value[1]
Socio-demographic factor				
Townsend quintile[2]	*n = 1,041*[3]	*n = 28,355*		
1 (least deprived)	122 (11.7)	4,564 (16.1)	1 (reference)	<0.001
2	160 (15.3)	4,594 (16.2)	1.30 (1.03-1.65)	
3	207 (19.9)	5,361 (18.9)	1.44 (1.15-1.81)	
4	225 (21.6)	5,861 (20.7)	1.44 (1.15-1.80)	
5 (most deprived)	327 (31.4)	7,886 (27.8)	1.55 (1.26-1.92)	
Maternal ethnicity	*n = 1,044*	*n = 28,355*		
White	715 (68.5)	15,807 (55.7)	1 (reference)	<0.001
Other	89 (8.5)	902 (3.2)	2.18 (1.73-2.75)	
Not known/ missing	240 (23.0)	11,646 (41.1)	0.46 (0.39-0.53)	
Maternal age at birth, years *(n = 29,400)*	*n = 1,044*	*n = 28,356*		
Mean +/- SD (year)	*28.3 +/- 6.5*	*28.2 +/- 6.2*		
≤ 24	318 (30.5)	8,514 (30.0)	1.02 (0.86-1.20)	0.228
25 – 29	288 (27.6)	7,835 (27.6)	1 (reference)	
30 – 34	239 (22.9)	7,129 (25.1)	0.91 (0.77-1.09)	
≥ 35	199 (19.1)	4,849 (17.1)	1.12 (0.93-1.34)	
Not known/ missing[2]	0 (0)	29 (0.1)		
Maternal factors				
Parity	*n = 1,044*	*n = 28,356*		
Nulliparous	385 (36.9)	11,115 (39.2)	1 (reference)	<0.001
≥ 1	606 (58.0)	14,116 (49.8)	1.24 (1.09-1.41)	
Not known/ missing	53 (5.1)	3,125 (11.0)	0.49 (0.37-0.65)	
Multiple fetus	*n = 1,044*	*n = 28,356*		
Yes	114 (10.9)	1,334 (4.7)	2.48 (2.03-3.04)	<0.001
No	930 (89.1)	27,022 (95.3)	1 (reference)	
Not known / missing	0 (0)	0 (0)		
Maternal smoking	*n = 1,044*	*n = 28,356*		
Smoker	261 (25.0)	4,712 (16.6)	1.24 (1.07-1.44)	<0.001
Non/ Ex smoker	541 (51.8)	12,110 (42.7)	1 (reference)	
Not known / missing	242 (23.2)	11,534 (40.7)	0.47 (0.40-0.55)	
Anomalies in previous pregnancies	*n = 1,044*	*n = 28,356*		
Yes	117 (11.2)	2,257 (8.0)	1.16 (0.95-1.41)	<0.001
No	724 (69.3)	16,153 (57.0)	1 (reference)	
Not known / missing	203 (19.4)	9,946 (35.1)	0.46 (0.39-0.53)	

Table 6.12 (continued): Comparison of maternal and infant variables between babies who died and survivors with any anomaly (isolated or multiple): Univariable analysis.

	Deaths, Frequency (%)	Alive one year, Frequency (%)	Unadjusted OR (95% CI)	P-value[1]
Infant factors				
Infant sex[2]	*n = 1,040*[3]	*n = 29,379*		
Male	566 (54.4)	17,810 (60.6)	1 (reference)	<0.001
Female	474 (45.6)	11,550 (39.3)	1.29 (1.14-1.46)	
Birthweight, grams[4]	*n = 1,044*	*n = 29,380*		
Median (IQR)	*2475 (1650-3150)*	*3250 (2780-3650)*		
< 2500 (low birthweight)	529 (50.7)	4,505 (15.3)	5.49 (4.84-6.22)	<0.001
≥ 2500	510 (48.9)	23,835 (81.1)	1 (reference)	
Not known/ missing	5 (0.5)	1,040 (3.5)	-	
Gestational age[2,4,5]**, week**	*n = 1,042*[3]	*n = 29,380*		
Median (IQR)	*37 (32-39)*	*39 (38-40)*		<0.001
< 37^{+0} (preterm)	480 (46.1)	4,510 (15.4)	4.53 (4.00-5.14)	
≥22^{+0} to < 28^{+0}	*102 (9.8)*	*328 (1.1)*	*13.2 (10.4-16.8)*	
≥ 28^{+0} to < 32^{+0}	*133 (12.8)*	*806 (2.7)*	*7.0 (5.7-8.6)*	
≥ 32^{+0} to < 37^{+0}	*245 (23.5)*	*3,376 (11.5)*	*3.1 (2.6-3.6)*	
≥ 37^{+0} (term)	562 (53.9)	23,935 (81.5)	1 (reference)	
Intervention factors				
Surgery	*n = 1,044*	*n = 29,380*		
Performed in the first year after birth	216 (20.7)	6,405 (21.8)	0.86 (0.73-1.01)	0.021
Not performed in the first year after birth[6]	465 (44.5)	11,833 (40.3)	1 (reference)	
Not known/ missing	363 (34.8)	11,142 (37.9)	0.83 (0.72-0.95)	

[1]P-value < 0.1 (from the LR test) was considered as statistically significant. [2]Missing categories for Townsend quintile, maternal age, infant sex, birthweight and gestational age were not included in the regression analysis due to their small proportion of missing values (< 5%). [3]Obervations with small number or risk of statistical disclosure were not included. [4]Birthweight and gestational age at birth were strongly correlated (Pearson's collinearity test: r = 0.7490, p < 0.001). [5]Gestational age was included as a binary variable in the analyses based on clinical relevance, test of departure from linearity is not significant (p = 0.836) in the final model. [6]Including a minority of conditions which were too severe for surgery. Note: Categories with observations n < 5 are not shown due to risk of statistical disclosure. Confirmed and probable cases were included in the analysis.

All isolated anomalies

Table 6.13 shows the results of the univariable analysis of the characteristics of babies who died and survivors for all isolated anomalies.

Infants born to mothers of non-White ethnicity had a significantly increased odds of infant case fatality, compared to infants born to mothers of White ethnicity (uOR = 1.77, 95% CI: 1.11-2.82). Infants had a significantly increased odds of case fatality in infancy if their mothers were parous (uOR = 1.48, 95% CI: 1.16-1.89), smokers (uOR = 1.52, 95% CI: 1.15-2.01) and they were born as multiples (uOR = 2.57, 95% CI: 1.80-3.65). A statistically significant odds of infant case fatality was shown among infants who were born preterm (uOR = 4.72, 95% CI: 3.78-5.90) and with a low birthweight (uOR = 5.32, 95% CI: 4.26-6.64). Area-based deprivation, maternal age at birth, and infant surgery status were not statistically significantly associated with infant case fatality, therefore they were not included in the multivariable logistic regression analysis.

Table 6.13: Comparison of maternal and infant variables between deaths and survivors of infants with an isolated anomaly: Univariable analysis.

	Deaths, Frequency (%)	Alive one year, Frequency (%)	Unadjusted OR (95% CI)	P-value[1]
Socio-demographic factor				
Townsend quintile	*n = 327*	*n = 18,919*		
1 (least deprived)	41 (12.5)	3,076 (16.3)	1 (reference)	0.340
2	54 (16.5)	3,126 (16.5)	1.30 (0.86-1.95)	
3	61 (18.7)	3,601 (19.0)	1.27 (0.85-1.89)	
4	69 (21.1)	3,821 (20.2)	1.35 (0.92-2.00)	
5 (most deprived)	102 (31.2)	5,232 (27.7)	1.46 (1.02-2.11)	
Not known/ missing[2]	0 (0)	63 (0.3)	-	
Maternal ethnicity	*n = 327*	*n = 18,919*		
White	198 (60.6)	9,540 (50.4)	1 (reference)	<0.001
Other	20 (6.1)	545 (2.9)	1.77 (1.11-2.82)	
Not known/ missing	109 (33.3)	8,834 (46.7)	0.59 (0.47-0.75)	
Maternal age at birth, years *(n = 19,247)*	*n = 327*	*n = 18,920*		
≤ 24	108 (33.0)	5,656 (29.9)	1.04 (0.79-1.37)	0.245
25 – 29	98 (30.0)	5,318 (28.1)	1 (reference)	
30 – 34	68 (20.8)	4,783 (25.3)	0.77 (0.56-1.05)	
≥ 35	53 (16.2)	3,136 (16.6)	0.92 (0.65-1.28)	
Not known/ missing[2]	0 (0)	27 (0.1)	-	
Maternal factors				
Parity	*n = 327*	*n = 18,920*		
Nulliparous	101 (30.9)	7,202 (38.1)	1 (reference)	0.002
≥ 1	192 (58.7)	9,258 (48.9)	1.48 (1.16-1.89)	
Not known/ missing	34 (10.4)	2,460 (13.0)	0.99 (0.67-1.46)	
Multiple fetus	*n = 327*	*n = 18,920*		
Yes	36 (11.0)	870 (4.6)	2.57 (1.80-3.65)	<0.001
No	291 (89.0)	18,050 (95.4)	1 (reference)	
Not known / missing	0 (0)	0 (0)	-	
Maternal smoking	*n = 327*	*n = 18,920*		
Smoker	79 (24.2)	2,763 (14.6)	1.52 (1.15-2.01)	<0.001
Non/ Ex smoker	138 (42.2)	7,337 (38.8)	1 (reference)	
Not known / missing	110 (33.6)	8,820 (46.6)	0.66 (0.52-0.85)	
Anomalies in previous pregnancies	*n = 327*	*n = 18,920*		
Yes	35 (10.7)	1,464 (7.7)	1.24 (0.86-1.79)	0.002
No	187 (57.1)	9,694 (51.2)	1 (reference)	
Not known / missing	105 (32.1)	7,762 (41.0)	0.70 (0.55-0.89)	

Table 6.13 (continued): Comparison of maternal and infant variables between deaths and survivors of infants with an isolated anomaly: Univariable analysis.

	Deaths, Frequency (%)	Alive one year, Frequency (%)	Unadjusted OR (95% CI)	P-value
Infant factors				
Infant sex	*n = 325*	*n = 19,681*		
Male	194 (59.7)	12,106 (61.5)	1 (reference)	0.496
Female	131 (40.3)	7,562 (38.4)	1.08 (0.86-1.35)	
Not known/ missing[2]	0 (0)	13 (0.1)	-	
Birthweight, grams[2,4]	*n = 325*[3]	*n = 19,681*		
< 2500 (low birthweight)	150 (46.2)	2,618 (13.3)	5.32 (4.26-6.64)	<0.001
≥ 2500	175 (53.8)	16,251 (82.6)	1 (reference)	
Gestational age[2,4,5]**, week**	*n = 326*[3]	*n = 19,681*		
$< 37^{+0}$ (preterm)	144 (44.2)	2,719 (13.8)	4.72 (3.78-5.90)	<0.001
$\geq 37^{+0}$ (term)	182 (55.8)	16,220 (82.4)	1 (reference)	
Intervention factor				
Surgery	*n = 327*	*n = 19,681*		
Performed in the first year after birth	53 (16.2)	3,711 (18.9)	0.80 (0.58-1.10)	0.377
Not performed in the first year after birth[6]	147 (45.0)	8,254 (41.9)	1 (reference)	
Not known/ missing	127 (38.8)	7,716 (39.2)	0.92 (0.73-1.17)	

[1]P-value < 0.1 (from the LR test) was considered as statistically significant. [2]Missing categories for Townsend quintile, maternal age, infant sex, birthweight and gestational age were not included in the regression analysis due to their small proportion of missing values (< 5%). [3]Obervations with small number or risk of statistical disclosure were not included. [4]Birthweight and gestational age at birth were strongly correlated (Pearson's collinearity test: r = 0.7474, p < 0.001 to 3 decimal places). [5]Gestational age was included as a binary variable in the analyses based on clinical relevance; test of departure from linearity was significant (p = 0.001) in the final model. [6]Including a minority of conditions which were too severe for surgery. Note: Categories with observations n < 5 are not shown due to risk of statistical disclosure. Confirmed and probable cases were included in the analysis.

All multiple anomalies

Table 6.14 shows the results of univariable analysis of the characteristics of babies who died and survivors for multiple anomalies.

The uOR of infant case fatality significantly increased as deprivation increased. For example, the uOR of infant case fatality among infants in the most deprived quintile was 1.56 (95% CI: 1.20-2.02) compared to infants in the most affluent quintile. Infants born to mothers of non-White ethnicity had a significantly increased odds of infant case fatality, compared to infants born to mothers of White ethnicity (uOR = 2.34, 95% CI: 1.78-3.08). Infants had a significantly increased case fatality in infancy if their mothers were parous (uOR = 1.18, 95% CI: 1.01-1.39) and they were born as multiples (uOR = 2.35, 95% CI: 1.83-3.04). Significant odds of infant case fatality were found among infants who were born preterm (uOR = 3.84, 95% CI: 3.29-4.49), with a low birthweight (uOR = 4.54, 95% CI: 3.88-5.30), and of female sex (uOR = 1.33, 95% CI: 1.14-1.55). Infants with multiple anomalies who required surgery before their first birthday had a significantly reduced case fatality, compared to infants who did not require surgery (uOR = 0.68, 95% CI: 0.56-0.82). Maternal age at birth was not statistically associated infant mortality (p = 0.533), therefore it was not included in the multivariable logistic regression analysis.

Table 6.14: Comparison of maternal and infant variables between deaths and survivors of infants with multiple anomalies: Univariable analysis.

	Deaths, Frequency (%)	Alive one year, Frequency (%)	Unadjusted OR (95% CI)	P-value[1]
Socio-demographic factor				
Townsend quintile[2]	*n = 711*[3]	*n = 9,397*		
1 (least deprived)	79 (11.1)	1,489 (15.8)	1 (reference)	0.012
2	104 (14.6)	1,466 (15.6)	1.29 (0.96-1.73)	
3	144 (20.2)	1,761 (18.7)	1.48 (1.12-1.96)	
4	158 (22.1)	2,016 (21.4)	1.37 (1.04-1.80)	
5 (most deprived)	226 (31.8)	2,640 (28.1)	1.56 (1.20-2.02)	
Maternal ethnicity	*n = 714*	*n = 9,397*		
White	516 (72.3)	6,242 (66.4)	1 (reference)	<0.001
Other	69 (9.7)	356 (3.8)	2.34 (1.78-3.08)	
Not known/ missing	129 (18.1)	2,799 (29.8)	0.56 (0.46-0.68)	
Maternal age at birth[2]**, years**	*n = 714*	*n = 9,395*[3]		
≤ 24	209 (29.3)	2,850 (30.3)	0.97 (0.79-1.19)	0.533
25 – 29	190 (26.6)	2,507 (26.7)	1 (reference)	
30 – 34	170 (23.8)	2,334 (24.8)	0.96 (0.78-1.19)	
≥ 35	145 (20.3)	1,704 (18.1)	1.12 (0.90-1.41)	
Maternal factors				
Parity	*n = 714*	*n = 9,397*		
Nulliparous	282 (39.5)	3,900 (41.5)	1 (reference)	<0.001
≥ 1	414 (58.0)	4,833 (51.4)	1.18 (1.01-1.39)	
Not known/ missing	18 (2.5)	664 (7.1)	0.37 (0.23-0.61)	
Multiple fetus	*n = 714*	*n = 9,397*		
Yes	77 (10.8)	459 (4.9)	2.35 (1.83-3.04)	<0.001
No	637 (89.2)	8,938 (95.1)	1 (reference)	
Not known / missing	0 (0)	0 (0)		
Maternal smoking	*n = 714*	*n = 9,397*		
Smoker	182 (25.5)	1,939 (20.6)	1.11 (0.92-1.33)	<0.001
Non/ Ex smoker	402 (56.3)	4,754 (50.6)	1 (reference)	
Not known / missing	130 (18.2)	2,704 (28.8)	0.57 (0.46-0.70)	
Anomalies in previous pregnancies	*n = 714*	*n = 9,397*		
Yes	82 (11.5)	788 (8.4)	1.25 (0.98-1.59)	<0.001
No	536 (75.1)	6,435 (68.5)	1 (reference)	
Not known / missing	96 (13.4)	2,174 (23.1)	0.53 (0.42-0.66)	

Table 6.14 (continued): Comparison of maternal and infant variables between deaths and survivors of infants with multiple anomalies: Univariable analysis.

	Deaths, Frequency (%)	Alive one year, Frequency (%)	Unadjusted OR (95% CI)	P-value
Infant factors				
Infant sex[2,4]	*n = 712*[3]	*n = 9,659*		
Male	369 (51.8)	5,683 (58.8)	1 (reference)	<0.001
Female	343 (48.2)	3,970 (41.1)	1.33 (1.14-1.55)	
Birthweight[2,5]**, grams**	*n = 711*[3]	*n = 9,659*		
< 2500 (low birthweight)	377 (53.0)	1,879 (19.5)	4.54 (3.88-5.30)	<0.001
≥ 2500	334 (47.0)	7,554 (78.2)	1 (reference)	
Gestational age[2,5,6]**, week**	*n = 713*[3]	*n = 9,659*		<0.001
< 37^{+0} (preterm)	336 (47.1)	1,782 (18.4)	3.84 (3.29-4.49)	
≥ 37^{+0} (term)	377 (52.9)	7,685 (79.6)	1 (reference)	
Intervention factor				
Surgery	*n = 714*	*n = 9,660*		
Performed in the first year after birth	163 (22.8)	2,689 (27.8)	0.68 (0.56-0.82)	<0.001
Not performed in the first year after birth[7]	318 (44.5)	3,414 (35.3)	1 (reference)	
Not known/ missing	233 (32.6)	3,557 (36.8)	0.76 (0.64-0.91)	

[1]P-value < 0.1 (from the LR test) was considered as statistically significant. [2]Missing categories for Townsend quintile, maternal age, infant sex, birthweight and gestational age were not included in the regression analysis due to their small proportion of missing values (< 5%). [3]Obervations with small number or risk of statistical disclosure were not included. [4]Indeterminate sex category was not included in the regression analysis due to its small number. [5]Birthweight and gestational age at birth were strongly correlated (Pearson's collinearity test: r = 0.7447, p < 0.0001). [6]Gestational age was included as a binary variable in the analyses based on clinical relevance; test of departure from linearity is not significant (p = 0.265) in the final model. [7]Including a minority of conditions which were too severe for surgery. Note: Categories with observations n < 5 are not shown due to risk of statistical disclosure. Confirmed and probable cases were included in the analysis.

Cardiovascular anomalies

Table 6.15 shows the results of univariable analysis of the characteristics of babies who died and survivors for cardiovascular anomalies.

Infants had a significantly increased odds if their mothers were active smokers during pregnancy (uOR = 1.91, 95% CI: 1.12-3.25), they were born preterm (uOR = 2.76, 95% CI: 1.75-4.35), and with a low birthweight (uOR = 3.34, 95% CI: 2.13-5.23). The uOR of infant case fatality significantly increased as severity of CHDs increased. Infants with the most severe types of CHDs had an infant case fatality which was 90.7 times greater (95% CI: 43.4-189), compared to infants with the least severe types of CHDs. Infants with a cardiovascular anomaly who required surgery before their first birthday had a significantly increased case fatality, compared to infants who did not require surgery (uOR = 2.93, 95% CI: 1.66-5.17). Deprivation, maternal age at birth, parity, multiple fetus, history of anomalies in previous pregnancies and infant sex were not statistically associated mortality of infants affected by cardiovascular anomalies, therefore they were not included in the multivariable logistic regression analysis.

Table 6.15: Comparison of maternal and infant variables between deaths and survivors of infants with a congenital heart defect, circulatory or peripheral vascular anomaly: Univariable analysis.

	Deaths, Frequency (%)	Alive one year, Frequency (%)	Unadjusted OR (95% CI)	P-value[1]
Socio-demographic factor				
Townsend quintile	*n = 84*	*n = 2,985*		
1 (least deprived)	12 (14.3)	515 (17.3)	1 (reference)	0.550
2	18 (21.4)	458 (15.3)	1.61 (0.76-3.41)	
3	16 (19.0)	547 (18.3)	1.25 (0.59-2.66)	
4	12 (14.3)	614 (20.6)	0.91 (0.41-2.01)	
5 (most deprived)	26 (31.0)	836 (28.0)	1.33 (0.67-2.66)	
Not known/ missing[2]	0 (0)	15 (0.5)		
Maternal ethnicity		*n = 2,985*		
White	a	1,694 (56.8)	1 (reference)	0.331
Other	a	94 (3.1)	1.00 (0.31-3.26)	
Not known/ missing	27 (32.1)	1,197 (40.1)	0.71 (0.44-1.13)	
Maternal age at birth, years[2] *(n = 3,070)*	*n = 84*	*n = 2,986*		
≤ 24	27 (32.1)	855 (28.6)	1.12 (0.64-1.96)	0.611
25 – 29	24 (28.6)	852 (28.5)	1 (reference)	
30 – 34	17 (20.2)	782 (26.2)	0.77 (0.41-1.45)	
≥ 35	16 (19.0)	496 (16.6)	1.14 (0.60-2.18)	
Maternal factors				
Parity	*n = 84*	*n = 2,986*		
Nulliparous	29 (34.5)	1,132 (37.9)	1 (reference)	0.817
≥ 1	47 (56.0)	1,584 (53.0)	1.16 (0.72-1.85)	
Not known/ missing	8 (9.5)	270 (9.0)	1.16 (0.52-2.56)	
Multiple fetus	*n = 84*	*n = 2,986*		
Yes	7 (8.3)	182 (6.1)	1.40 (0.64-3.08)	0.422
No	77 (91.7)	2,804 (93.9)	1 (reference)	
Not known / missing	0 (0)	0 (0)		
Maternal smoking	*n = 84*	*n = 2,986*		
Smoker	24 (28.6)	488 (16.3)	1.91 (1.12-3.25)	0.019
Non/ Ex smoker	34 (40.5)	1,317 (44.1)	1 (reference)	
Not known / missing	26 (31.0)	1,181 (39.6)	0.85 (0.51-1.43)	
Anomalies in previous pregnancies		*n = 2,986*		
Yes	a	241 (8.1)	0.56 (0.20-1.56)	0.488
No	a	1,757 (58.8)	1 (reference)	
Not known / missing	28 (33.3)	988 (33.1)	0.96 (0.60-1.53)	

Table 6.15 (continued): Comparison of maternal and infant variables between deaths and survivors of infants with a congenital heart defect, circulatory or peripheral vascular anomaly: Univariable analysis.

	Deaths, Frequency (%)	Alive one year, Frequency (%)	Unadjusted OR (95% CI)	P-value
Infant factors				
Infant sex[2]	*n = 84*	*n = 3,065*		
Male	38 (45.2)	1,498 (48.9)	1 (reference)	0.288
Female	46 (54.8)	1,566 (51.1)	0.79 (0.51-1.22)	
Birthweight, grams[2,4]	*n = 83*[3]	*n = 3,065*		
< 2500 (low birthweight)	34 (41.0)	513 (16.7)	3.34 (2.13-5.23)	<0.001
≥ 2500	49 (59.0)	2,469 (80.6)	1 (reference)	
Gestational age[2,4,5]**, week**	*n = 83*[3]	*n = 3,065*		<0.001
< 37^{+0} (preterm)	31 (37.3)	533 (17.4)	2.76 (1.75-4.35)	
≥ 37^{+0} (term)	52 (62.7)	2,468 (80.5)	1 (reference)	
CHD severity	*n = 84*	*n = 3,065*		
Less severity	12 (14.3)	1,975 (64.4)	1 (reference)	<0.001
Moderate severity	19 (22.6)	309 (10.1)	10.1 (4.9-21.1)	
Most severity	27 (32.1)	49 (1.6)	90.7 (43.4-189)	
PDA and other CHDs unclassified	26 (31.0)	732 (23.9)	5.8 (2.9-11.6)	
Not known/ missing	0 (0)	0 (0)		
Intervention factor				
Surgery	*n = 84*	*n = 3,065*		
Performed in the first year of life	25 (29.8)	331 (10.8)	2.93 (1.66-5.17)	<0.001
Not performed in the first year of life[6]	25 (29.8)	970 (31.6)	1 (reference)	
Not known/ missing	34 (40.5)	1,764 (57.6)	0.75 (0.44-1.26)	

[1]P-value < 0.1 (from the LR test) considered as statistically significant. [2]Missing categories for Townsend quintile, maternal age, infant sex, birthweight and gestational age were not included in the regression analysis due to their small proportion of missing values (< 5%). [3]Obervations with small number or risk of statistical disclosure were not included. [4]Birthweight and gestational age at birth were strongly correlated (Pearson's collinearity test: r = 0.7704, p < 0.001 to 3 decimal places). [5]Gestational age was included as a binary variable in the analyses after it showed significant departure from linearity (p = 0.005) in the final model. [6]Including a minority of conditions which were too severe for surgery. Note: Categories with observations n < 5 (or a) are not shown due to risk of statistical disclosure. Confirmed and probable cases were included in the analysis.

6.4.5 Multivariable analysis

Tables 6.16-6.19 present the results of the multivariable logistic regression, which identified independent factors associated with anomaly-associated infant mortality after adjustment in the final model.

All (isolated and multiple) anomalies

Having adjusted for the factors in Table 6.16, several factors remained independently associated with case fatality. Of the socio-demographic factors, infants born to non-White mothers had more than a two-fold increase in case fatality compared to infants born to White mothers (aOR = 2.25, 95% CI: 1.77-2.86). Of the maternal factors, infants born to parous mothers had a 24% increase in case fatality compared to infants born to nulliparous mothers (aOR = 1.24, 95% CI: 1.08-1.41); and infants born to mothers who smoked during pregnancy had a 20% increase in case fatality compared to infants born to mothers who never smoked or had given up smoking (aOR = 1.20, 95% CI: 1.02-1.40). Of the infant factors, infants who were born preterm had more than a four-fold increase in infant case fatality compared to infants who were born at term (aOR = 4.38, 95% CI: 3.86-4.98). Subgroup analysis of gestational age showed that the adjusted odds of case fatality increased as gestational age at birth decreased. Infants who were born extremely preterm ($\geq 22^{+0}$ to $< 28^{+0}$) had a 14 fold increased odds of case fatality (uOR = 14.3, 95% CI: 11.1-18.3) compared to infants who were born at term. Girls with an anomaly were 28% more likely to die than boys with an anomaly in infancy (aOR = 1.28, 95% CI: 1.13-1.46). Of the intervention factor, infants who required surgery during infancy had a 20% decrease in case fatality compared to infants who did not require surgery (Including a minority of conditions which were too severe for surgery).

Table 6.16: Crude and adjusted odds ratios for infant mortality: isolated or multiple anomalies.

Risk factors	Crude OR (95% CI)	P-value[1]	aOR[2] (95% CI) in final model	P-value[3]
Maternal ethnicity				
White	1 (reference)	<0.001	1 (reference)	<0.001
Other	2.18 (1.73-2.75)		2.25 (1.77-2.86)	
Not known/ missing	0.46 (0.39-0.53)		0.66 (0.54-0.81)	
Parity				
Nulliparous	1 (reference)	<0.001	1 (reference)	0.003
≥ 1	1.24 (1.09-1.41)		1.24 (1.08-1.41)	
Not known/ missing	0.49 (0.37-0.65)		0.92 (0.67-1.27)	
Maternal smoking				
Smoker	1.24 (1.07-1.44)	<0.001	1.20 (1.02-1.40)	<0.001
Non/ Ex smoker	1 (reference)		1 (reference)	
Not known / missing	0.47 (0.40-0.55)		0.73 (0.60-0.90)	
Infant sex				
Male	1 (reference)	<0.001	1 (reference)	<0.001
Female	1.29 (1.14-1.46)		1.28 (1.13-1.46)	
Gestational age, week				
< 37^{+0} (preterm)	4.53 (4.00-5.14)	<0.001	4.38 (3.86-4.98)	<0.001
≥22^{+0} to < 28^{+0}	*13.2 (10.4-16.8)*		*14.3 (11.1-18.3)*	
≥ 28^{+0} to < 32^{+0}	*7.0 (5.7-8.6)*		*7.0 (5.7-8.6)*	
≥ 32^{+0} to < 37^{+0}	*3.1 (2.6-3.6)*		*3.0 (2.5-3.5)*	
≥ 37^{+0} (term)	1 (reference)		1 (reference)	
Surgery				
Performed in the first year after birth	0.86 (0.73-1.01)	0.021	0.80 (0.68-0.95)	<0.001
Not performed in the first year after birth[4]	1 (reference)		1 (reference)	
Not known/ missing	0.83 (0.72-0.95)		0.76 (0.66-0.88)	

[1]P < 0.1 was considered as statistically significant. [2]Mutually adjusted odds ratios for other factors in the table. [3]P < 0.05 was considered as statistically significant. [4]Including a minority of conditions which were too severe for surgery. Note: Confirmed and probable cases were included in the analysis.

All isolated anomalies

Having adjusted for the factors in Table 6.17, several factors remained independently associated with case fatality. Infants born to non-White mothers had an almost two-fold increase in case fatality compared to infants born to White mothers (aOR = 1.87, 95% CI: 1.16-3.02). Infants born to parous mothers had a 48% increase in case fatality compared to infants born to nulliparous mothers (aOR = 1.48, 95% CI: 1.16-1.89). Infants born to mothers who smoked during pregnancy had a 44% increase in case fatality compared to infants born to mothers who never smoked or had given up smoking (aOR = 1.44, 95% CI: 1.07-1.92). Infants who were born preterm had more than a 4.5 fold increase in infant case fatality compared to infants who were born at term (aOR = 4.53, 95% CI: 3.62-5.67). Infant sex was not significantly associated with infant case fatality (aOR = 1.06, 95% CI: 0.85-1.33).

Table 6.17: Crude and adjusted odds ratios for infant mortality: isolated anomaly.

Risk factors	Crude OR (95% CI)	P-value[1]	aOR[2] (95% CI) in final model	P-value[3]
Maternal ethnicity				
White	1 (reference)	<0.001	1 (reference)	0.012
Other	1.77 (1.11-2.82)		1.87 (1.16-3.02)	
Not known/ missing	0.59 (0.47-0.75)		0.77 (0.55-1.09)	
Parity				
Nulliparous	1 (reference)	0.002	1 (reference)	0.004
≥ 1	1.48 (1.16-1.89)		1.48 (1.16-1.89)	
Not known/ missing	0.99 (0.67-1.46)		1.55 (1.00-2.40)	
Maternal smoking				
Smoker	1.52 (1.15-2.01)	<0.001	1.44 (1.07-1.92)	0.014
Non/ Ex smoker	1 (reference)		1 (reference)	
Not known / missing	0.66 (0.52-0.85)		0.89 (0.62-1.26)	
Infant sex				
Male	1 (reference)	0.496	1 (reference)	0.602
Female	1.08 (0.86-1.35)		1.06 (0.85-1.33)	
Gestational age, week				
$< 37^{+0}$ (preterm)	4.72 (3.78-5.90)	<0.001	4.53 (3.62-5.67)	<0.001
$\geq 37^{+0}$ (term)	1 (reference)		1 (reference)	

[1]P < 0.1 was considered as statistically significant. [2]Mutually adjusted odds ratios for other factors in the table. [3]P < 0.05 was considered as statistically significant. Note: Confirmed and probable cases were included in the analysis.

All multiple anomalies

After adjustment for the factors in Table 6.18, there was more than a two-fold increase in case fatality for infants born to non-White mothers compared to infants born to White mothers (aOR = 2.38, 95% CI: 1.79-3.16). Infants born to parous mother had a 19% increase in case fatality compared to infants born to nulliparous mothers (aOR = 1.19, 95% CI: 1.02-1.40). Infants who were born preterm had an almost four-fold increase in infant case fatality compared to infants who were born at term (aOR = 3.86, 95% CI: 3.30-4.53). Girls with multiple anomalies were 37% more likely to die than boys with multiple anomalies (aOR = 1.37, 95% CI: 1.17-1.61). Finally, infants with multiple anomalies who required surgery during infancy had a 29% decrease in case fatality compared to infants with multiple anomalies who did not require surgery in infancy (aOR = 0.71, 95% CI: 0.58-0.86).

Table 6.18: Crude and adjusted odds ratios for infant mortality: multiple anomalies.

Risk factors	Crude OR (95% CI)	P-value[1]	aOR[2] (95% CI) in final model	P-value[3]
Maternal ethnicity				
White	1 (reference)	<0.001	1 (reference)	<0.001
Other	2.34 (1.78-3.08)		2.38 (1.79-3.16)	
Not known/ missing	0.56 (0.46-0.68)		0.63 (0.51-0.78)	
Parity				
Nulliparous	1 (reference)	<0.001	1 (reference)	0.002
≥ 1	1.18 (1.01-1.39)		1.19 (1.02-1.40)	
Not known/ missing	0.37 (0.23-0.61)		0.54 (0.32-0.93)	
Infant sex				
Male	1 (reference)	<0.001	1 (reference)	<0.001
Female	1.33 (1.14-1.55)		1.37 (1.17-1.61)	
Gestational age, week				
$< 37^{+0}$ (preterm)	3.84 (3.29-4.49)	<0.001	3.86 (3.30-4.53)	<0.001
$\geq 37^{+0}$ (term)	1 (reference)		1 (reference)	
Surgery				
Performed in the first year after birth	0.68 (0.56-0.82)	<0.001	0.71 (0.58-0.86)	<0.001
Not performed in the first year after birth[4]	1 (reference)		1 (reference)	
Not known/ missing	0.76 (0.64-0.91)		0.77 (0.64-0.92)	

[1]P < 0.1 was considered as statistically significant. [2]Mutually adjusted odds ratios for other factors in the table. [3]P < 0.05 was considered as statistically significant. [4]Including a minority of conditions which were too severe for surgery. Note: Confirmed and probable cases were included in the analysis.

Cardiovascular anomalies

After adjustment for the factors in Table 6.19, infants who were born preterm had a 3.7 fold increase in infant case fatality compared to infants who were born at term (aOR = 3.67, 95% CI: 2.19-6.15). Infants who were affected by the most severe types of CHDs had a 229 fold increase in infant case fatality compared to infants who were affected by the least types of severe CHDs (aOR = 229, 95% CI: 90.8-579). Finally, infants with a cardiovascular anomaly who required surgery during infancy have a 66% decrease in case fatality compared to infants with a cardiovascular anomaly who did not require for surgery in infancy (aOR = 0.34, 95% CI: 0.15-0.75). Maternal ethnicity and infant sex were not significantly associated with infant mortality after adjustments in the final model.

Table 6.19: Crude and adjusted odds for infant mortality: congenital heart defects, circulatory or peripheral vascular anomalies.

Risk factors	Crude OR (95% CI)	P-value[1]	aOR[2] (95% CI) in final model	P-value[3]
Maternal ethnicity				
White	1 (reference)	0.331	1 (reference)	0.282
Other	1.00 (0.31-3.26)		1.08 (0.29-4.04)	
Not known/ missing	0.71 (0.44-1.13)			
Infant sex				
Male	1 (reference)	0.288	1 (reference)	0.349
Female	0.79 (0.51-1.22)		1.26 (0.78-2.06)	
Not known/ missing				
Gestational age, week				
$< 37^{+0}$ (preterm)	2.76 (1.75-4.35)	<0.001	3.67 (2.19-6.15)	<0.001
$\geq 37^{+0}$ (term)	1 (reference)		1 (reference)	
CHD severity				
Less severity	1 (reference)	<0.001	1 (reference)	<0.001
Moderate severity	10.1 (4.9-21.1)		18.4 (8.10-41.7)	
Most severity	90.7 (43.4-189)		229 (90.8-579)	
PDA and other CHDs unclassified	5.8 (2.9-11.6)		6.29 (3.14-12.6)	
Surgery				
Performed in the first year of life	2.93 (1.66-5.17)	<0.001	0.34 (0.15-0.75)	0.025
Not performed in the first year of life[4]	1 (reference)		1 (reference)	
Not known/ missing	0.75 (0.44-1.26)		0.60 (0.34-1.06)	

[1]P < 0.1 was considered as statistically significant. [2]Mutually adjusted odds ratios for other factors in the table. [3]P < 0.05 was considered as statistically significant. [4]Including a minority of conditions which were too severe for surgery. Note: Confirmed and probable cases were included in the analysis.

6.4.6 Further exploratory analyses

Two exploratory analyses were conducted to investigate the hypotheses described in the Section 6.3.9.

First, the odds ratios for surgical-related case fatality were different across anomaly subgroups (Table 6.20). In particular, 'Surgery performed during infancy' was associated with a significantly decreased infant case fatality for the majority of the anomaly subgroups including the nervous system, respiratory and clefts, abdominal wall defects and diaphragmatic hernias, lower and upper gastrointestinal, genitourinary, limb and skeletal, and syndrome and laterality anomalies. The overall effect of surgery for infants with anomalies therefore appeared protective.

Table 6.20: Unadjusted odd ratios for surgery and mortality stratified by congenital anomaly subgroups: All isolated and multiple anomalies.

	Surgery performed in infancy		Surgery not performed (including conditions too severe for surgery) in infancy		OR (95% CI) for surgery performed vs. surgery not performed.
Anomaly subgroup[1,2]	**Total**	**Died %**	**Total**	**Died %**	
Nervous system	367	7.08	511	13.89	0.51 (0.33-0.78)
Eye, ear, face and neck	560	6.25	1,398	4.94	1.27 (0.85-1.88)
CHDs, circulatory and peripheral vascular diseases	2,619	8.86	2,374	8.00	1.11 (0.92-1.33)
Respiratory and clefts	1,071	2.52	440	19.55	0.13 (0.09-0.20)
Abdominal wall defects and diaphragmatic hernias	503	4.97	81	48.15	0.10 (0.07-0.16)
Lower and upper gastrointestinal	2,113	2.37	443	15.06	0.18 (0.13-0.26)
Genitourinary	1,252	1.52	5,173	1.57	0.97 (0.59-1.59)
Limb and skeletal	1,566	1.53	1,666	3.84	0.40 (0.25-0.64)
Endocrine and metabolic	120	9.17	897	4.24	2.16 (1.14-4.12)
Syndrome and laterality anomalies	1,720	14.22	3,593	20.31	0.70 (0.61-0.80)
Maternal infection leading to malformation	194	7.73	882	8.28	0.93 (0.55-1.59)
Total	12,439	5.78	18,511	8.32	0.69 (0.64-0.76)

[1]Anomalies within each anomaly subgroup can be isolated anomalies or part of multiple anomalies. [2]Observations in categories may not add up to the total, as some of the categories are not shown due to small number or risk of statistical disclosure. Note: confirmed and probable cases were included in the analysis.

Second, there were no significant differences in odds of infant case fatality between boys and girls in the anomalies subgroups of the nervous system, eye, ear, face and neck, cardiovascular system, respiratory and clefts, genitourinary system, endocrine and metabolic systems, abdominal wall defects and diaphragmatic hernias, neoplasm and maternal infections leading to malformations (Table 6.21). However, for the anomaly subgroups of lower and upper gastrointestinal (GI) system, blood disorders and syndromes, girls had a significantly higher risk of case fatality compared to boys. Further analysis of anomaly subtypes in the lower and upper GI system showed that the birth prevalence of pyloric stenosis (which is rarely associated with case fatality in liveborn infants) was 5.8 times higher in boys compared to girls leading to a higher proportion of male survivors. The analyses of the blood disorders and syndromes subtypes show no significant difference in the odds of infant case fatality between boys and girls in the specific conditions investigated.

Table 6.21: Unadjusted odd ratios for sex and mortality stratified by congenital anomaly subgroups: All isolated and multiple anomalies.

	Female infants		Male infants		OR (95% CI) for female vs. male
Anomaly subgroup[1,2]	**Total**	**Died %**	**Total**	**Died (%)**	
Nervous system	734	12.26	847	11.22	1.09 (0.83-1.43)
Eye, ear, face and neck	1,826	4.50	2.032	4.72	0.95 (0.71-1.28)
CHDs, circulatory and peripheral vascular diseases	4,580	7.47	4,837	6.86	1.09 (0.94-1.26)
Respiratory and clefts	811	7.64	1,076	7.71	0.99 (0.72-1.36)
Abdominal wall defects and diaphragmatic hernias	272	10.29	378	11.38	0.89 (0.57-1.40)
Lower and upper gastrointestinal (GI)	961	5.41	2,377	3.83	1.41 (1.01-1.97)
Some subtypes of lower and upper GI					
Anomalies of the tongue and mouth, oesophageal atresia or stenosis and tracheoesophageal fistula	124	7.26	208	6.25	1.16 (0.51-2.64)
Pyloric stenosis	185	2.70	1081	0.74	3.65 (1.21-11.04)
Atresia/ stenosis of duodenum and small intestine	163	3.68	196	8.16	0.45 (0.18-1.13)
Hirschsprung's disease and other malformations of intestine[3]	230	4.35	276	3.26	1.33 (0.55-3.23)
Other digestive diseases[4]	194	9.28	565	7.26	1.28 (0.75-2.17)
Genitourinary	1,658	1.57	7,489	1.26	1.25 (0.81-1.92)
Limb and skeletal	3,150	1.97	2,875	3.76	0.52 (0.39-0.71)
Blood disorders	142	9.86	253	4.35	2.27 (1.06-4.86)
Diseases of blood and blood-forming organs/ disorders involving the immune mechanism	36	25.00	46	15.22	1.64 (0.68-3.99)
Endocrine and metabolic	770	4.81	810	4.44	1.08 (0.69-1.69)

Table 6.21 (continued): Unadjusted odd ratios for sex and mortality stratified by congenital anomaly subgroups: All isolated and multiple anomalies.

	Female infants		Male infants		OR (95% CI) for female vs. male
Anomaly subgroup[1,2]	**Total**	**Died %**	**Total**	**Died (%)**	
Neoplasm	400	5.25	358	3.35	1.57 (0.78-3.14)
Syndrome	3,087	21.61	3,691	14.90	1.45 (1.31-1.61)
Some subtypes of syndrome					
DiGeorge syndrome	119	7.56	145	11.03	0.69 (0.31-1.50)
Down syndrome (T21)	723	13.83	877	11.86	1.17 (0.90-1.51)
Edward syndrome (T18)	201	85.07	94	84.04	1.01 (0.91-1.13)
Patau syndrome (T13)	80	87.50	39	87.18	1.00 (0.87-1.17)
Congenital malformation syndromes	674	18.25	1,110	14.50	1.26 (1.02-1.56)
Whole, major and minor partial Trisomy of chromosomes/ autosomes	251	10.36	315	11.75	0.78 (0.49-1.24)
Duplications with other complex rearrangements/ at prometaphase/ extra marker chromosomes/ Triploidy/ polyploidy	110	20.00	105	25.71	0.77 (0.47-1.28)
Angelman syndrome	430	7.67	575	5.04	1.32 (0.80-2.16)
Maternal infection leading to malformation	751	9.85	1,121	8.03	1.23 (0.92-1.65)
Total	19,535	8.00	28,738	5.80	1.38 (1.29-1.47)

[1]Anomalies within each anomaly subgroup can be isolated anomalies or part of multiple anomalies. [2]Observations in categories may not add up to the total, as some of the observations are not shown due to small number or risk of statistical disclosure. [3]Included malrotation, ectopic anus, fistula of rectum/ anus, cloaca, megaloduodenum, maldevelopment/ duplication of intestine, macrosigmoid and Meckel's diverticulum, congenital malformations of the spleen, adrenal gland, endocrine glands, situs inversus and multiple congenital malformations. [4]Included congenital diseases of oral cavity, salivary glands and jaws, hernias, hepatic failure, calculus of gallbladder and obstruction of bile duct. Note: Categories with observations n < 5 are not shown due to risk of statistical disclosure. Confirmed and probable cases were included in the analysis. Note: confirmed and probable cases were included in the analysis.

6.4.7 Sensitivity analyses

The results in the final models of the multivariable analyses remained essentially unchanged in the sensitivity analyses carried out using confirmed cases of congenital anomalies only, complete case analysis and multiple imputation (Appendices 6.6-6.9).

6.5 Discussion

6.5.1 Summary of findings

This population-based cohort study used Welsh national data for the 1998-2016 birth cohort from CARIS, and identified 30,424 infants who were affected by one or more congenital anomalies in this period; this represented a total livebirth prevalence of 480 per 10,000 livebirths. There were 1,044 deaths of infants who were affected by an anomaly; these deaths accounted for almost one-third of all infant deaths and an anomaly-associated IMR of 16.5 deaths per 10,000 livebirths. Infants who were born with anomalies overall had a greater risk of infant deaths (case fatality = 3.4%, i.e. 96.6% survived their first birthday), compared to infants who were born without an anomaly (fatality = 0.4%, i.e. 99.6% survived their first birthday). Infants with multiple and structural anomalies contributed the highest infant mortality. For example, cardiovascular anomalies were associated with the greatest number of infant deaths with IMR of 1.33 deaths per 10,000 livebirths; and abdominal wall defects and congenital diaphragmatic hernias were associated with the highest case fatality at 8.2%.

This study is one of a few studies to investigate the causes of death of neonates and post-neonatal infants affected by congenital anomalies. This study has shown that approximately 41% of deaths of babies with a congenital anomaly occurred in the neonatal period, and 59% of deaths of babies with a congenital anomaly occurred in the post-neonatal period. Among infants with congenital anomalies who died, congenital anomalies were the most frequently recorded main or underlying cause of death, contributing more than half of the main conditions or diseases

contributing to death of neonates, and underlying causes of post-neonatal deaths of infants affected by congenital anomalies. In addition, infants affected by an anomaly who died also frequently died from other associated comorbidities and complications, the pattern of which generally followed the timing in which deaths occurred and was anomaly-specific. For example, the main conditions contributing to death of neonates with a CHD were frequently associated with the anomaly itself, CHD-related complications or immaturity-related conditions.

Significant increases in infant case fatality were found among infants born to mothers who were non-White, parous, smokers during pregnancy, and infants who were born preterm and of female sex. Infants who required and had surgery performed in the first year of life had a lower odds of infant case fatality, compared to infants who had not. A protective effect of surgery in infant case fatality was also shown for infants with cardiovascular anomalies. Preterm birth was consistently shown to be a significant factor associated with an increased risk of infant case fatality in all anomaly subgroups investigated. The effect of the other characteristics on case fatality of infants with an anomaly varied according to the anomaly subgroup.

6.5.2 Comparison with other anomaly registries and the literature

1. Anomaly definitions and reporting rates

CARIS adopts a wider definition of congenital anomalies compared to EUROCAT, and collects data about congenital anomalies involving structural, metabolic, genetic defects, as well as rare diseases of congenital origin (CARIS 2018; EUROCAT 2013a). Consequently, this study has included diseases such as metabolic and endocrine disorders (commonly cystic fibrosis and congenital hypothyroidism) and congenital blood disorders (commonly hereditary spherocytosis, Haemophilia A and von Willebrand disease) etc., i.e. those non-'Q', non-'P35' and non-'P37' codes which are not routinely collected by EUROCAT. As a result, this may account for a higher livebirth

prevalence for overall congenital anomalies reported in this study, compared to studies using data from other EUROCAT registries.

2. Mortality rates, patterns and risk

Congenital anomalies are a leading cause of infant mortality. In the 1998-2016 Welsh birth cohort, there were 1,044 deaths out of a total of 30,338 liveborn infants affected by congenital anomalies, which accounted for approximately one third of all infant deaths in Wales. The significant contribution of congenital anomalies to infant deaths found in this study is consistent with previous studies conducted in other high-income countries (Dastgiri et al. 2003; Rosano et al. 2000; Wen et al. 2000; Linhart et al. 2000; Wen et al. 1999; CDC 1998; Yang et al. 1997; Lynberg et al. 1990; Powell-Griner et al. 1990; Kalter 1991; Oakley et al. 2009). Comparing with a similar UK population-based study by Dastgiri et al. (2002) using data from the Glasgow Register of Congenital Anomaly between 1980 and 1997 with a similar anomaly definition which showed that 11.0% of infants affected by anomalies died in infancy, the 3.4% case fatality found in this study suggests that there has been an overall improvement in the survival of infants with congenital anomalies over time in the UK which are likely due to advanced treatment, improved prenatal screening and access to termination of pregnancy. It is important however to note that, as outlined in Chapter 1, congenital anomalies include a wide spectrum of heterogeneous diseases and conditions, and therefore variations in the mortality risk actually depend on the anomaly subtypes and disease severity. This was highlighted and evidenced in findings from the subgroup analyses in this study.

Among infants born with anomalies, infants with multiple and structural anomalies contributed the greatest proportions of anomaly-related infant deaths. As discussed in the systematic reviews in Chapters 3 and 4, multiple anomalies are an indicator of disease complications and severity, which have been shown to be a significant risk factor associated with infant death (Bol et al. 2006; Wong et al. 2001); therefore infants affected by multiple anomalies tend to have a poorer

prognosis, compared to infants affected by isolated anomalies (Springett et al. 2013; Bakker et al. 2019; Wu et al. 2013; Schneuer et al. 2019; Agha et al. 2016; Druschel et al. 1996). In addition, infant mortality was highest among infants affected by structural defects such as abdominal wall defects and diaphragmatic hernias, anomalies of the nervous system, cardiovascular and respiratory anomalies. This is probably due to the complex anatomies and disease complications which these anomalies often represent (Springett et al. 2014).

3. Causes of death

Assigning cause of infant death has been a common difficulty in studies investigating congenital anomalies (Roncancio et al. 2018; Cockerill et al. 2012). This study used the main condition or disease contributing to death of neonates (i.e. section a in the neonatal death certificate), and the underlying cause of death of post-neonatal infants for the analysis of neonatal and post-neonatal causes of death respectively. These recorded codes of cause of death were the most complete cause of death data available in the ONS and SAIL datasets.

Infants affected by a congenital anomaly were at risk of dying from a variety of causes. Congenital anomalies were the most frequent main or underlying cause of death, which were recorded on the death certificates for more than half of the affected neonates and post-neonatal infants who died, particularly among those who were affected by nervous system anomalies, cardiovascular anomalies, congenital diaphragmatic hernias, abdominal wall defects and gastrointestinal anomalies. A possible explanation is that, since many of these structural anomalies involve major organs which are survival dependent, it is likely that these anomalies, especially in their most severe forms, play a more significant role in the cause of death of the affected infants, compared to other comorbidities and competing causes.

In addition, infants with anomalies who died frequently died from anomaly-associated comorbidities and complications. For example, infants with CHDs who died often died from

diseases complications related to (e.g. post-operation) circulatory system and infections (Benavidez et al. 2007; McCracken et al. 2018), and immunity-related conditions. It is important to note however, preterm births are often strongly associated with major congenital anomalies such as nervous system anomalies and CHDs, although they might independently impact on survival (Honein et al. 2009; Rocha et al. 2018); the EPICARD study has shown that preterm infants with CHDs, especially those who were born at < 35 gestation weeks, had a significantly high risk of mortality (Laas et al. 2017). These results suggested that preterm birth and congenital anomalies may have an independent and synergistic effect on infant mortality.

Furthermore, the pattern of the cause of death generally followed with the timing when death occurred. For example, conditions such as antepartum infections, immaturity-related conditions, asphyxia, anoxia or trauma represented over a quarter of main conditions contributing to death of neonates with congenital anomalies who died, which suggests that perinatal period represents a particularly critical and high mortality risk period for neonates affected by anomalies. Whereas infections, sudden infant deaths, external and other specific conditions represented over one third of the underlying causes of death of post-neonatal infants with congenital anomalies who died.

These findings are similar to those of a Canadian study (Ontario, birth cohort 1979-1986) using the Canadian Congenital Anomalies Surveillance System (CCASS), which also showed that congenital anomalies, conditions originating perinatally and respiratory conditions were the leading causes of death of infants with congenital anomalies overall (Agha et al. 2016).

However, only one tenth (10.5%) of infants with an anomaly who died had a post-mortem to confirm the causes of death. Further analysis of the ONS cause groupings of death has shown that between 7.8% and 30.0% of infants with congenital anomalies who died and had ‘Congenital anomalies’, ‘Immaturity related conditions’, ‘Other specific conditions’ and ‘Sudden infant deaths’ as the coded causes of death had a post-mortem; while a relatively small number of infants with

congenital anomalies who died and had 'Asphyxia, anoxia, or trauma', 'External conditions' or 'Infections' as the recorded cause of death had a post-mortem to confirm it. Therefore, it was likely that the majority of the assigned causes of death of infants with congenital anomalies were based on clinical information and decisions of the clinicians who cared for these infants.

4. Mortality risk factors and comparison with other studies

Several risk factors were shown to be significantly associated with an increased risk of case fatality of infant affected by an anomaly.

Maternal ethnicity

Infants born to mothers of non-White ethnicity had up to a three-fold increased odds of dying in infancy (infant case fatality) compared to infants born to mothers of White ethnicity.

Substantial inequalities in infant mortality rates exist between White and ethnic minority groups in England and Wales (Gray et al. 2009). The explanations for variation in the risk of infant death between different ethnic groups are complex, involving the interplay of socio-demographic (e.g. deprivation, social barriers and inequality in access to healthcare and preventive interventions), cultural (e.g. attitude to healthcare and interventions), behavioural (e.g. maternal smoking) and genetic factors (Weightman et al. 2012; Evandrou et al. 2016; Gray et al. 2009; Dominguez et al. 2008; Shin et al. 2012; Fiscella et al. 1996; Goldenberg et al. 1996; Gray et al. 2009; Sokal et al. 1980; Gonzalez et al. 2003). The excess mortality from congenital anomalies in ethnic minority groups may be due to cultural differences in attitude regarding the acceptability of congenital anomalies and termination of pregnancy when anomalies are diagnosed prenatally (Hewison et al. 2007; Arif et al. 2008). Previous studies have shown that women of Pakistani ethnicity have much lower rates of termination of pregnancy compared to mothers of White ethnicity, which may partly account for a higher anomaly-associated IMR compared with the population of England and Wales overall (Arif et al. 2008; Ahmed et al. 2008; Ahmed et al. 2006). In addition,

the excess mortality from congenital anomalies in Pakistani infants may also be mediated by an effect on incidence related to consanguinity as suggested in the Born in Bradford study (Firth et al. 2018). However, it is also possible that the observed ethnic disparities were in part due to differences in the main/underlying causes that were unrelated to having an anomaly.

Parity

Infants with an anomaly had a 24% increase in the odds of dying in infancy if they were born to parous mothers, compared to infants who were born to nulliparous mother.

Although this study did not have an adequate sample size of mother with parity ≥2 to precisely examine the full effect of higher parity on case fatality, it has been well documented in the literature that mortality rates increase as parity increases (Sonneveldt et al. 2013; Hobcraft et al. 1983; Stover and Ross 2010), or a U-shaped relationship has been observed between parity and mortality (Rutstein and Winter 2014).

A possible explanation is that high parity is more likely to be associated with older age; and older mothers have a higher chance of mutations in their eggs, which can be inherited to the embryo leading to chromosomal anomalies (Cuckle 2005), thus a tendency for more lethal anomalies (Hook et al. 1985). In addition, findings from studies conducted in low-income countries have suggested that high order births are less likely to receive critical maternal and child health interventions compared to lower order births (Montgomery and Lloyd 1996; Edmonston 1983; Garg et al. 1996). However, the exact mechanism in which high parity impacts on infant mortality is not well understood (Sonneveldt et al. 2013). Further research is needed to examine the relationship between higher parity and anomaly-related infant mortality.

Maternal smoking during pregnancy

Maternal smoking during pregnancy increased the odds of death of infants born with a congenital anomaly by up to 40%.

The association between smoking during pregnancy and risk of perinatal death has been extensively studied since the 1960s (Underwood et al. 1965; Downing et al. 1966; Comstock et al. 1967). A more recent systematic review by Pineles et al. (2016) further supports prior conclusions that maternal smoking is a cause of perinatal and neonatal death (Satcher et al. 2002; US Department of Health and Human Services 2004; US Department of Health and Human Services 1980).

The mechanism in which maternal smoking leads to perinatal death includes fetal asphyxia due to placental abruption and maternal haemorrhage (Shobeiri et al. 2017; Tikkanen 2011), and post-neonatal infant death due to an increased risk of sudden infant death syndrome (Mitchell 1995; Anderson and Cook 1997). In addition, smoking during pregnancy is a well-recognised cause of intrauterine growth restriction which is a known important risk factor for infant mortality (Andres and Day 2000).

Infant sex

Girls with anomalies were associated with a higher risk of infant case fatality compared to boys with anomalies overall.

While there is no clear evidence in the literature about the direct effect of sex on case fatality of infants with congenital anomalies, subgroup analysis in this study showed that this was likely due to male excess in birth prevalence for certain congenital anomalies such as pyloric stenosis and hypospadias, which are sex-specific and rarely fatal. The surgical outcomes and long-term prognosis for pyloric stenosis and hypospadias are usually excellent; for example, the CARIS

annual report suggests that the survival rate of infants with pyloric stenosis is in excess of 99% (CARIS 2020e). In addition, the effect of infant sex was shown non-significant for infant case fatality in the subgroup analysis of cardiovascular anomalies in this study.

However, as boys have been shown to have an increased risk of intrauterine growth restriction, prematurity, respiratory distress syndrome and mortality in previous studies (Lisi et al. 2005; Tennant et al. 2011; Zhao et al. 2017; Stevenson et al. 2000; Mulla et al. 2013; Peelen et al. 2016; Steen et al. 2014; Melamed et al. 2009; Speakman 2013; Barford et al. 2006), one might have reasonably anticipated that boys would have had a higher mortality than girls.

Preterm birth

Infants with a congenital anomaly who were born preterm (< 37^{+0} gestational weeks) had about a four-fold increase in the odds of dying in infancy. Those with any anomaly who were born extremely preterm (≥ 22^{+0} to < 28^{+0} gestational weeks) had a 14-fold increase in the odds of dying in infancy compared to those infants who were born at term. The excess odds of dying in infancy increased as gestational age at birth decreased.

Preterm birth contributes significantly to infant death (Alexander et al. 2003; Petrini et al. 2002; CDC 2003; Laas et al. 2017) due to an increased risk of immaturity-related comorbidities and complications such as chronic lung disease of prematurity, necrotising enterocolitis and intraventricular haemorrhage (Butler and Behrman 2007; Rocha et al. 2018). Previous studies have shown that infant mortality risk increases proportionally with decreasing birthweight and/or gestational age (Allen et al. 2000; Lemons et al. 2001; Alexander et al. 1999; CDC 2003).

It is also important to note that, having a major anomaly increases the risk of an infant being born preterm, both of which are independently associated with an increased risk of infant death with a likely synergistic effect (Honein et al. 2009; Kase and Visintainer 2007; Norman et al. 2020). The mechanism in which congenital anomalies contribute to preterm birth remains largely unknown,

although some studies suggest that common risk factors such as maternal smoking and obesity which are associated with both conditions are a possible pathway (Honein et al. 2009). In addition, environmental exposure such as valproic acid during pregnancy or inadequate periconceptional folic acid can lead to an anomaly (e.g. spinal bifida), which could be part of the mechanism leading to preterm birth (Clayton-Smith et al. 2019; Siega-Riz et al. 2004).

Disease severity

For CHDs, a strong correlation was found between mortality risk and disease severity which is expected. Infants who were affected by the most severe types of CHDs such as single ventricle, tricuspid atresia and stenosis, Ebstein's anomaly, hypoplastic left heart and hypoplastic right heart were significantly more likely to die compared with infants with less severe types of CHDs such as ventricular or atrial septal defects. The CHD severity classification used in this analysis was based on a previously defined hierarchical severity ranking according to perinatal mortality rate for each of these specific CHDs (EUROCAT 2020a; Khoshnood et al. 2012). However, classifications of disease severity among other anomaly subgroups are rare and less well recognised, as the aetiology of many congenital anomalies is not known (WHO 2020).

Surgery

Finally, this study showed that surgery performed in infants with an anomaly overall, multiple anomalies or a cardiovascular anomaly during infancy is associated with a decreased risk of death in infancy, compared to infants who did not have surgery (including a minority of conditions which were too severe for surgery). The 'surgery' variable was heterogeneous in which infants who did not have surgery included a minority of infants whose conditions were too severe for surgery. Consequently, the protective effect of surgery could be potentially overestimated in this study as a number of infants who did not have surgery and were more likely to die not because of not having the surgery *per se* but rather due to severity of their conditions, which could not be

adjusted in 'All anomalies' and 'Multiple anomalies' subgroups. For infants with cardiovascular anomalies where the severity of the anomalies could be classified and adjusted for, surgery was shown to be a protective factor for survival in this study. However, prognosis can vary even within CHDs anomaly subtypes, which presents a limitation in the interpretation of these findings (see Section 6.5.3: Limitations). Nonetheless, there is emerging evidence suggesting that progress in medical and surgical treatment and management, especially for preterm infants with a CHD has generally resulted in a more favourable prognosis over time (Oppido et al. 2004; Wernovsky et al. 2001), while infant mortality rates remain high in the many severe anomalies despite surgical interventions, for example, infants with the most severe types of CHDs (such as hypoplastic heart syndrome and single ventricle) continue to experience a significant risk of post-operative cardiovascular sequelae and other complications (McCracken et al. 2018). Further population-based studies using big data are necessary to investigate the association between intervention/treatment factors and infant case fatality by specific anomaly subtype where possible.

6.5.3 Strengths and limitations of the study

Strengths

This is the first UK population-based cohort study investigating the impact of overall and selected groups of congenital anomalies and rare diseases on infant mortality.

The main strengths of this study include the national study population and the robust study design. The study cohort was identified from CARIS, which is a high-quality, population-based congenital anomaly registry which covers all livebirths in Wales. Higher reporting rates from CARIS compared to anomaly registers in England and most other EUROCAT registries are attributed to better reporting and its robust surveillance system. For anomaly case ascertainment, CARIS uses a multiple sources reporting system to maximise case finding and to gain the most complete

information possible. In addition, all complex cases and multiple anomalies were reviewed by geneticists; diagnoses were confirmed by serological testing and postmortem where appropriate so that ascertainment bias was minimised. Additional checks were performed on diagnostic coding and plausible ranges of values of the included variables in order to optimise the internal validity.

Another strength is that CARIS collects data based on a broad definition of congenital anomalies. In addition to structural and chromosomal defects, this study has uniquely included other rare diseases of congenital origin such as metabolic, endocrine and congenital blood disorders which are not routinely included in other EUROCAT registries. Consequently therefore, this study was able to generate epidemiological findings and assess the full impact of a wider group of congenital anomalies and rare diseases on infant mortality. In addition, this study analysed the subgroup of multiple anomalies separately and therefore was able to assess the extent of impact to which co-occurring abnormalities have on infant death compared to isolated anomalies.

Very few studies have been conducted to investigate the cause of death of infants with congenital anomalies to date. This study has comprehensively explored and interpreted the patterns of the main and underlying causes of death of neonates and post-neonatal infants by anomaly subgroups according to the ONS cause (of death) group hierarchical classification and ICD chapter headings. Importantly, these findings provide a better understanding of the impact of congenital anomalies, their associated comorbidities and complications on infant mortality, and the critical time to which these affected babies are particularly vulnerable and exposed. This information is crucially important for clinicians to plan and prioritise interventions to target anomaly-/ immaturity- related conditions and complications, and get an early access to specialised care for infants affected by congenital anomalies in order to minimise the risk of infant deaths.

Finally, this study has generated findings about risk factors associated with an increased risk of case fatality of infant affected by an anomaly, and thus has advanced knowledge about the

contributions of socio-demographic, maternal, infants and interventional characteristics of congenital anomalies to excess infant case fatality. In addition, all missing data for the risk factors were thoroughly examined and dealt with accordingly to check the robustness of final models, and the results were consistent.

Limitations

There are a number of limitations in this study.

As the livebirth prevalence of certain anomaly subtypes and rare diseases (especially for certain severe types of metabolic, endocrine and chromosomal conditions) was low and the occurrence of anomaly-related infant deaths is rare, further analyses of specific/ individual congenital anomalies were not possible. Due to rarity of some anomalies, particular efforts were made to combine similar anomaly subtypes where appropriate based on clinical relevance in order to optimise the sample size and statistical stability. Consequently, heterogeneity inevitably existed within anomaly groups in terms of infant mortality risk. Therefore, the estimates and associations found in this study should be interpreted with caution. Further mortality studies of infants with specific anomalies are needed using big data such as a national multi-centre study design.

In addition, international variations exist between countries in the definitions and registering practices of stillbirths and livebirths (Smith et al. 2018; OECD 2019), and these can have a significant impact on reported IMRs (Kramer et al. 2002; Joseph et al. 2012). Therefore, caution is needed when comparing and interpreting the estimates of neonatal and infant mortality rates in this study with studies conducted in other countries.

Assigning the main/underlying cause of neonatal and post-neonatal deaths on the death certificates is not always a straightforward practice even by the most experienced clinicians who care for babies with congenital anomalies. This is because infants with congenital anomalies often have other competing causes of death from severe comorbidities such as prematurity and

systemic infections. This study has shown that the majority of infants with congenital anomalies who died did not have a post-mortem to confirm the cause of death, therefore these may potentially lead to uncertainty in assigning and coding the cause of death of infants with congenital anomalies in some cases; and misclassification bias on the specific causes of infant death cannot be excluded. Comprehensive national guidelines and training for paediatricians and clinical coders on completing neonatal and post-neonatal death certificates and coding can minimise any potential errors and variations.

Finally, very few congenital anomalies have severity classifications. In this analysis CHDs were classified broadly into 'less', 'moderate' and 'most' severity based on previously defined hierarchical severity rankings according to the associated perinatal mortality rate (EUROCAT 2020a; Khoshnood et al. 2012). However, the ICD coding system does not have detailed information about the severity of the CHDs, which can vary within the anomaly subtypes. For example, although a ventricular septal defect (VSD) was classified as a 'less severe' CHDs, the ICD classification system does not provide important details with regard to the size of the defects which can affect the prognosis given that a larger VSD is often associated with a poorer prognosis compared to a smaller VSD and more likely to require surgery (Best and Rankin 2016). The mortality risk estimates presented for the severity groups of CHDs would therefore potentially be either under- or over- estimated.

6.5.4 Implications for clinical practice and population health

The findings of this study have significant implications for clinical practice and public health interventions aiming to reduce anomaly-associated infant mortality.

In relation to primary prevention, the findings of this study have advanced our knowledge of potentially modifiable risk factors for mortality of infants affected by congenital anomalies. An

example of which includes smoking cessation advice for women of reproductive age to reduce infant death including anomaly-related infant deaths.

For secondary prevention, ethnic inequality in anomaly-related infant mortality in Wales would justify public health interventions to be targeted more widely, and to minimise social barriers and inequality in access to healthcare, for example, to ensure consistent provision of the fetal anomaly screening programme nationally.

For tertiary prevention, this study has advanced the knowledge about the main and underlying causes of death of neonates and post-neonatal infants affected by different subgroups of congenital anomalies. This knowledge can help clinicians to plan and prioritise care and interventions to target anomaly-associated conditions, comorbidities and complications in high-risk population. These include, for example, a multidisciplinary approach to prevent, treat and care for immaturity-related conditions (e.g. premature lung disease, necrotising enterocolitis and neonatal infections etc.), and an early access to specialists and nutritional support in order to optimise neonatal outcomes of infants affected by congenital anomalies. Previous studies have demonstrated that an effective management of complications related to prematurity plays a crucial role in reducing infant mortality in general and of those affected by congenital anomalies (Behrman and Butler 2007).

Finally, the findings of this study provide a general reference for clinicians to assess the prognosis and counsel parents about their babies affected by an anomaly.

Table 6.22: What this mortality study adds

- This is the first UK population-based cohort study investigating the impact of overall and selected groups of congenital anomalies and rare diseases on infant mortality.

- Anomaly-related deaths represented about one-third of all infant deaths in Wales (1998-2016 birth cohort).

- Infants born with an anomaly have a greater risk of death in infancy, compared to infants without an anomaly.

- Infants with multiple and structural anomalies (e.g. CHDs) contribute the greatest proportion of anomaly-related infant deaths. Abdominal wall defects and congenital diaphragmatic hernias were associated with the highest infant case fatality.

- Congenital anomalies, and their associated diseases and complications were the most frequently recorded main or underlying causes of death for infants with anomalies who died.

- Preterm birth is the strongest risk factor significantly associated with excess infant mortality in all anomaly subgroups investigated. The odds of excess infant mortality significantly increased as gestational age at birth decreased.

- The effects of maternal ethnicity, maternal smoking, parity, infant sex, CHD severity and surgery on excess infant case fatality vary according to the anomaly subgroup.

- Variations in the mortality risk depend critically on the anomaly subtypes and disease severity.

- Further mortality studies of infants with specific anomalies are needed using a larger dataset to minimise heterogeneity.

Chapter 7: Hospitalisation Of Infants Born With Congenital Anomalies: A Structured Literature Review

7.1 Introduction

Congenital anomalies are an important cause of infant morbidities and a leading cause of paediatric hospitalisation (Billet et al. 2008; McCandless et al. 2004; Yoon et al. 1997). Infants who are born with congenital anomalies are at an increased risk of morbidity and hospitalisation due to the short- and long-term sequelae and complications associated with the anomalies, compared to infants born without an anomaly (Colvin and Bower 2009). For many infants affected by an anomaly, the chronicity of the condition and burden of hospitalisation has a profound impact on the child's wellbeing and development (Newacheck and Kim 2005).

There is little existing research investigating the impact of all congenital anomalies on infant morbidity and hospitalisation at a population health scale, with many previous studies based in single-centre settings or studies focusing on only one anomaly group involving a major system such as nervous system anomalies, congenital heart defects (CHDs), respiratory system anomalies and Down syndrome. Such knowledge however, is essential for informing clinicians about the potential risk of anomaly-associated morbidities and complications, counseling of parents and carers about the reasons for and patterns of anomaly-related hospitalisation of their affected infant, planning and commissioning health and specialist service, as well as informing future research.

A structured literature review was conducted to summarise the current evidence about hospitalisation of infants with congenital anomalies.

7.1.1 Aim and objectives

The overall aim of this structured literature review was:

- To investigate the current evidence about the impact of congenital anomalies on infant hospitalisation.

The specific objectives were:

7a) To describe the rates of hospitalisation by anomaly subgroups;

7b) To describe the pattern (i.e. causes, frequency and length of stay) of hospitalisation by anomaly subgroups;

7c) To describe the risk factors for hospitalisation of infants with a congenital anomaly.

7.2 Methods

7.2.1 Search sources and strategy

Comprehensive literature searches of Pubmed and Google Scholar were conducted from 1st January, 1998 to 6th October, 2020 in order to identify relatively contemporary evidence. Based on the concepts of Population, Exposure(s), Comparison(s) and Outcome (PECO), MeSH terms and key words were entered systematically into the search databases as follow:

For Pubmed: *congenital abnormalities* and *hospitalization* and *infant* [MeSH].

For Google Scholar: *"birth defects" hospitalizations infant* [controlled vocabulary].

The detailed search terms are shown in Table 7.1. There were no restrictions on language on searching the articles. Additional studies found in the references of relevant publications that met the inclusion criteria were added.

The literature searches were conducted with the assistance of a specialist information librarian (NR) from the Bodleian Libraries who advised on the search terms and databases for this review.

The literature search of the structured literature review was originally conducted from 1st January, 1998 to 26th April, 2018 the date when the search strategy was finalised. This search was later updated to 6th October, 2020 when the full draft of this thesis was being reviewed and finalised.

Table 7.1: Detailed search terms (an example from PubMed search).

Detailed Search Terms Using PubMed Online Database
("congenital abnormalities"[MeSH Terms] AND "hospitalization"[MeSH Terms]) AND "infant"[MeSH Terms] AND (("1998/01/01"[PDAT] : "2020/10/06"[PDAT]) AND "humans"[MeSH Terms] AND ("infant"[MeSH Terms] OR "child"[MeSH Terms] OR "adolescent"[MeSH Terms]))

7.2.2 Selection criteria

Titles and abstracts of all identified studies were screened by the author (PH) according to the inclusion criteria. For articles which satisfied the first screen, full articles were retrieved and screened by PH for their eligibility according to the full inclusion and exclusion criteria. Any screening problems were discussed, reviewed and resolved by the authors' review team (PH, MQ and JK).

Inclusion criteria

Population-based studies were included if they:

(1) provided data or analyses of the rates of hospitalisation of infants with a congenital anomaly;

(2) provided data or analyses of patterns (i.e. causes, frequency and length of stay), and risk factors of hospitalisation of infants with a congenital anomalies; and

(3) were conducted in high-income countries as defined by the World Bank (The World Bank 2019).

Exclusion criteria

Studies were excluded if:

(1) they did not provide hospitalisation data of infants with a congenital anomaly; and

(2) they were interventional studies investigating mainly the efficacy of medical or surgical treatment.

All major and minor congenital anomalies were included if they met the inclusion criteria.

For rare anomaly subtypes where population-based studies were limited, studies from single centres were included in order to optimise the available data.

7.2.3 Data extraction

Data extraction was performed according to the methods recommended in the Cochrane data collection (Higgins et al. 2008). The data extraction form was piloted (by PH) prior to use to ensure standardised methodology.

For each included study, the following data were extracted: study population, study design, data source(s), sample size (this included the total number of livebirths affected by anomaly), country of study, year of birth cohort, anomaly type, anomaly diagnostic code, main outcomes and measures, age of the study cohort, co-morbidities and complications, the cause(s) or reason(s) for hospitalisation, incidence, frequency (i.e. number of admissions per child admitted) and length of stay (LOS) (i.e. median and mean LOS in a single admission or across all admissions) in hospital, and descriptive/ hospitalisation data about socio-demographic, maternal, infant and organisational factors etc.

7.2.4 Main outcomes and measures

The main outcomes and measures were:

1. Rates of infant hospitalisation (by anomaly subgroups), which was defined as the number of admissions per person year in the first year after birth.
2. Pattern (i.e. causes, frequency and LOS) of hospitalisation of infants with an anomaly in the first year after birth or early childhood;
3. Risk factors for hospitalisation of infants affected by a congenital anomaly.

Rates and pattern of hospitalisation of infant with a congenital anomaly were compared with those of infants without a congenital anomaly (the comparison group) where appropriate.

7.2.5 Data synthesis and analysis

The extracted data from the included studies were categorised and analysed by congenital anomaly subgroups according to the EUROCAT classification (EUROCAT 2013).

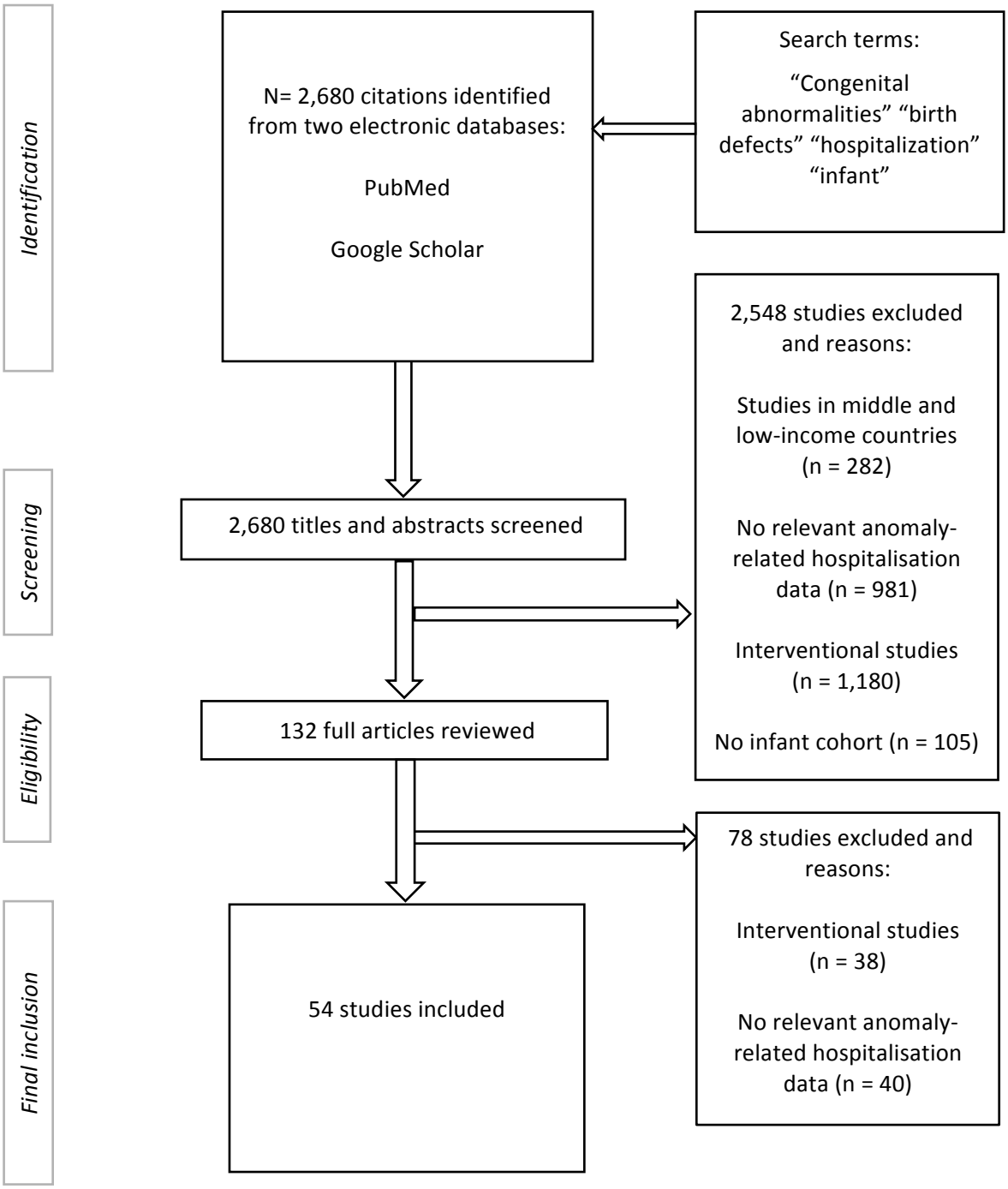
Data for each anomaly subgroup were reviewed to assess the inclusion in a quantitative analysis where possible. Where quantitative analysis was not possible due to limited data or studies, study data were described qualitatively by anomaly subgroup. Rates, means, medians, risk ratios and the corresponding 95% confidence intervals (CI) were reported or calculated where appropriate. P-value < 0.05 was considered as statistically significant.

The reporting of the results from the literature searches was in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram (Moher et al. 2015).

7.3 Results

The flow of literature through the review is summarised in the PRISMA diagram (Figure 7.1). Of 2,680 articles identified, 54 met the inclusion criteria.

Figure 7.1: PRISMA diagram for the flow of studies through the structured literature review (1.1.1998 to 6.10.2020).



7.3.1 Study characteristics

Study population and design

Of the 54 included studies, there were 30 population-based cohort studies, 18 multi-centre cohort studies, three single-centre cohort studies, one multi-centre case-control studies, as well as one cross-sectional study and one case series (Table 7.2). All the included studies were conducted in high-income countries: 35 studies were conducted in North America: the U.S. (29) and Canada (6); five in Australia; 11 in Europe: the UK (4), Denmark (1), Spain (2), Sweden (1), France (1), Norway (1) and Switzerland (1); and three were conducted by international collaborations. These studies included a total study population of more than 538,000 liveborn infants with any congenital anomalies (median: 842, range: 58 – 200,344). The years of birth spanned 1977 to 2015.

Anomaly subgroups included

There were three studies which reported hospitalisation of infants with all specific congenital anomaly subgroups or anomalies overall. In addition, there were three studies which reported hospitalisation of infants with anomalies of the nervous system; one study which reported hospitalisation of infants with eye, ear, face and neck anomalies; 16 studies which reported hospitalisation of infants with CHDs; three studies which reported hospitalisation of infants with anomalies of the respiratory system; five studies which reported hospitalisation of infants with orofacial clefts; five studies which reported hospitalisation of infants with anomalies of the digestive system; eight studies which reported hospitalisation of infants with abdominal wall defects; two studies which reported hospitalisation of infants with anomaly of the genital system; one study reported hospitalisation of infants and children with musculoskeletal anomalies; and nine studies which reported hospitalisation of infants with chromosomal disorders.

Table 7.2: Description of included studies. *(Note: the included studies are ordered by birth year and EUROCAT anomaly subgroup heading (EUROCAT 2013a))*

EUROCAT subgroup: All anomalies							
Author, study location	**Birth years**	**Study design**	**Data source**	**Sample size (N)**	**Disease code**	**Main outcomes and measures**	**Age of study cohort**
Colvin and Bower (2009) Western Australia	1980-1999	Population-based cohort	Birth defect registry linked to hospital admission data.	25,734	ICD-9-CM[1]	Pattern of and risk factors for hospitalisation of children with a congenital anomaly.	0-5 years
Rutkowski (2017) Florida, USA	2006-2010	Population-based case-control	Birth defect registry linked to hospital discharge records.	Cases = 40,409; controls = 172,720.	ICD-9-CM	Risk factors for hospitalisation due to injuries in children with birth defects.	0-3 years
Hardy (2019) USA	2006-2013	Population-based cohort	Premier Healthcare Database.	200,344	ICD-9-CM	Risk of hospitalisation for common neonatal morbidities in preterm and term infants with a congenital anomaly.	0-1 year
EUROCAT subgroup: Nervous System							
Author, study location	**Birth years**	**Study design**	**Data source**	**Sample size (N)**	**Disease code**	**Main outcomes and measures**	**Age of study cohort**
Radcliff (2012) Florida, USA	1998-2007	Population-based cohort	Florida Birth defect registry linked to hospital discharge records.	615	ICD-9-CM	Pattern of hospitalisation of infants with spina bifida.	0-1 year

Table 7.2 (continued): Description of included studies.

EUROCAT subgroup: Nervous System (continued)							
Author, study location	**Birth years**	**Study design**	**Data source**	**Sample size (N)**	**Disease code**	**Main outcomes and measures**	**Age of study cohort**
Wes (2017) Philadelphia, USA	2004-2015	Population based cohort	Paediatric Health Information System (49 institutions).	13,112	ICD-9-CM	Pattern of and risk factors for hospitalisation of children who underwent craniosynostosis surgery.	0-5+ years
Cherian (2016) USA	2013-2014	Population-based cohort	NSQIP-P[1]	114	Current Procedural Terminology and ICD-9.	Risk factors for complications in infants who underwent postnatal myelomeningocele repair.	0-30 days
EUROCAT subgroup: Eye							
Author, study location	**Birth years**	**Study design**	**Data source**	**Sample size (N)**	**Disease code**	**Main outcomes and measures**	**Age of study cohort**
Dharmasena (2017) England, UK	1999-2011	Population-based cohort	Linked Hospital Episodes Statistics data to Hospital In-Patient Enquiry, Oxford Record Linkage Study and ONS.	Anophthalmia, n < 100; microphthal-mia, n ~ 500; lacrimal malformation, n < 50.	ICD-9 and 10.	Pattern of hospitalisation of children with congenital orbital/ lacrimal malformation.	0-1 year

Table 7.2 (continued): Description of included studies.

EUROCAT subgroup: Congenital heart defects (CHDs)							
Author, study location	**Birth years**	**Study design**	**Data source**	**Sample size (N)**	**Disease code**	**Main outcomes and measures**	**Age of study cohort**
Dyamenahalli (2000) Toronto, Canada	1987-1994	Single-centre cohort	Sick Kids' hospital records, cardiac surgery database and autopsy reports.	89	Not specified.	Risk factors for ICU[1] hospitalisation of infants with Tetralogy of Fallot.	0-18 months
Mackie (2008) Québec, Canada	1990-2005	Population-based cohort	Administrative database.	3,675	ICD-9	Pattern of and risk factors for (< 30 days) readmissions of children with CHD.	0-17 years
Billett (2008) England and Wales, UK	1995-2004	Population-based cohort	Hospital Episode Statistics and mortality statistics.	~83,000 (estimated no. of admissions)	ICD- 9 and 10.	Pattern of hospitalisation of children with CHD.	0-1 year
Duppenthaler (2004) Switzerland	1997-2003	Population-based cohort	Surveillance programme and registry.	729	ICD-10	Pattern of RSV-related hospitalisation of infants with HS-CHD[1].	0-24 months
Jortveit (2016) Norway	1994-2009	Population-based cohort	Birth registry, registry of CHDs and death registry.	3,495	ICD- 8, 9 and 10.	Complications of isolated VSD[1] requiring hospitalisation or interventions.	From birth
Medrano (2007) Spain	2004-2005	Multi-centre cohort	Medical records from 53 Spanish hospitals.	760	ICD-10	Pattern of and risk factors for RSV-related hospitalisation in infants with HS-CHD[1].	0-24 months

Table 7.2 (continued): Description of included studies.

EUROCAT subgroup: Congenital heart defects (CHDs) (continued)							
Author, study location	**Birth years**	**Study design**	**Data source**	**Sample size (N)**	**Disease code**	**Main outcomes and measures**	**Age of study cohort**
Simsic (2009) Atlanta, USA	2003-2006	Population-based cohort	Cardiac surgical database.	609	Not specified.	Pattern of hospitalisation of children who underwent CHDs surgery.	0-28 days
Li (2016) Sweden	2000-2010	Population-based cohort	National database.	1,499	ICD-10	Pattern of and risk factors for hospitalisation of children with CHDs.	0-11 years
Desai (2017) USA	2003, 2006, 2009 and 2012.	Multi-centre cohort	Kids' Inpatient Database (KID).	27,434	ICD-9-CM	Risk factors for hospitalisation of preterm infants with CHDs (ASD[1] were excluded).	0-28 days
Ghimire (2020) USA	2003, 2006, 2009 and 2012.	Multi-centre cohort	KID	7,094	ICD-9-CM	Risk factors for hospitalisation of infants underwent TOF and TA[1] surgery.	0-1 year
Islam (2018) Canada	2005-2014	Population-based cohort	Hospital records linked with Vital Statistics Birth/ Death Database, and Healthcare Insurance Registry.	7,007	ICD-10	Pattern of and risk factors for hospitalisation of children with CHDs.	0-5 years
Saharan (2014) Oregon, USA	2008-2012	Multi-centre cohort	Hospital records, surgical database.	811	Not specified.	Risk factors for 30-day readmissions of children who underwent CHDs operations.	0 to > 1 year

Table 7.2 (continued): Description of included studies.

EUROCAT subgroup: Congenital heart defects (CHDs) (continued)							
Author, study location	**Birth years**	**Study design**	**Data source**	**Sample size (N)**	**Disease code**	**Main outcomes and measures**	**Age of study cohort**
Smith (2015) USA	2011-2012	Multi-centre cohort	Inpatient database from 43 tertiary hospitals.	17,871	ICD-9	Readmissions patterns of children who underwent CHD surgery within 30 days of discharge.	0 to <5 years
Peyvandi (2017) California, USA	2011-2013	Multi-centre cohort	Fetal Consortium (five tertiary centres).	296	ICD-9	Risk factors for hospitalisation of infants who required complex-CHD surgery within 30 days of life.	0-28 days
Kogon (2019) USA	2014-2016	Multi-centre cohort	The Society of Thoracic Surgeons Congenital Heart Surgery Database.	56,429	Not specified.	Pattern of and risk factors for hospitalisation of children who underwent CHD surgery.	0-18 years
Soliman (2015) *(Abstract)* Michigan, USA	Not specified	Single-centre cohort	Hospital records.	117	Not specified.	Pattern of and risk factors for readmissions of children with hypoplastic left heart syndrome/ transposition of great arteries.	Not specified

Table 7.2 (continued): Description of included studies.

EUROCAT subgroup: Respiratory system							
Author, study location	**Birth years**	**Study design**	**Data source**	**Sample size (N)**	**Disease code**	**Main outcomes and measures**	**Age of study cohort**
Altman (1999) Philadelphia, USA	1991-1996	Case series	Hospital records in a tertiary center.	174	ICD-9	Pattern of hospitalisation of children with congenital airway abnormalities.	0-1+ years
Marston (2019) USA	2012-2015	Population-based cohort	American College of Surgeons' NSQIP-P[1].	178	ICD-9	Risk factors for hospitalisation of infants and children who underwent choanal atresia.	0-1+ years
EUROCAT subgroup: Orofacial clefts							
Author, study location	**Birth years**	**Study design**	**Data source**	**Sample size (N)**	**Disease code**	**Main outcomes and measures**	**Age of study cohort**
Leclerc (1999) Québec, Canada	1983-1995	Population-based cohort	MED-ECHO database[1].	Branchial cyst and sinus: ~2,850; choanal atresia: ~330; cleft palate/lips: ~2,040; thyroglossal duct and cyst: ~2,580.	ICD-9	Pattern of hospitalisation of children with a choanal atresia, isolated cleft lip, isolated cleft palate, branchial cyst-sinus and thyroglossal duct cyst-sinus.	From birth
Razzaghi (2015) Florida, USA	1998-2006	Population-based cohort	Birth registry linked with hospital discharge data.	2,129	ICD-9-CM	Pattern of and risk factors for hospitalisation of infants and children with a cleft lip.	0-2 years

Table 7.2 (continued): Description of included studies.

EUROCAT subgroup: Orofacial clefts (continued)							
Author, study location	**Birth years**	**Study design**	**Data source**	**Sample size (N)**	**Disease code**	**Main outcomes and measures**	**Age of study cohort**
Fitzsimons (2013) England, UK	1997-2008	Population-based cohort	Hospital Episode Statistics, procedure information and birth registry data.	10,892	ICD-10 and OPCS-4[1].	Pattern of and risk factors for hospitalisation of infants and children with a cleft lip and/or palate.	0-2 years
Wu (2019) USA	2000-2009	Multi-centre cohort	KID[1]	22,972	ICD-9-CM	Risk factors for hospitalisation of infants and children who underwent cleft palate repair.	0- <3 years
Lo (2015) Western Australia	2000-2010	Population-based cohort	National Hospital Morbidity database, birth defect registries and monitoring programs.	3,778	ICD-10-AM[1]	Pattern of and risk factors for hospitalisation of children with a cleft lip and/or palate.	All ages
EUROCAT subgroup: Digestive system							
Author, study location	**Birth years**	**Study design**	**Data source**	**Sample size (N)**	**Disease code**	**Main outcomes and measures**	**Age of study cohort**
Sayari (2016) USA	1997, 2000, 2003, 2006 and 2009.	Population-based cohort	KID[1]	861	ICD-9-CM	Patterns of hospitalisation of children with oesophageal atresia and tracheoesophageal fistula who underwent repair.	Not stated

Table 7.2 (continued): Description of included studies.

EUROCAT subgroup: Digestive system (continued)							
Author, study location	**Birth years**	**Study design**	**Data source**	**Sample size (N)**	**Disease code**	**Main outcomes and measures**	**Age of study cohort**
Burgos (2017) International collaboration	2001-2015	Multi-centre cohort	CDH Study Group Database (70 centres).	3,906	Not specified.	Risk factors for hospitalisation of newborns with congenial diaphragmatic hernia (CDH).	All ages
Putnam (2016) International collaboration	2007-2014	Multi-centre cohort	>50 international children's hospitals in the CDH study group.	3,665	Not specified.	Patterns of hospitalisation and morbidity of infants and children with CDH.	0- <3 months
Benoist (2016) France	2009-2013	Multi-centre cohort	Hospital records in three tertiary centres from the Respirare database.	86	Not specified.	Pattern of wheeze-related readmission of children with CDH.	0-2 years
Garcia (2018) USA	2012-2015	Multi-centre cohort	NSQIP-P[1]	190	Current Procedural Terminology.	Risk factors for hospitalisation of children who underwent surgery for biliary atresia.	0-6 months

Table 7.2 (continued): Description of included studies.

EUROCAT subgroup: Abdominal wall defects							
Author, study location	**Birth years**	**Study design**	**Data source**	**Sample size (N)**	**Disease code**	**Main outcomes and measures**	**Age of study cohort**
Sharp (2000) Western Australia	1986-1996	Population-based cohort	Birth defect registry.	58	Not specified.	Pattern of hospitalisation of infants with gastroschisis.	0-1 year
Weinsheimer & Yanchar (2008) Canada	2005-2006	Multi-centre cohort	Canadian Pediatric Surgery Network (CAPSNet[1]).	114	Not specified.	Risk factors for hospitalisation of infant with gastroschisis.	-
Boutros (2009) Canada	2005-2007	Population-based cohort	CASPNet[1]	192	Not specified.	Risk factors for hospitalisation of infants with gastroschisis.	0-1+ years
Bradnock (2011) UK and Ireland	2006-2008	Population-based cohort	National congenital anomalies surveillance system.	301	Not specified.	Pattern of hospitalisation of infants with gastroschisis.	0-1 year
Youssef (2016) International collaboration	2003-2012 (USA) 2005-2013 (Canada)	Multi-centre cohort	CASPNet[1] and KID[1]	5,216 (USA) and 695 (Canada).	ICD-9 and ICD-9-CM.	Pattern of and risk factors for hospitalisation of children with gastroschisis between USA and Canada.	From birth to discharge
Raymond (2020) USA	2005-2013	Multi-centre cohort	Multi-institutional database.	566	ICD-9-CM	Risk factors for hospitalisation of neonates with gastroschisis.	0-28 days

Table 7.2 (continued): Description of included studies.

EUROCAT subgroup: Abdominal wall defects (continued)							
Author, study location	**Birth years**	**Study design**	**Data source**	**Sample size (N)**	**Disease code**	**Main outcomes and measures**	**Age of study cohort**
Apfeld (2017) California, USA	2008-2014	Population-based cohort	130 CPQCC[1] NICUs[1].	1,588	CPQCC birth defects codes.	Risk factors for hospitalisation of newborns with gastroschisis.	0-1 year
Fullerton (2017) USA	2009-2014	Multi-centre cohort	Vermont Oxford Network (VON): 175 North American centers.	4,420	Vermont Oxford field code.	Pattern of hospitalisation of neonates with gastroschisis.	0-1 year
EUROCAT subgroup: Genital system							
Author, study location	**Birth years**	**Study design**	**Data source**	**Sample size (N)**	**Disease code**	**Main outcomes and measures**	**Age of study cohort**
Meyer (2015) USA	1998-2010	Multi-centre cohort	Inpatient discharge data (Nationwide).	5,323	ICD-9-CM	Patterns of hospitalisation of children with hypospadias.	0-18+ years
Roth (2018) USA	2004-2015	Multi-centre cohort	Paediatric Health Information System.	45,264	ICD-9-CM	Risk factors for hospitalisation of children with hypospadias.	0-18+ years
EUROCAT subgroup: Chromosomal disorders							
Author, study location	**Birth years**	**Study design**	**Data source**	**Sample size (N)**	**Disease code**	**Main outcomes and measures**	**Age of study cohort**
Zhu (2013) Denmark	1977-2008	Population-based cohort	National health registry.	3,212	ICD- 8 and 10.	Pattern of hospitalisation of infants with Down syndrome.	0-1 year

Table 7.2 (continued): Description of included studies.

EUROCAT subgroup: Chromosomal disorders (continued)							
Author, study location	**Birth years**	**Study design**	**Data source**	**Sample size (N)**	**Disease code**	**Main outcomes and measures**	**Age of study cohort**
Fitzgerald (2013) Western Australia	1983-2004	Population-based cohort	Birth records linked to intellectual Disability database, and Hospital Morbidity Data.	405	ICD-9-CM and 10.	Pattern of RSV[1]-related hospitalisation of children and adults with Down syndrome.	0-22 years
Hilton (1999) New South Wales, Australia	1991-1998	Single-centre cohort	Health Service Disease Index system.	232	Disease index system coding.	Pattern of and risk factors for respiratory-related hospitalisation of children with Down syndrome.	0-17 years
So (2007) Tennessee, USA	1997-1999	Population-based cohort	Tennessee Hospital Discharge Data System.	217	ICD 9	Pattern of hospitalisation in Down syndrome children with CHD vs. without CHD.	0-3 years
Zachariah (2012) Colorado, USA	1995-2006	Population-based cohort	Health and Hospital Association database linked with birth data from Department of Public Health and Environment.	630	ICD-9-CM	Pattern of RSV-related hospitalisation of infants with Down syndrome.	0-2 years

Table 7.2 (continued): Description of included studies.

EUROCAT subgroup: Chromosomal disorders (continued)							
Author, study location	**Birth years**	**Study design**	**Data source**	**Sample size (N)**	**Disease code**	**Main outcomes and measures**	**Age of study cohort**
Derrington (2013) Massachusetts, USA	1999-2004	Population-based cohort	Birth certificates linked to birth defects registry and hospital discharge data.	504	ICD-9-CM/ BPA[1].	Pattern of hospitalisation of children with Down syndrome.	0-3 years
Nelson (2012) USA	1997, 2000, 2003, 2006 and 2008.	Cross-sectional	KID[1]	Trisomy 13 (4,309), Trisomy 18 (6,630).	ICD-9-CM	Pattern of hospitalisation of children with Trisomy 13 and Trisomy 18.	0 to 20 years
Stagliano (2015) USA	2005-2011	Population-based cohort	National health system database.	842	ICD-9-CM	Pattern of RSV-related hospitalisation of children with Down syndrome.	0-3 years
Sánchez-Luna (2017) Spain	2012-2013	Multi-centre case-control	Neonatal/ Cardiology medical records in 50 acute-care hospitals.	161	Not specified.	Pattern of RSV-related hospitalisation in infants with Down syndrome.	0-1 year

[1]ASD = atrial septal defect; BPA = British Paediatric Association Classification of Diseases; CASPNet = Canadian Pediatric Surgery Network; CDH = Congenital diaphragmatic hernia; CHDs = Congenital heart defects; CPQCC = California Perinatal Quality Care Collaborative; HS-CHD = Haemodynamically significant congenital heart disease, which is a clinical diagnosis with various definitions but generally including cyanotic heart disease (i.e. tetralogy of Fallot), moderate to severe pulmonary hypertension and acyanotic heart disease requiring medication for congestive heart failure and cardiac surgical procedures; non HS-CHD include small patent arterial ducts, small ASD, small VSD, and those children with fully repaired CHDs; ICD-CM/ -AM = International Classification of Diseases Clinical Modification/ Australian Modification; KID = Kids' inpatient Database; the MED-ECHO database = a provincial database which records data on acute care hospital admissions in Québec, Canada; NICU = Neonatal intensive care unit; OPCS-4 = Classification of Surgical Operations and Procedures 4th Revision; NSQIP-P = The American College of Surgeons' National Surgery Quality Improvement Program-Pediatric database; PICU = Paediatric intensive care unit; RSV = Respiratory Syncytial Virus; TA = Truncus arteriosus; TOF = Tetralogy of Fallot; VSD = ventricular septal defect.

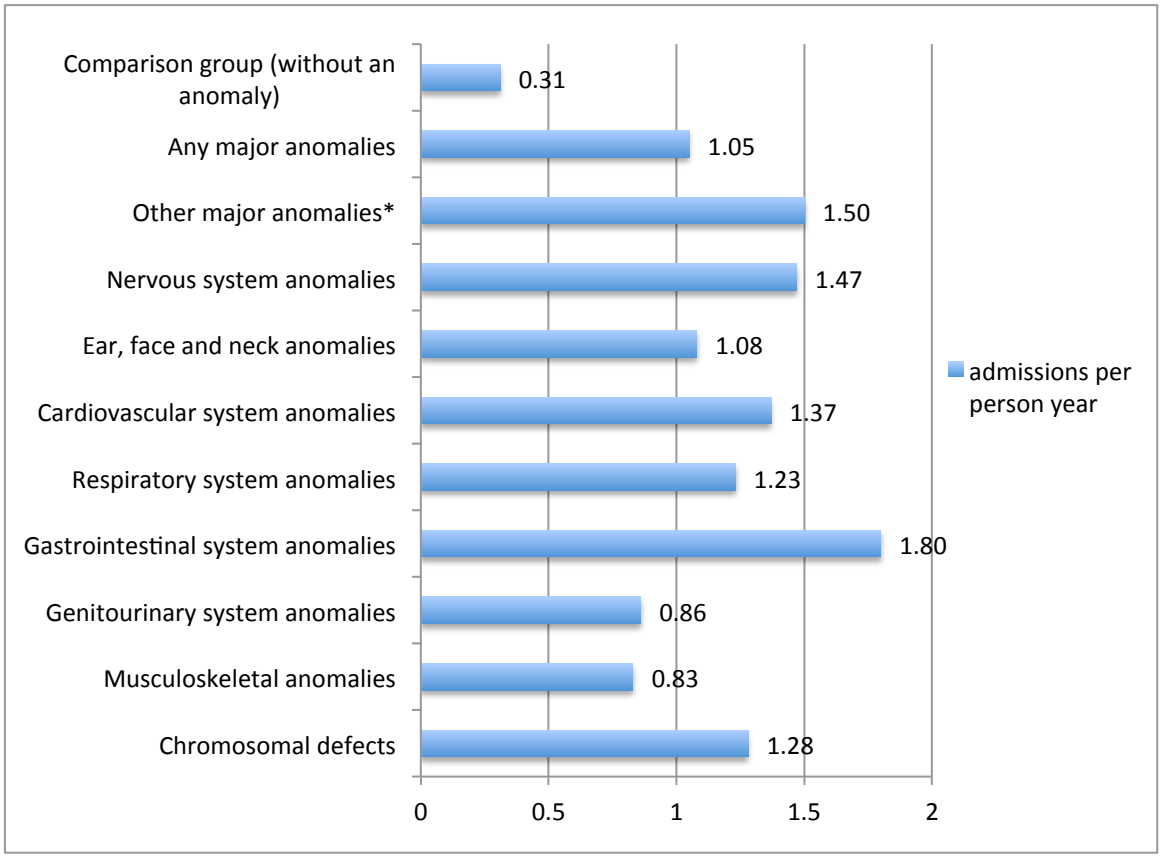
7.3.2 Hospitalisation associated with congenital anomalies overall

Three studies reported hospitalisation of infants and children with all specific congenital anomaly subgroups or anomalies overall (Colvin and Bower 2009; Hardy et al. 2019; Rutkowski et al. 2017). These studies included a total study population of 266,487 infants and children born with anomalies, in which they spanned birth cohorts from 1980 to 2013. The age of study cohort ranged from 0 to 5 years.

Admission rate

The admission rate for infants with a major anomaly was significantly higher than that for infants without an anomaly. The rate of hospitalisation (excluding birth admissions) for infants born with a major anomaly (as defined by CDC (CDC2019a), excluding other and unspecified congenital anomalies, cystic fibrosis, congenital hypothyroidism, hereditary haemolytic anaemias, coagulation defects, neurofibromatosis, muscular dystrophies and other myopathies) was 1.05 admissions per person year between 1980 and 1999, compared to 0.31 admission per person year for infants without an anomaly in Western Australia (Figure 7.2). The rate ratio of admission for an infant with a major anomaly versus an infant without a major anomaly was 2.48 (95% CI: 2.45-2.52) (Colvin and Bower 2009).

Figure 7.2: Infant admission rates by anomaly group, excluding birth admissions, births 1980-1999. (Colvin and Bower 2009)



Note on admission rates: Admission records were merged into one admission record (i.e. counted as one admission) when a child was transferred between hospitals.

**These included other and unspecified congenital anomalies, cystic fibrosis, hereditary haemolytic anaemias, congenital hypothyroidism, coagulation defects, neurofibromatosis, muscular dystrophies and other myopathies.*

The hospitalisation rate for infants with an anomaly increased over time in Western Australia between 1980 and 1994 across all anomaly groups: these included anomalies of the nervous system, eye, ear, face and neck, cardiovascular, respiratory, gastrointestinal, genitourinary, musculoskeletal systems, and chromosomal defects, while the hospitalisation rate for infants without an anomaly has decreased over time in the same period (Colvin and Bower 2009).

Patterns of hospitalisation

Causes of hospitalisation

Overall, the most common causes for hospitalisation of children (0-5 years) with a congenital anomaly were respiratory-related conditions such as asthma and respiratory infections (Colvin and Bower 2009).

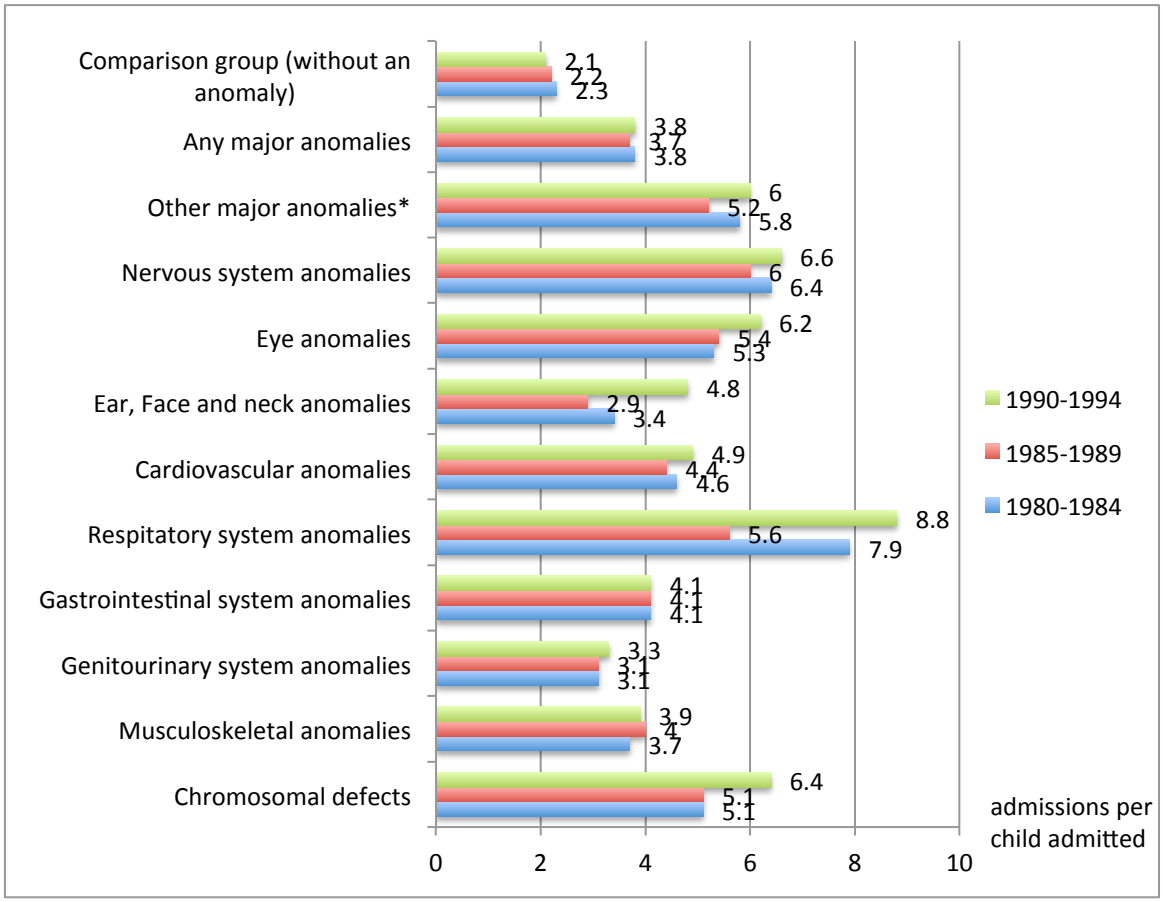
The first five leading specific causes of hospitalisation for infants with a major congenital anomaly were: 1. congenital anomalies of genital organs, 2. asthma, 3. non-suppurative otitis media and Eustachian tube disorders, 4. acute upper respiratory tract infections (URTIs) and 5. general symptoms; whereas the first five leading causes of hospitalisation for infants without a major congenital anomaly were: 1. asthma, 2. general symptoms, 3. other persons seeking consultation without complaint or sickness, 4. acute bronchitis and bronchiolitis and 5. acute laryngitis and tracheitis (Colvin and Bower 2009).

In addition, a case-control study conducted in the U.S. by Rutkowski et al. (2017) found that the risk of hospital admissions due to injuries was higher in children with an anomaly (especially those with a chromosomal disorder such as Down syndrome), compared to children without any anomaly in the first three years of age (adjusted odd ratio, aOR = 1.40, 99% CI: 1.36-1.44).

Frequency of hospital admission

Children (0-5 years) with a major congenital anomaly were admitted more frequently to hospital compared to children (0-5 years) without an anomaly (Figure 7.3). For infants born with a major anomaly, the mean number of hospital admissions was relatively constant between 1980 and 1999 at 2.2 admissions per infant admitted, compared to 1.6 admissions per infant admitted for infants without an anomaly in Western Australia (Colvin and Bower 2009).

Figure 7.3: Mean number of admissions per child (0-5 years) admitted by anomaly subgroup between 1980-1999, excluding birth admissions. (Colvin and Bower 2009)



**These included other and unspecified congenital anomalies, cystic fibrosis, hereditary haemolytic anaemias, congenital hypothyroidism, coagulation defects, neurofibromatosis, muscular dystrophies and other myopathies.*

The largest number of admissions per child was for thalassaemia at 50.5 admissions per child admitted, compared to 2.2 admissions per child admitted for children without an anomaly. The second largest number of admissions per child was for isolated congenital hydrocephalus (8.4 admissions per child admitted) (Figure 7.4).

Furthermore, undescended testis had the greatest proportion of anomaly-related admissions overall for boys up to the first five years of age; whereas developmental dysplasia of hip had the greatest proportion of anomaly-related admissions for girls (Figure 7.5).

Figure 7.4: Most admissions per child admitted by anomaly (0-5 years of age) between 1980 and 1995, excluding birth admissions. (Colvin and Bower 2009)

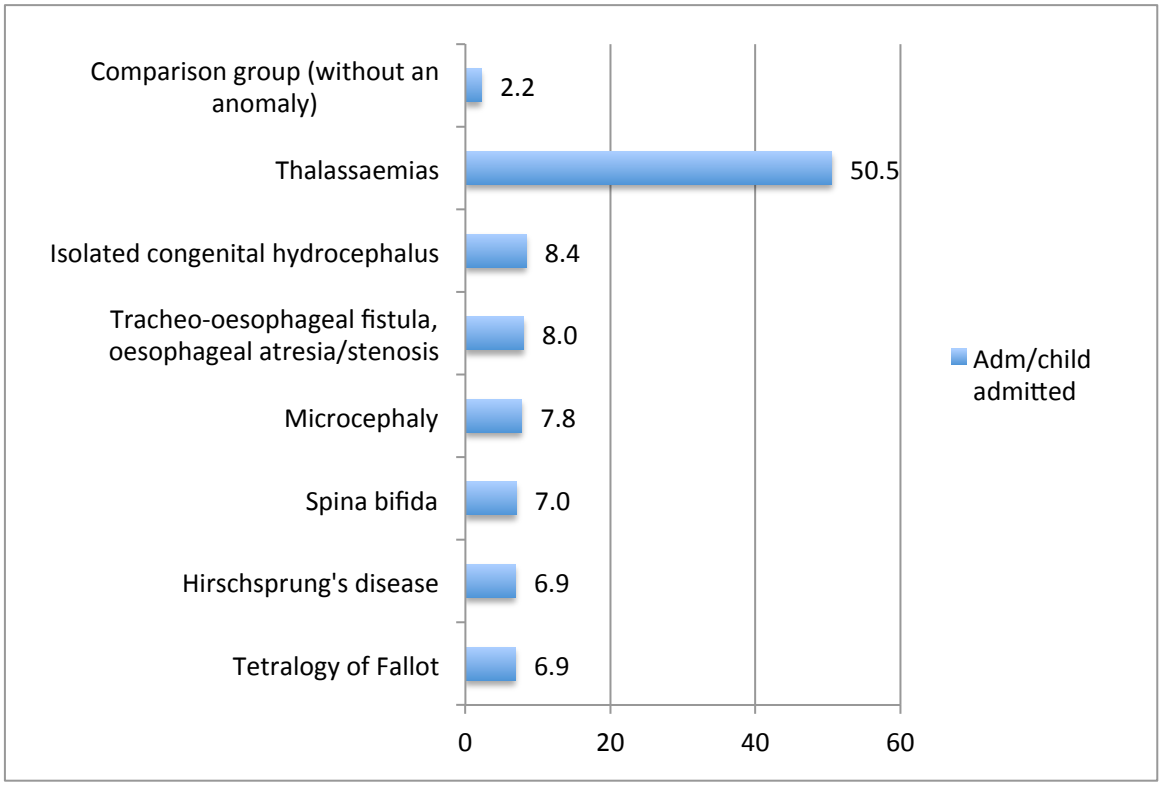
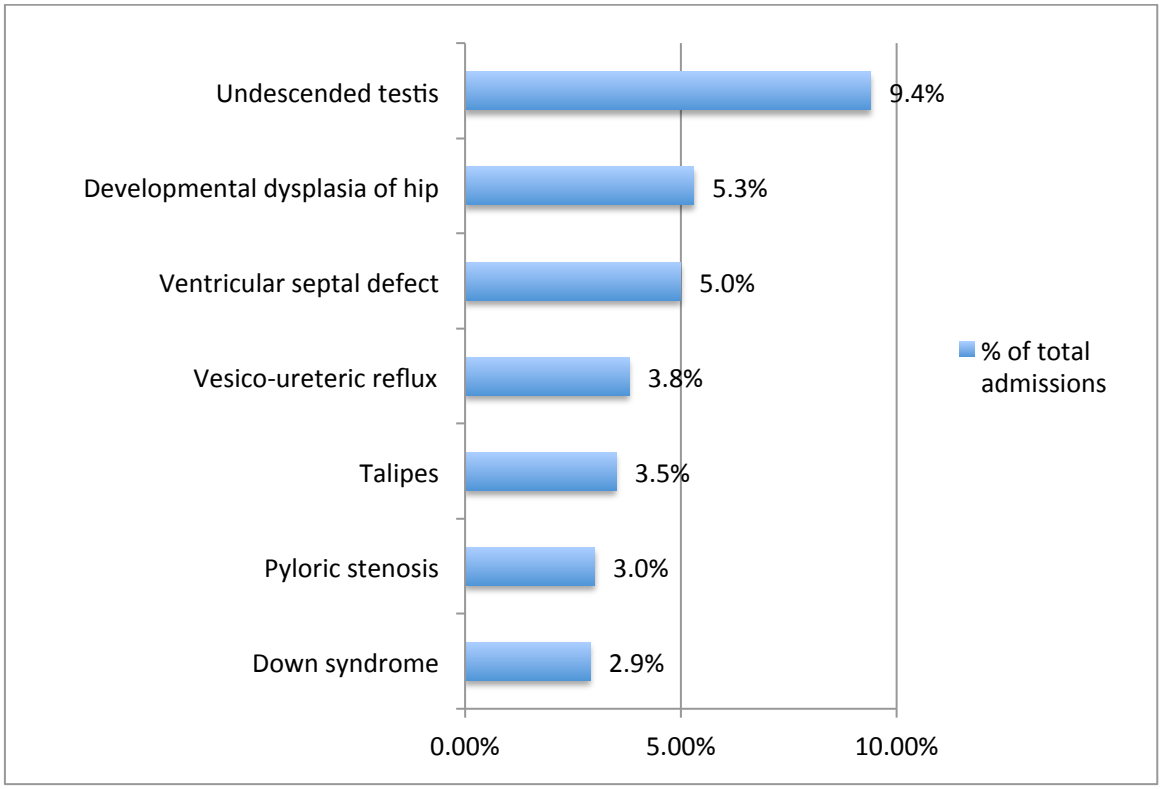


Figure 7.5: Largest number of admissions by anomaly (0-5 years of age) between 1980 and 1995, excluding birth admissions. (Colvin and Bower 2009)



Hospital length of stay (LOS)

Of those infants admitted, infants with a major anomaly had a significantly greater total mean LOS of 10.7 days during infancy, compared to infants without an anomaly (5.5 days) (Figure 7.6). In particular, children with microcephaly had the longest mean total LOS across all admissions (62.5 days), followed by children with Hirschsprung's disease (49.7 days) and cystic fibrosis (49.2 days), compared to children without an anomaly (6.1 days) (Figure 7.7) (Colvin and Bower 2009).

Figure 7.6: Mean total length of stay (LOS) for a single admission and per infant by anomaly subgroup between 1980-1999, excluding birth admissions. (Colvin and Bower 2009)

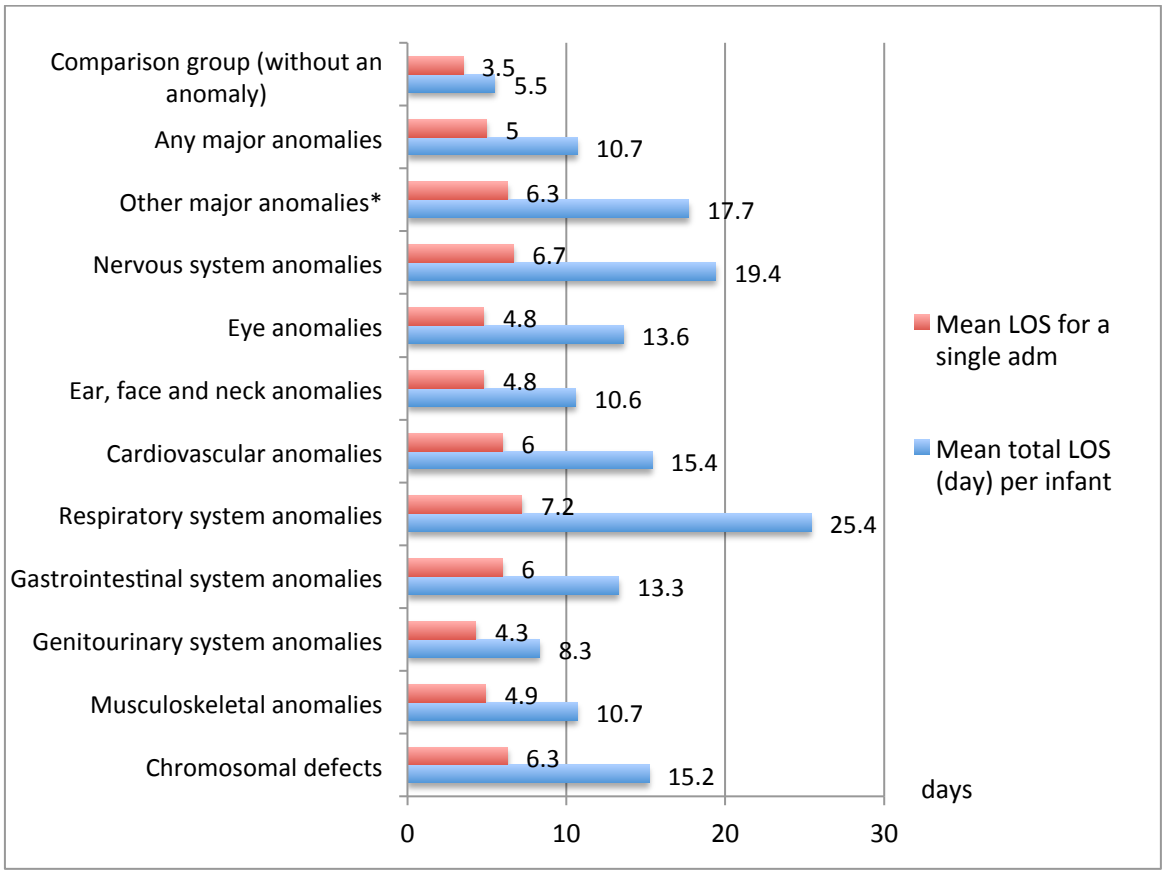
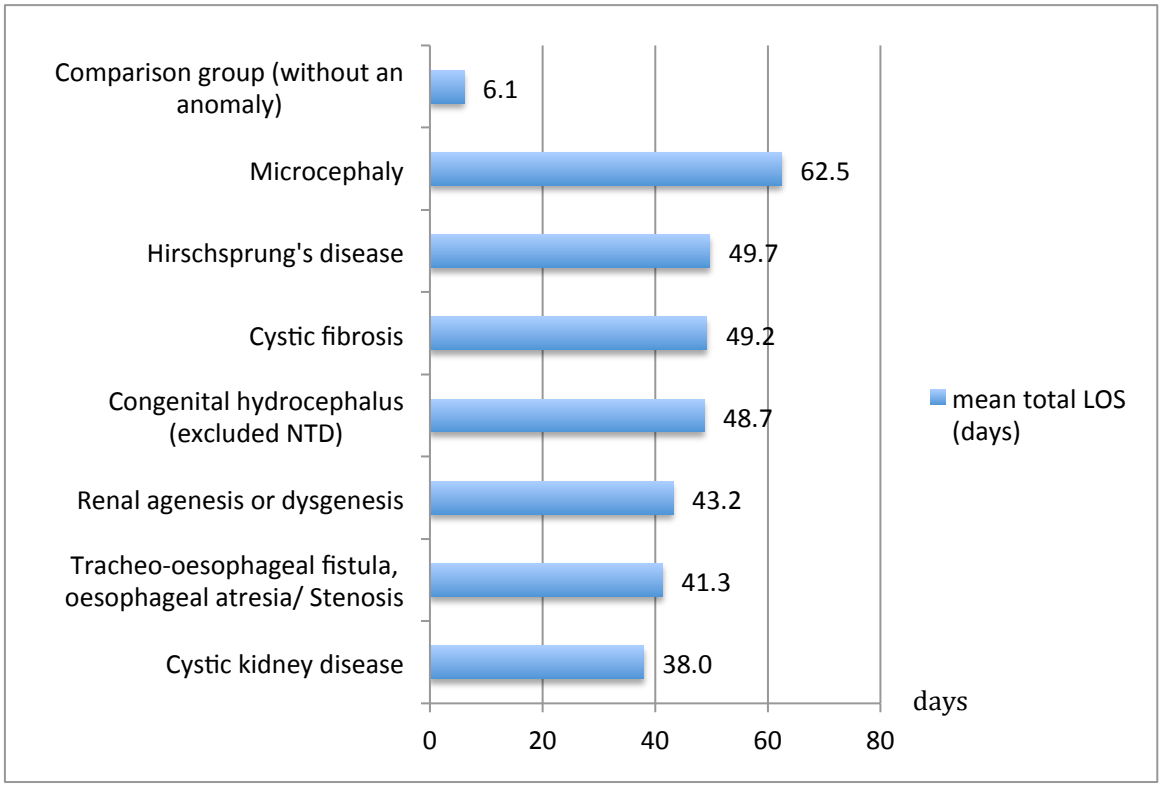


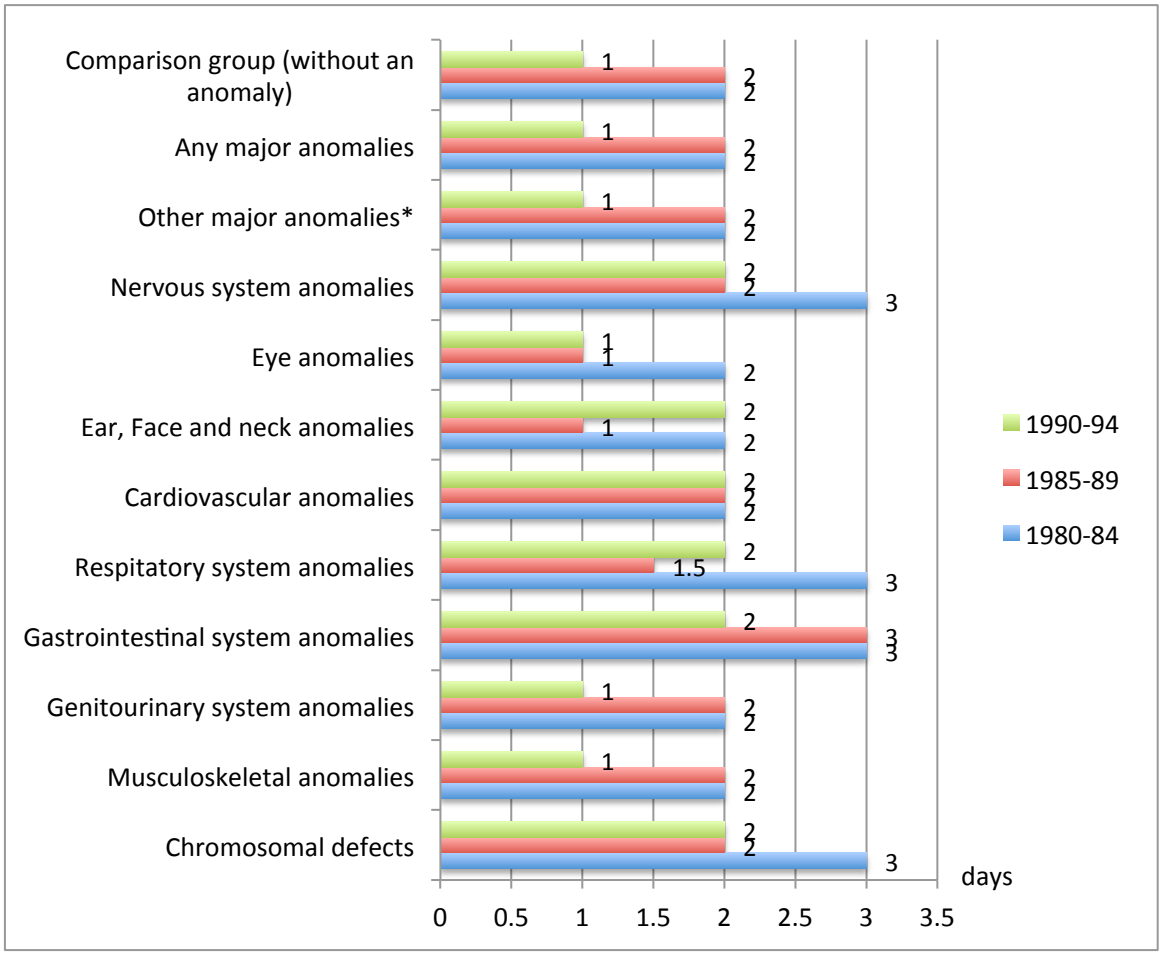
Figure 7.7: Longest mean total length of stay (LOS) by specific anomaly (0-5 years of age) between 1980 and 1995, excluding birth admissions. (Colvin and Bower 2009)



However, the median LOS per admission for infants with and without an anomaly was the same over time in Western Australia (1980-84: 2 days, 1985-89: 2 days, 1990-94: 1 day) (Figure 7.8) (Colvin and Bower 2009). Children (0-5 years) with gastrointestinal defects had the longest median LOS per admission (1980-1989: 3 days).

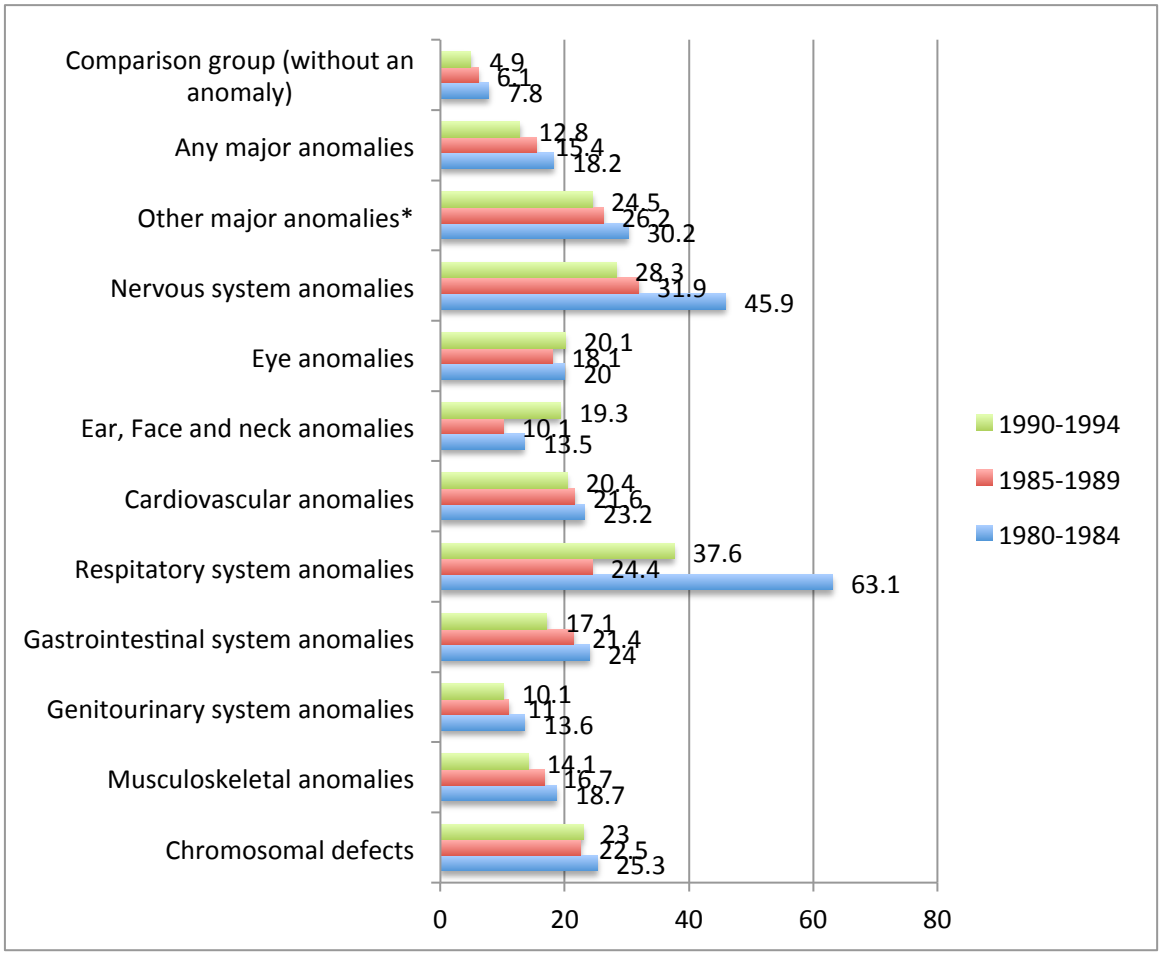
In addition, the mean and median LOS per admission of children aged under five years have declined over time for most major congenital anomalies, as well as in the general population between 1980 and 1994 in Western Australia (Figure 7.8).

Figure 7.8: Median length of stay (days) per admission by anomaly subgroups excluding birth admissions (0-5 years of age), births 1980-1994. (Colvin and Bower 2009)



**These included other and unspecified congenital anomalies, cystic fibrosis, hereditary haemolytic anaemias, congenital hypothyroidism, coagulation defects, neurofibromatosis, muscular dystrophies and other myopathies.*

Figure 7.9: Mean total length of stay (days) per child admitted by anomaly subgroups excluding birth admissions (0-5 years of age), births 1980-1994. (Colvin and Bower 2009)



**These included other and unspecified congenital anomalies, cystic fibrosis, hereditary haemolytic anaemias, congenital hypothyroidism, coagulation defects, neurofibromatosis, muscular dystrophies and other myopathies.*

Risk factors for hospitalisation

Preterm birth was significantly associated with an increased risk of morbidities including respiratory distress syndrome, sepsis, apnoea, any infectious diseases and hyperbilirubinaemia of infants born with congenital anomalies (Hardy et al. 2019).

7.3.3 Hospitalisation associated with anomalies of the nervous system

Four studies reported hospitalisation of infants and children with anomalies of the nervous system (Colvin and Bower 2009; Cherian et al. 2016; Radcliff et al. 2012; Wes et al. 2017). These included a total study population of more than 729 infants with a spina bifida, and 13,112 infants and children with a craniosynostosis; they spanned birth cohorts from 1980 to 2015. The age of study cohort ranged from 0 and 5+ years.

Admission rate

The admission rate for infants with an anomaly of the nervous system (1.47 admissions per person year, excluding birth admissions) was significantly higher than that for infants without an anomaly (0.31 admission per person year) between 1980 and 1999 in Western Australia (Figure 7.2) (Colvin and Bower 2009).

Patterns of hospitalisation

Causes of hospitalisation

Overall, anomalies of the nervous system and associated disorders (such as epilepsy and general symptoms) were the most common causes for hospitalisation of children with an anomaly of the nervous system (Colvin and Bower 2009). For infants who underwent postnatal spina bifida surgical repairs, over one-quarter of them had complications, most commonly post-surgical wound infections during neonatal period (Cherian et al. 2016). For infants born with craniosynostosis, it was estimated that 13% of them experienced vascular, cardiac, neurological or pulmonary complications, in which infection, wound dehiscence, haematoma, haemorrhage, seroma and transfusion-related complications were the most common.

Frequency of hospital admission

Children (0-5 years) with an anomaly of the nervous system were admitted more frequently (mean = 6.0-6.6 admissions per child admitted) to hospital compared to children without an anomaly (mean = 2.1-2.3 admissions per child admitted) between 1980 and 1994 in Western Australia (Colvin and Bower 2009) (Figure 7.3). Among all anomalies of the nervous system, conditions with the most admissions per child (0-5 years) admitted were isolated congenital hydrocephalus (8.4 admissions per child admitted); this was followed by microcephaly (7.8 admissions per child admitted) and spina bifida (7.0 admissions per child admitted), compared to infants without an anomaly (2.2 admissions per child admitted) (Figure 7.4).

Hospital LOS

Infants with an anomaly of the nervous system had a significantly greater mean total LOS of 19.4 days during infancy, compared to infants without an anomaly (5.5 days) (Figure 7.6) (Colvin and Bower 2009). In particular, children with microcephaly and isolated congenital hydrocephalus had some of the longest hospital LOS for infants with any anomaly in infancy with a mean total LOS of 62.5 days and 48.7 days respectively (Figure 7.7). In addition, the median LOS for children (0-5 years) and mean total LOS per child admitted (0-5 years) with an anomaly of the nervous system have declined over time from 3.0 to 2.0 days and 45.9 to 28.3 days respectively between 1980 and 1994 in Western Australia (Figures 7.8 and 7.9) (Colvin and Bower 2009).

Risk factors for hospitalisation

The risk factors for hospital readmissions of infants who underwent surgical repair for spina bifida included low birthweight (< 2500g) (Radcliff et al. 2012) and surgical repair within the first 24 hours after birth (Cherian et al. 2016). In addition, infants who underwent surgery for craniosynostosis in a high-volume surgical centre (i.e. managing > 40 cases per year) were significantly less likely to develop complications (aOR = 0.76, 95% CI: 0.68-0.86) or have an

extended hospital LOS of more than five days (aOR = 0.62, 95% CI: 0.53-0.74), compared to those who underwent surgery in a low-volume surgical centre (Wes et al. 2017).

7.3.4 Hospitalisation associated with eye, ear, face and neck anomalies

Two studies reported hospitalisation of infants with eye, ear, face and neck anomalies (Colvin and Bower 2009; Dharmasena et al. 2017). This included more than 650 infants with anophthalmia, microphthalmia and lacrimal malformations. They spanned birth cohorts from 1980 to 2011. The age of study cohorts was 0-1 year.

Admission rate

The admission rates for infants with an anomaly of the eye anomalies and, ear, face and neck anomalies were 1.80 and 1.08 admissions per person year (excluding birth admissions) respectively, which were significantly higher than that for infants without an anomaly (0.31 admission per person year) between 1980 and 1999 in Western Australia (Figure 7.2) (Colvin and Bower 2009). For infant born with congenital microphthalmia, there was a linear increase in hospital admission rates from 1999 to 2011 (an increase of 3.2%, 95% CI: 0.8-5.7% per year). Similarly, there was an increase in hospital admission rates in infants born with congenital malformation of orbit/ agenesis of lacrimal apparatus from 2002 to 2011. However, hospital admission rate for infants born with congenital anophthalmia were unchanged between 2002 and 2011 (Dharmasena et al. 2017).

Patterns of hospitalisation

Causes of hospitalisation

Overall, anomaly complications and acute upper respiratory tract infections (URTIs) were the most common causes for hospitalisation of children with an anomaly of the eye, ear, face and

neck (Colvin and Bower 2009). Post-operational complications were relatively rare in children with these anomalies Dharmasena et al. 2017).

Frequency of hospital admission

Children (0-5 years) with an anomaly of the eye, ear, face and neck anomaly were admitted to hospital more frequently than children without an anomaly. The mean number of hospital admissions for children with an eye anomaly was 5.3-6.2 admissions per child admitted; and for children born with an ear, face and neck anomaly was 2.9-4.8 admissions per child admitted, compared to 2.1-2.3 admissions per child admitted for children without an anomaly between 1980 and 1994 in Western Australia (Figure 7.3) (Colvin and Bower 2009).

Hospital LOS

Infants with an eye anomaly had a significantly greater mean total LOS of 13.6 days during infancy, compared to infants without an anomaly (5.5 days). Similarly, infants with an ear, face and neck anomaly had a significantly greater mean total LOS of 10.6 days during infancy compared to infants without an anomaly (Figure 7.6) (Colvin and Bower 2009).

In addition, the median LOS for children (0-5 years) with an eye anomaly has declined over time from 2.0 to 1.0 days between 1980 and 1994, while the mean total LOS per child admitted (0-5 years) with an eye anomaly has remained largely unchanged over time from 20.0 to 20.1 days between 1980 and 1994 in Western Australia (Figures 7.8 and 7.9) (Colvin and Bower 2009). The mean total LOS per child admitted (0-5 years) with an ear, face and neck anomaly has increased from 13.5 to 19.3 days between 1980 and 1994 (Figure 7.9) (Colvin and Bower 2009). For infants born with a choanal atresia, brachial cyst-sinus and thyroglossal duct cyst-sinus, there has been an overall trend toward reduced hospital LOS and increased utilisation of outpatient resources over time (Leclerc 1999).

Risk factors for hospitalisation

The risk factors for 30-day hospital readmission of infants who underwent surgery for choanal atresia included younger age (i.e. < 10 days after birth) at repair and presence of a syndrome (Marston et al. 2019).

7.3.5 Hospitalisation associated with cardiovascular anomalies

Seventeen studies reported hospitalisation of infants and children with cardiovascular anomalies (Colvin and Bower 2009; Billett et al. 2008; Desai et al. 2017; Duppenthaler et al. 2004; Dyamenahalli et al. 2000; Islam et al. 2018; Jortveit et al. 2016; Kogon et al. 2019; Li et al. 2016; Mackie et al. 2008; Medrano et al. 2007; Peyvandi et al. 2017; Saharan et al. 2014; Ghimire et al. 2020; Simsic et al. 2009; Smith et al. 2015; Soliman et al. 2015). These included a total study population of more than 120,821 infants and children born with a CHD. They spanned the birth cohorts from 1980 to 2016. The age of study cohort ranged from 0 to 18 years.

Admission rate

The admission rate for infants with a cardiovascular anomaly (1.37 admissions per person year, excluding birth admissions) was significantly higher than that for infants without an anomaly (0.31 admission per person year) between 1980 and 1999 in Western Australia (Figure 7.2) (Colvin and Bower 2009; Islam et al. 2018).

Patterns of hospitalisation

Causes of hospitalisation

Overall, cardiac and respiratory illnesses, commonly respiratory syncytial virus (RSV) bronchiolitis, acute URTIs and asthma were the most common causes for hospitalisation of infants born with a cardiovascular anomaly (Mackie et al. 2008; Colvin and Bower 2009; Kogon et al. 2019). For

children who underwent surgery for CHDs, post-operative infections and pleural effusion were common causes for hospital readmissions, with the 30-day readmission rate being between 7 and 10% (Smith et al. 2015; Saharan et al. 2014; Dyamenahalli et al. 2000). For children with isolated ventricular septal defects (VSD), cardiac complications were relatively rare (Jortveit et al. 2016).

Frequency of hospital admission

Children (0-5 years) with a cardiovascular anomaly were admitted more frequently to hospital than children without an anomaly. For children born with a cardiovascular anomaly, the mean number of hospital admissions was relatively constant at 4.4-4.9 admissions per child admitted, compared to 2.1-2.3 admissions per child admitted for children without an anomaly between 1980 and 1994 in Western Australia (Figure 7.3) (Colvin and Bower 2009). Among cardiovascular anomalies, tetralogy of Fallot had largest number of admissions per child, with 6.9 admissions per child admitted, compared to 2.2 admissions per child admitted for children without an anomaly (Figure 7.4); ventricular septal defects (VSD) had the largest number (5%) of total child (0-5 years) admissions (Figure 7.5) (Colvin and Bower 2009).

Hospital LOS

Infants with a cardiovascular anomaly had a significantly greater mean total LOS of 15.4 days during infancy, compared to infants without an anomaly (5.5 days) (Figure 7.6) (Colvin and Bower 2009). Up to 16% of the admitted children with a CHD required admission for paediatric intensive care and approximately 5% of admitted children required mechanical ventilation (Medrano et al. 2007). The median LOS for children (0-5 years) with a cardiovascular anomaly was 2.0 days, which was unchanged over time between 1980 and 1994 in Western Australia (Figure 7.8), while the mean total LOS per child admitted (0-5 years) with a cardiovascular anomaly has declined over time from 23.2 to 20.4 days between 1980 and 1994 (Figure 7.9) (Colvin and Bower 2009).

Risk factors for hospitalisation

The risk factors for RSV-related hospitalisation of children with a CHD included haemodynamically significant congenital heart disease (hsCHD), 22q11 deletion (aOR = 8.2, 95% CI: 2.5-26.3), small for gestational age (aOR = 5.2, 95% CI: 1.6-17.4), previous respiratory disease (aOR = 4.5, 95% CI: 2.3-8.6), incomplete immunoprophylaxis against RSV (aOR = 2.2, 95% CI: 1.2-3.9), trisomy 21 (aOR = 2.1, 95% CI: 1.1-4.2) and cardiopulmonary bypass (aOR = 2.0, 95% CI: 1.1-3.4) (Medrano et al. 2007; Duppenthaler et al. 2004).

For children who underwent CHD surgery, the risk factors for 30-day hospital readmissions post-surgery included social deprivation, Hispanic ethnicity, younger age at repair, severe CHDs, multiple comorbidities or a chromosomal/ genetic syndrome (e.g. 22q11.2 deletion), having an invasive procedure, complex procedure, prolonged post-operative LOS, previous cardiac surgery, use of extra corporeal membrane oxygenation (ECMO) support, having an emergency department visit within the preceding 6 months and nasogastric feeding at discharge (Smith et al. 2015; Dyamenahalli et al. 2000; Saharan et al. 2014; Mackie et al. 2008; Islam et al. 2018; Simic et al. 2009; Li et al. 2016; Kogon et al. 2019; Ghimire et a. 2020).

For neonates with a complex or critical CHD such as hypoplastic heart syndrome and transposition of great arteries, higher gestational age at birth was associated with a lower risk of hospital readmissions (unadjusted odd ratio, uOR = 0.14, 95% CI: 0.04-1.03) (Soliman et al. 2015) and hospital LOS (Peyvandi et al. 2017).

7.3.6 Hospitalisation associated with anomalies of the respiratory system

Three studies reported hospitalisation of infants and children with anomalies of the respiratory system (Colvin and Bower 2009; Altman et al. 1999; Marston et al. 2019). This included a total study population of more than 174 infants and children with congenital airway abnormalities, and

178 infants and children with a choanal atresia. They spanned birth cohort from 1980 to 2015. The age of study cohort ranged from 0 to 1+ years.

Admission rate

The admission rate for infants with a respiratory anomaly (1.23 admissions per person year, excluding birth admissions) was significantly higher than that for infants without an anomaly (0.31 admission per person year) between 1980 and 1999 in Western Australia (Figure 7.2) (Colvin and Bower 2009).

Patterns of hospitalisation

Causes of hospitalisation

Overall, respiratory anomalies and illnesses (such as acute URTI, acute laryngitis and tracheitis, non-suppurative otitis media and Eustachian tube disorders) were the most common causes for hospitalisation of children with a respiratory anomaly (Colvin and Bower 2009). For congenital airway abnormalities, the common causes for hospitalisation of the affected children included laryngomalacia, glottis web, subglottic stenosis, vocal-cord paralysis, subglottic haemangioma, tracheomalacia, external compression and tracheal stenosis. In addition, infants with a congenital airway anomaly commonly presented with stridor within the first three months of life; it was estimated that about one-fifth of the affected infants required tracheostomy (Altman et al. 1999).

Frequency of hospital admission

Children (0-5 years) with a respiratory anomaly were more frequently admitted (mean = 5.6-8.8 admissions per child admitted) to hospital than children without an anomaly (mean = 2.1-2.3 admissions per child admitted) between 1980 and 1994 in Western Australia (Figure 7.3) (Colvin and Bower 2009).

Hospital LOS

Infants with a respiratory anomaly had a significantly greater mean total LOS of 25.4 days during infancy, compared to infants without an anomaly (5.5 days) (Figure 7.6) (Colvin and Bower 2009). Children (0-5 years) with cystic fibrosis had one of the longest mean LOS for a single admission (9.4 days) and for total admissions (49.2 days) among children with any anomaly (Figure 7.7). The median LOS for children (0-5 years) and mean total LOS per child admitted (0-5 years) with a respiratory anomaly have declined over time from 3.0 to 2.0 days and from 63.1 to 37.6 days respectively between 1980 and 1994 in Western Australia (Figures 7.8 and 7.9) (Colvin and Bower 2009).

7.3.7 Hospitalisation associated with orofacial clefts

Five studies reported hospitalisation of infant and children with orofacial clefts (Fitzsimons et al. 2013; Leclerc 1999; Lo et al. 2015; Razzaghi et al. 2015; Wu et al. 2019). These included a total study population of more than 39,771 infants with a cleft lip and/or palate. They spanned birth cohorts from 1983 to 2010. The age of study cohort ranged from 0 and all years.

Admission rate

For all age groups, admission rates and hospital LOS were higher for infants with cleft lip and palate, or a cleft palate, compared to infants with an isolated cleft lip (Lo et al. 2015).

Frequency and LOS of hospital admission

The mean number of all-cause hospitalisation of infants with orofacial clefts (OFC) has not changed significantly between 1997 and 2008, with more than half (54.9%) of all hospital admissions for OFC were during the first year after birth (Lo et al. 2015). However, there was a

significant reduction in overall LOS for cleft-related procedures from 6.8 days to 5.3 days among infants with isolated clefts between 1997 and 2008 (Fitzsimons et al. 2013; Leclerc 1999).

Risk factors for hospitalisation

The risk factors for hospital admissions and LOS were younger age, syndromic cleft, severe cleft types, female sex, low birthweight < 2500g, multiple defects and Black ethnicity (Lo et al. 2015; Fitzsimons et al. 2013; Razzaghi et al. 2015; Wu et al. 2019).

7.3.8 Hospitalisation associated with gastrointestinal anomalies

Six studies reported hospitalisation of infants and children with anomalies of the digestive system (Colvin and Bower 2009; Benoist et al. 2016; Burgos et al. 2017; Garcia et al. 2018; Putnam et al. 2016; Sayari et al. 2016). These included a total study population of 7,657 infants and children born with a congenital diaphragmatic hernia (CDH), 861 infants and children born with a tracheoesophageal fistula (TOF) and oesophageal atresia (OA), and 190 infants born with a biliary atresia. They spanned birth cohorts from 1980 to 2015. The age of study cohort ranged from 0 to all ages.

Admission rate

The admission rate for infants with a gastrointestinal (GI) anomaly was significantly higher (1.80 admissions per person year, excluding birth admissions) than that for infants without an anomaly (0.31 admission per person year) between 1980 and 1999 in Western Australia (Figure 7.2) (Colvin and Bower 2009).

Patterns of hospitalisation

Causes of hospitalisation

Overall, GI conditions and complications, and respiratory illnesses (such as non-suppurative otitis media and asthma) were the most common causes for hospitalisation of children with a gastrointestinal anomaly (Colvin and Bower 2009). For infants born with a CDH, the common morbidities and causes for hospitalisation included pulmonary hypertension, intestinal adhesion and obstruction, acute gastroenteritis, feeding difficulties, disease recurrence and neurological complications (Putnam et al. 2016).

Frequency of hospital admission

Children (0-5 years) with a GI anomaly were more frequently admitted to hospital compared to children without an anomaly. For children born with a gastrointestinal anomaly, the mean number of hospital admissions was constant at 4.1 admissions per child admitted, compared to 2.1-2.3 admissions per child admitted for children without an anomaly between 1980 and 1994 in Western Australia (Figure 7.3) (Colvin and Bower 2009). Among all gastrointestinal anomalies, children with TOF and OA, and Hirschsprung's disease had the most admissions per child admitted, with 8.0 and 6.9 admissions per child admitted respectively, compared to 2.2 admissions per child admitted for children without an anomaly (Figure 7.4); in addition, children with pyloric stenosis had the greatest number (3%) of total child (0-5 years) admissions (Figure 7.5) (Colvin and Bower 2009).

Hospital LOS

Infants with a GI anomaly had a significantly greater mean total LOS of 13.3 days during infancy, compared to infants without an anomaly (5.5 days) (Figure 7.6) (Colvin and Bower 2009). Among children (0-5 years) with GI anomalies, children with Hirschsprung's disease had the longest mean

total LOS (49.7 days), followed by renal agenesis and dysgenesis (43.2 days), and TOF and OA (41.3 days) (Figure 7.7). The median LOS for children (0-5 years) and mean total LOS per child admitted (0-5 years) with a GI anomaly have declined over time from 3.0 to 2.0 days and from 24.0 to 17.1 days respectively between 1980 and 1994 in Western Australia (Figures 7.8 and 7.9) (Colvin and Bower 2009).

Risk factors for hospitalisation

For infants affected by a CDH, the risk factors for morbidities and hospitalisation included preterm birth, APGAR scores < 7 at 5 mins, larger defects, the presence of a chromosomal or cardiac anomaly, thoracic herniation of the liver and need for oxygen therapy at home (Benoist et al. 2016; Putman et al. 2016). There was no significant difference in hospital LOS between infants born by different delivery methods (Burgos et al. 2017). In addition, the risk of complications/morbidities has remained unchanged over time for large defects but has declined in small defects (Putnam et al. 2016).

For infants who underwent surgical repair for TOF and OA, the risk factors for post-surgical complications included Black ethnicity (aOR = 6.53, 95% CI: 1.80-23.7) and surgical operation at the weekend (aOR = 2.20, 95% CI: 1.01-4.80). The risk factors for a prolonged hospital LOS were Black ethnicity (aOR = 9.31, 95% CI: 2.87-30.2) and surgical operation at a non-teaching hospital (aOR = 3.21, 95% CI: 1.05-9.77) (Sayari et al. 2016).

For infants who underwent a surgical repair for biliary atresia, the risk factors for post-surgical complications and 30-day readmissions were peri-operative blood transfusion and cardiac comorbidities (Garcia et al. 2018).

7.3.9 Hospitalisation associated with abdominal wall defects

Eight studies reported hospitalisation of infants and children with gastroschisis (Apfeld et al. 2017; Boutros et al. 2009; Bradnock et al. 2011; Fullerton et al. 2017; Raymond et al. 2020; Sharp et al. 2000; Weinsheimer and Yanchar 2008; Youssef et al. 2016). These included a total study population of more than 13,150 infants born with a gastroschisis. They spanned birth cohorts from 1986 to 2014. The age of study cohort ranged from 0 to 1+ years (or to age of discharge).

Patterns of hospitalisation

Causes of hospitalisation

For infants who underwent surgery for gastroschisis, the most common complications included wound infection and break down, sepsis, adhesive obstruction, conjugated hyperbilirubinaemia, and complications related to total parenteral nutrition (TPN) (Sharp et al. 2000; Raymond et al. 2020).

Hospital LOS

The median hospital LOS was 36 days (range: 8 - 365 days) for simple gastroschisis, and 84 days (range: 20 - 365 days) for complex gastroschisis (i.e. gastroschisis with a bowel perforation, necrosis or atresia) (Bradnock et al. 2011; Raymond et al. 2020).

Risk factors for hospitalisation

The risk factors for hospital LOS, ventilatory support and duration of TPN included preterm birth, low birthweight, small for gestational age, complex gastroschisis, sepsis, necrotising enterocolitis, having had bowel resection, the presence of multiple anomalies, maternal smoking, maternal illicit drug use, admission to neonatal intensive care unit with a low gastroschisis volume and early

birth cohort (Apfeld et al. 2017; Bourtos et al. 2009; Weinsheimer and Yanchar 2008; Youssef et al. 2016; Bradnock et al. 2011; Fullerton et al. 2017; Sharp et al. 2000; Raymond et al. 2020).

7.3.10 Hospitalisation associated with genitourinary anomalies

Three studies reported hospitalisation of infants and children with genitourinary (GU) anomalies (Colvin and Bower 2009; Meyer et al. 2015; Roth et al. 2018). These included a total study population of more than 50,587 infants born with a hypospadias. They spanned birth cohorts from 1980 to 2015. The age of study cohort ranged from 0 to 18+ years.

Admission rate

The admission rate for infants with a GU anomaly was significantly higher (0.86 admissions per person year, excluding birth admissions) compared to that for infants without an anomaly (0.31 admission per person year) between 1980 and 1999 in Western Australia (Figure 7.2) (Colvin and Bower 2009). However, there has been a decline in the trend in inpatient admissions over time for surgical repair among infants born with hypospadias (Meyer et al. 2015).

Patterns of hospitalisation

Causes of hospitalisation

Overall, GU anomalies and associated disorders (such as disorders of the urethra, urinary tract, kidney and ureter), and asthma were the most common reasons for hospitalisation of children with a GU anomaly (Colvin and Bower 2009).

Frequency of hospital admission

Children (0-5 years) with a GU anomaly were more frequently admitted (mean = 3.1-3.3 admissions per child admitted) to hospital compared to children without an anomaly (mean = 2.1-

2.3 admissions per child admitted) between 1980 and 1994 in Western Australia (Figure 7.3). The highest number of total child (0-5 years) admissions among children with any anomaly was for undescended testis, representing an almost one tenth of the total anomaly-related admissions (Figure 7.5) (Colvin and Bower 2009).

Hospital LOS

Infants with a GU anomaly had a significantly greater mean total LOS of 8.3 days during infancy, compared to infants without an anomaly (5.5 days) (Figure 7.6). The median LOS for children (0-5 years) and mean total LOS per child admitted (0-5 years) with a GU anomaly have declined from 2.0 to 1.0 days and from 13.6 to 10.1 days respectively between 1980 and 1994 in Western Australia (Figures 7.8 and 7.9) (Colvin and Bower 2009).

Risk factors for hospitalisation

For children who underwent surgical repair for hypospadias, the risk factors for 30-day readmissions included young age (< 5 years), and Black and Asian ethnicity (Roth et al. 2018). Post-surgical complications were rare (< 5%), and usually related to low-volume surgical centres and the presence of comorbidity (Meyer et al. 2015).

7.3.11 Hospitalisation associated with musculoskeletal anomalies

One study reported hospitalisation of infants and children with musculoskeletal anomalies (Colvin and Bower 2009). These included a total study population of 2,393 infants and children born with a musculoskeletal anomaly. They spanned birth cohorts from 1980 to 1999. The age of study cohort ranged from 0 to 5 years.

Admission rate

The admission rate for infants with a musculoskeletal anomaly was significantly higher (0.83 admissions per person year, excluding birth admissions) compared to that for infants without an anomaly (0.31 admission per person year) between 1980 and 1999 in Western Australia (Figure 7.2) (Colvin and Bower 2009).

Patterns of hospitalisation

Causes of hospitalisation

Overall, congenital musculoskeletal deformities and anomalies, orthopaedic aftercare and asthma were the most common reasons for hospitalisation of children with a musculoskeletal anomaly (Colvin and Bower 2009).

Frequency of hospital admission

Children (0-5 years) with a musculoskeletal anomaly were more frequently admitted (mean = 3.7-4.0 admissions per child admitted) to hospital compared to children without an anomaly (mean = 2.1-2.3 admissions per child admitted) between 1980 and 1994 in Western Australia (Figure 7.3). The highest number of total child (0-5 years) admissions among girls with any anomaly was for developmental dysplasia of hip, representing 5.3% of the total anomaly-related admissions (Figure 7.5) (Colvin and Bower 2009).

Hospital LOS

Infants with a musculoskeletal anomaly had a significantly greater mean total LOS of 10.7 days during infancy, compared to infants without an anomaly (5.5 days) (Figure 7.6). The median LOS for children (0-5 years) and mean total LOS per child admitted (0-5 years) with a musculoskeletal

anomaly have declined from 2.0 to 1.0 days and from 18.7 to 14.1 days respectively between 1980 and 1994 in Western Australia (Figures 7.8 and 7.9) (Colvin and Bower 2009).

7.3.12 Hospitalisation associated with chromosomal disorders

Ten studies reported hospitalisation of infants and children with chromosomal disorders (Colvin and Bower 2009; Derrington et al. 2013; Fitzgerald et al. 2013; Hilton et al. 1999; Nelson et al. 2012; Sánchez-Luna et al. 2017; So et al. 2007; Stagliano et al. 2015; Zachariah et al. 2012; Zhu et al. 2013). These included a total study population of more than 6,203 infants and children with Down syndrome (Trisomy 21), 4,309 children with Patau syndrome (Trisomy 13) and 6,630 children with Edward syndrome (Trisomy 18). They spanned birth cohorts from 1977 to 2013. The age of study cohort ranged from 0 to 22 years.

Admission rate

The admission rate for infants with a chromosomal disorder was significantly higher (1.28 admissions per person year, excluding birth admissions) than that for infants without an anomaly (0.31 admission per person year) between 1980 and 1999 in Western Australia (Figure 7.2) (Colvin and Bower 2009).

Among all admissions of children with Down syndrome, more than a quarter of them occurred in infancy, in which one-third of these admissions occurring in the neonatal period. About ten percent of the admitted children with Down syndrome required paediatric intensive care (Fitzgerald et al. 2013; Hilton et al. 1999).

Patterns of hospitalisation

Causes of hospitalisation

Overall, respiratory illnesses (such as non-suppurative otitis media, Eustachian tube disorders, acute UTRI, acute laryngitis and tracheitis) were the most common causes for hospitalisation of children with a chromosomal disorder (Colvin and Bower 2009).

More than half of all admissions of children with Down syndrome were respiratory-related (Hilton et al. 1999; Zachariah et al. 2012; Stagliano et al. 2015; Sánchez-Luna et al. 2017). These included URTIs (commonly adenoid/ tonsillitis and croup) and lower respiratory tract infections (commonly RSV bronchiolitis, influenza and pneumococcus pneumonia) (Fitzgerald et al. 2013; Sánchez-Luna et al. 2017; Hilton et al. 1999). In addition, associated cardiovascular anomalies (commonly cardiac septal defects), endocrine disorders (e.g. neonatal jaundice), conditions affecting the nervous systems and sensory organs (e.g. ear and hearing conditions and disorders of oral cavity), gastrointestinal, nutritional and immune related diseases were also common causes for hospitalisation of infants with Down syndrome (Zhu et al. 2013; Derrington et al. 2013).

For children with Edward or Patau syndrome, 3-5% of hospitalisation were for a tracheotomy (Nelson et al. 2012).

Frequency of hospital admission

Children (0-5 years) with a chromosomal disorder were more frequently admitted (5.1-6.4 admissions per child admitted) to hospital compared to children without an anomaly (2.1-2.3 admissions per child admitted) between 1980 and 1994 in Western Australia (Figure 7.3). In particular, Down syndrome had the highest number of child (0-5 years) admissions among all chromosomal disorders, with 5.6 admissions per child admitted and 2.9% of total anomaly-related hospital admissions (Figure 7.5) (Colvin and Bower 2009).

Hospital LOS

Infants with a chromosomal disorder had a significantly higher mean total LOS of 15.2 days during infancy, compared to infants without an anomaly (5.5 days) (Figure 7.6) (Colvin and Bower 2009). Infants with Down syndrome had a two to three times higher median hospital LOS due to RSV or common respiratory illnesses such as asthma or pneumonia, compared to infants without a Down syndrome (Stagliano et al. 2015; Sánchez-Luna et al. 2017).

In general, the median LOS for children (0-5 years) and mean total LOS per child admitted (0-5 years) with a chromosomal disorder declined over time from 3.0 to 2.0 days and from 25.3 to 23.0 days respectively between 1980 and 1994 in Western Australia (Figures 7.8 and 7.9) (Colvin and Bower 2009). However, hospitalisation can vary depending on the specific chromosomal disorder. For example, while the overall trend of all-cause hospitalisation of children with Down syndrome declined over time between 1983 and 2005 in Western Australia (Fitzgerald et al. 2013), hospital admissions and LOS of children with Edward syndrome (Trisomy 18) significantly increased over time between 1997 and 2008; where hospital admissions and LOS of children with Patau syndrome (Trisomy 13) have not changed significantly over time over the same period (Nelson et al. 2012).

Risk factors for hospitalisation

The risk factors for all-cause hospitalisation in children (0-3 years) with Down syndrome included preterm birth (RR = 1.3, 95% CI: 1.0-1.5), low birthweight (RR = 1.3, 95% CI: 1.0-1.5), male sex (RR = 1.2, 95% CI: 1.1-1.5), associated cardiac anomalies (RR = 1.5, 95% CI: 1.3-2.2), the presence of a major non-cardiac anomalies (RR = 1.3, 95% CI: 1.1-1.6) and Hispanic ethnicity (RR = 1.4, 95% CI: 1.1-1.7 vs. non-Hispanic White) (Zhu et al. 2013; Derrington et al. 2013; So et al. 2007).

7.4 Discussion

7.4.1 Summary of findings

Congenital anomalies are a major cause of paediatric morbidity. This structured literature review aimed to examine the contemporary evidence on the admission rates, patterns of and risk factors for hospitalisation of infants and children born with a range of different congenital anomalies, and has included studies from high-income countries across North America, Europe and Australia published between 1st January, 1998 and 6th October, 2020. This study period was chosen given that some important public health interventions and development began in 1990's in high-income countries; for example, considerable advances have been made in prenatal screening for congenital anomalies since the 1990's, as well as changes in management in pregnancy (RCOG 2010) and recommendations of uptake of periconceptional folic acid supplementation and folic acid food fortification (MRC Vitamin Study Research Group 1991; Czeizel 1998; Berry et al. 1999).

This review included 54 studies from the literature, the majority of which were either population-based or multi-centre cohort studies. In addition, there was a cross-sectional study which examined the hospitalisation of infants with Trisomy 13 and Trisomy 18 (Nelson et al. 2012), and a case series which examined the inpatient care for infants with congenital airways abnormalities (Altman et al. 1999); due to rarity of these conditions, population-based studies were not readily available.

Together, this review included a total population of more than 538,000 liveborn infants with congenital anomalies of all anomaly subgroups according to the EUROCAT classification (EUROCAT 2013). The review spanned birth cohorts from 1977 to 2015. The outcomes were reported based on generally good quality evidence, although this was not formally assessed as part of this review.

The admission rate of infants with a major congenital anomaly has generally increased over time. Compared to infants without an anomaly, infants with a major anomaly were admitted more frequently and for a longer stay. Anomaly-related complications and respiratory-related conditions were the most common causes for hospitalisation of infants with anomalies. In addition, preterm birth, disease severity and comorbidity were significantly associated with an increased risk of excess hospitalisation among infants with congenital anomalies.

7.4.2 Admission rates

This review has shown that the admission rates of infants with many major congenital anomalies of the nervous system, eye, ear, face and neck, cardiovascular, respiratory system, genitourinary anomalies and chromosomal defects have generally increased over time, and were significantly higher than that of infants without an anomaly in Western Australia between 1980 and 1994 (Colvin and Bower 2009). As medical and surgical advances have improved the survival of infants born with major congenital anomalies over time, many of these infants would require ongoing treatment and follow ups. For example, advances in surgical techniques and new catheter devices have expanded the treatment options for infants with CHDs in the past decade (Larsen et al. 2017). As a consequence, this has led to significantly improved survival for infants with CHDs, who would be likely to require regular hospital admissions for preventative procedures, further investigations and interventions (Leonard et al. 2000; Sánchez-Luna et al. 2017; Bloemer et al. 2007; Thomas et al. 2011; Hilton et al. 1999). Similarly, the improved survival of infants with a Down syndrome over time due to recent advances in intensive care and improved access to early cardiac surgery was reported in some reviewed studies (Rankin et al. 2012; Kucik et al. 2013; Leonard et al. 2020); this has led to an increased number of the affected infants requiring regular hospitalisation for ongoing conditions including cardiac (e.g. repair for septal defects), orthopaedic (e.g. tendon release or lengthening) and dental procedures in order to improve the quality of life (Slack-Smith et al. 2009; Nelson et al. 2012). In addition, the higher admission rate is

also likely due to a higher susceptibility of comorbidities and complications that children with major congenital anomalies often experience and develop. For example, previous studies have consistently shown that infants with a Down syndrome had an increased rate of hospitalisation (9.9%) due to RSV-related respiratory tract infections, compared to their siblings without a Down syndrome (0.7%) independently of the presence or absence of a CHD (Bloemers et al. 2007), or compared to the general paediatric population (0.5%-2%) (Glezen et al. 1986; Zachariah et al. 2012; Stagliano et al. 2015).

For some minor anomalies, advances in peri-operative care have resulted in a decreased rate of hospital admissions, and an increased number of surgical repairs being transferred from inpatient procedures to day cases (Fitzgerald et al. 2013; Thomas et al. 2010). For example, the surgical repairs for hypospadias, choanal atresia, brachial cyst-sinus and thyroglossal duct cyst-sinus exemplify this trend, in which the rate of day surgery for these anomalies has significantly increased while inpatient repairs have declined over time (Meyers et al. 2015; Leclerc 1999). Post-operative morbidities and complications are relatively rare for these isolated minor anomalies (Roth et al. 2018).

7.4.3 Patterns of hospitalisation

Causes of hospitalisation

This review has shown that congenital anomalies and associated comorbidities and complications are the leading causes of hospitalisation of infants with congenital anomalies. For example, studies have shown that infants with a complex gastroschisis were frequently hospitalised due to gastrointestinal complications such as intestinal failure and sepsis, and treatment complications such as liver diseases secondary to prolonged total parental nutrition (TPN) in infancy (Bradnock et al. 2011; Synder 1999); these infants were also susceptible to developing gastro-oesophageal reflux disease in later life, which often requires long-term follow up and hospitalisation (Sharp et

al. 2000). Similarly, infants with a congenital diaphragmatic hernia often develop gastrointestinal morbidities such as gastro-oesophageal reflux disease and feeding problems in infancy (Putnam et al. 2016; Wynn et al. 2013; Bagolan and Morini 2007); these infants are also susceptible to have recurrent wheeze due to abnormal lung development and require supplemental oxygen which are common causes for their readmissions (Benoist et al. 2016; Cauley et al. 2015). These findings have highlighted the significant impact of congenital anomalies as a leading cause of morbidity and hospitalisation of infants affected by congenital anomalies.

Respiratory-related conditions such as pneumonia and bronchiolitis were the most common cause of morbidity and hospitalisation of infants with major congenital anomalies such as CHDs and Down syndrome at all ages (Kristensen et al. 2009; Medrano et al. 2007; So et al. 2007; Zachariah et al. 2012). There are several explanations. First, the high risk of RSV-related hospitalisation in infants with a Down syndrome are likely caused by an increased susceptibility and severity of respiratory tract infections associated with a Down syndrome, in which the proposed mechanisms are multifactorial (Bloemers et al. 2007; Fjaerli et al. 2004; Hilton et al. 1999; Yang et al. 2002; IMpact-RSV Study Group 1998). Previous studies have suggested that this may be due to abnormal development of the lungs and decreased airway branching in infants with Down syndrome (Schloo et al. 1991). Consequently, abnormal cilia, anatomy of the upper respiratory tract and bronchial reactivity together with other Down syndrome associated comorbidities such as neuromuscular disorders, swallowing disorders and gastro-oesophageal reflux disease predispose these infants to recurrent aspiration, and hence an increased risk of respiratory infections and hospitalisation (Medrano et al. 2007; Hilton et al. 1999). Fundoplication and gastrostomy insertion are often necessary interventions for some of these children with the most severe cases (Hilton et al. 1999). In addition, some studies suggested that the high incidence and susceptibility of respiratory tract infections in infants with Down syndrome may also be due to impairment of T and B lymphocytes leading to various degree of impairment of the immune system and immunosuppression (de Hingh et al. 2005; Scotese et al. 1998). This mechanism may

also explain the reasons for an increased susceptibility and incidence of infants with Down syndrome being admitted and hospitalised for haematological malignancies such as acute leukaemias and immunity-related disorders such as recurrent infections (Shott 2006).

Frequency of hospital admission

Infants with a major congenital anomaly (such as CHDs, Down syndrome and congenital diaphragmatic hernia) are admitted more frequently per infant admitted due to comorbidities, complications, ongoing investigations and interventions, compared to infants without an anomaly. For example, studies have shown that infants with a CHD were hospitalised more frequently and used inpatient care more intensively than infants without a CHD (Frid et al. 2002). Infants who underwent CHD surgery were particularly at an increased risk of a range of respiratory, renal and infectious complications and require frequent hospitalisation (Dyamenahalli et al. 2000; Kongon et al. 2019). In addition, the CIVIC study has shown that infants with a Down syndrome were admitted more frequently due to RSV-related infections compared to infants without Down syndrome (Medrano et al. 2007). Furthermore, infants with congenital diaphragmatic hernias were admitted more often than the general paediatric population due to long-term gastrointestinal, pulmonary and neurological morbidities (Wynn et al. 2013; Bagolan and Morini 2007; Bevilacqua et al. 2014; Valfrè et al. 2011; Safavi et al. 2012; Bairdain et al. 2015). In practice, some clinicians may lower the threshold for hospitalisation of infants with a major anomaly because of worries that their symptoms may lead to a severe course of illness. These findings have shown that the frequency and burden of hospitalisation of infants with an anomaly are significantly greater than their peers without an anomaly.

Hospital length of stay (LOS)

Hospital LOS is a direct marker of morbidity. Prolonged hospital stay of infants with congenital anomalies is often due to greater complexity in the treatment of the anomaly, and identification

and treatment of associated co-morbidities whilst these infants are hospitalised (Colvin and Bower 2009; Saharan et al. 2014).

Infants with a complex or syndromal/chromosomal anomaly are more likely to be admitted to hospital for a longer stay due to complications and comorbidities, compared to infants without an anomaly or with a less complex or non-syndromal anomaly (Yoon et al. 1997; McCandless et al. 2004; Hall et al. 1978; Carnevale et al. 1985). For example, infants with a Down syndrome and an associated CHD require longer hospitalisation for clinical assessment and treatment in infancy, compared to infants with Down syndrome who did not have a co-morbid CHD (Dawson et al. 2014; Zhu et al. 2013; Hilton et al. 1999; Frid et al. 2002; So et al. 2007), or compared to the general paediatric population (Freeman et al. 2008; Freeman et al. 2009; Torfs and Christianson 1998; Roizen 2003; Zhu et al. 2013). Other studies have shown that infants with a congenital airway abnormality as part of a syndrome required significantly longer hospital stay following surgical repair (mean LOS of 27 days) due to case complexity and increased risk of general anaesthesia, compared to infants with a non-syndromal airway anomaly (mean LOS of 8 days) (Marston et al. 2019; Blake et al. 2009). Similarly, infants with a syndromal orofacial cleft were more likely to be hospitalised longer after surgical repair due to case complexity and an increased risk of post-surgical complications, compared to infants with an isolated orofacial cleft (Fitzsimon et al. 2013). Furthermore, infants with a complex gastroschisis (i.e. gastroschisis with a bowel perforation, necrosis or atresia) were significantly more likely to develop complications such as intestinal failure and TPN-related liver diseases, and require a longer hospital LOS due to unplanned operations, as well as longer time to achieve full enteral feed, compared to infants with a simple gastroschisis (Bradnock et al. 2011; Mills et al. 2010).

This review has shown that the mean and median hospital LOS have generally decreased over time for infants both with and without an anomaly. As discussed in Section 7.4.1, this may be due to the fact that many procedures for minor anomalies which once required a longer hospital admission have now been carried out as day cases (Colvin and Bower 2009).

7.4.4 Risk factors for hospitalisation

Maternal ethnicity

Ethnic disparity in the access to healthcare has been well described in literature (CDC 2001; Yang et al. 2002; Rasmussen et al. 2006); however evidence was limited and less clear in its association with hospitalisation due to congenital anomalies. The study by Derrington et al. (2013) in the U.S. has shown that infants with Down syndrome born to mothers of Black ethnicity had significantly fewer hospital admissions, compared to infants with Down syndrome born to mothers of White ethnicity. Increased environmental stress, racial disparity leading to delayed and limited access to healthcare resources among Black ethnic population have been suggested as possible mechanisms (Wu et al. 2019; Kogon et al. 2012; Ghanayem et al. 2012; McLaren 2007; Gee et al. 2008; Adler and Ostrove 1999; Saha et al. 2003; Jiang et al. 2005). In addition, the studies by Kongon et al. (2012 and 2019) have shown that infants born to Hispanic mothers who underwent CHD surgery had a higher risk of hospital readmission, compared to infants born to White mothers; this could be due to medical issues or a language barrier affecting the post-discharge course. Whilst these findings have suggested that ethnicity is an important socio-demographic factor for hospitalisation of infants with congenital anomalies, current evidence is limited and more population-based research is needed in order to establish the consistency of these effects.

Gestational age at birth

Preterm birth has been shown to be an independent significant factor for an increased risk of morbidities and hospitalisation among infants with a congenital anomaly. For example, in a large multi-centre cohort study, Hardy et al. (2019) has shown that extremely preterm infants (< 24 gestation weeks) with a congenital anomaly were associated with a significantly increased risk of comorbidities and disease complications such as respiratory distress syndrome, sepsis, apnoea, hyperbilirubinaemia and any infectious disease, compared to term infants with a congenital

anomaly. In addition, the study by Weinsheimer and Yanchar (2008) has shown that moderately preterm infants (<36 weeks) born with gastroschisis were significantly more likely to have intestinal necrosis, compared to term infants born with gastroschisis. Furthermore, preterm birth was shown to be a significant factor for an increased risk of wheeze symptom and poor short-term prognosis among infants born with a congenital diaphragmatic hernia (Doné et al. 2013; Harting and Lally 2014). Possible explanations of the effect of preterm birth on increased hospitalisation of infants with anomalies include lower physiologic reserve, and higher susceptibility to infections and viral illness associated with prematurity (Björ and Bråbäck. 2003). However, it is also possible that clinicians are more cautious with a lower hospital admission threshold for preterm infants with a congenital anomaly when complications arise (Mackie et al. 2008). In addition, previous studies have shown that having a major anomaly increases the risk of an infant being born preterm; and both congenital anomaly and prematurity are likely to have a synergistic adverse effect on infant morbidity and hospitalisation (Honein et al. 2009; Kase and Visintainer 2007).

Disease severity and comorbidity

Disease severity and comorbidity were significantly associated with an increased risk of hospitalisation among infants with a congenital anomaly (Kongon et al. 2019; Kogon et al. 2012; Saharan et al. 2014; Smith et al. 2015; Beck et al. 2006; Edwards et al. 2010). Studies have consistently shown that the use of inpatient resource among infants with the most severe CHD was significantly higher compared to infants with a less severe CHD (Islam et al. 2016; Islam et al. 2016a; Mackie et al. 2017). Infants with a more severe anomaly are more likely to have complex aetiology and multiple co-morbid conditions, which predispose them to an increased risk of disease complications and hospitalisation (Marston et al. 2019). For example, infants with a syndromal CHD such as DiGeorge syndrome or Down syndrome had a significantly greater risk of respiratory infections and hospitalisation compared to infants with an isolated CHD, regardless of

surgical status (Kongon et al. 2019; Kongon et al. 2012; Saharan et al. 2014; Mackie et al. 2018; Brunetti et al. 2015; Fixler et al. 2012; Ghimire et al. 2020). The higher susceptibility of respiratory infections among infants with Down syndrome is thought to be multifactorial and related to a combination of abnormal lung physiology and impairment of immune system as described earlier in Section 7.4.2. Similarly, studies have shown that infants who were affected by a congenital diaphragmatic hernia with an additional cardiac anomaly or chromosomal defect had a significantly greater risk of morbidity compared to infants who were affected by an isolated congenital diaphragmatic hernia (Putman et al. 2016). Furthermore, complex gastroschisis carries a considerably greater risk of morbidities and adverse prognostic outcomes due to a more complex aetiology and severe clinical manifestations associated with the condition, compared to simple gastroschisis (Bergholz et al. 2014; Emil et al. 2012; Snyder 1999; Molik et al. 2001).

Level of care

Several studies have examined the effect of the level of inpatient/ surgical care on morbidity and hospitalisation outcomes of infants with congenital anomalies. The study by Wes et al. (2017) has shown that infants undergoing surgery for craniosynostosis in a high-volume surgical centre were associated with a significantly lower risk of complications, compared to infants undergoing surgery for craniosynostosis in a low-volume surgical centre, having adjusted for disease complexity. The studies by Apfeld et al. (2017) and Yousef et al. (2016) have shown that infants with a gastroschisis who were cared in a lower volume surgical centre had a greater risk of a longer hospital LOS, inpatient ventilatory support and duration of TPN, compared to infants with a gastroschisis who were cared for in a higher volume surgical centre. It is probable that staff in high-volume centres were more experienced in optimising post-operative care, and consequently, potential morbidities and hospital readmissions were minimised in high-volume centres (Wes et al. 2017).

Day of discharge

Several studies have examined the effect of weekend versus weekday discharge on hospital readmissions of infants who underwent surgery for a CHD, and TOF and OA (Beck et al. 2006; Mackie et al. 2008; van Walraven and Bell 2002; Kongon et al. 2019; McAlister et al. 2013; Smith et al. 2015; Sayari et al. 2016). These studies hypothesised that premature discharge of the infants and limited community medical services available on the weekends might contribute to their readmissions.

Although there were no consistent findings about the effect of the day of discharge on hospital readmission between these studies, a comprehensive discharge care plan was recommended when discharging these vulnerable infants at the beginning of the weekend in order to minimise the impact of potential complications.

Age at surgery

Previous studies have examined the relationship between age at surgical repair and hospital readmissions of infants with congenital anomalies. For example, younger age at surgical repair (i.e. ≤ 10 days of age) has been shown as a risk factor for hospital readmissions for infants undergoing surgery for congenital airway abnormalities, compared to older age (i.e. > 10 days of age) at the time of surgery (Uzomefuna et al. 2012). For hypospadias however, surgical repair at younger age in infancy was associated with a lower risk of complications, compared to surgical repair at older age. For infants with orofacial clefts, delayed surgery could result in multiple operative complexities which might require further hospital admissions (Wu et al. 2019). Studies suggest that this can be due to differences in wound healing, vascularity and hormonal factors between infants and older children (Dodson et al. 2007; Marrocco et al. 2004). These findings have shown that the effect of age at surgery on complications and hospitalisation varies according to the specific anomalies.

7.4.5 Strengths and limitations

Strengths

This is the first literature review examining the contemporary evidence of hospitalisation and morbidities of infants with congenital anomalies. The main strengths of this review include its comprehensive and systematic search strategy, with no restrictions of eligible studies of any congenital anomalies to be included from the literature. Consequently, this review was able to assess hospitalisation and morbidities of infants on a wide range of congenital anomaly subgroups. Another strength is that the majority of the included studies were population-based or multi-centre cohort studies, in which cases were well ascertained from national birth defects registry or paediatric surgical network linked to hospital records. Findings of these studies were generally based on large sample sizes and hence were representative of the relevant populations. A further strength is that this review was able to address different aspects of hospitalisation including its rates, causes, LOS and risk factors, thus providing a comprehensive assessment of the disease burden which infants with a congenital anomaly may experience.

Limitations

The principal limitation of this review relates to heterogeneity between studies. The prevalence of congenital anomalies and admission rates can vary over time and between countries due to methodological differences such as various definitions and inclusion criteria of congenital anomalies and study populations, differences in healthcare systems as well as different study periods (Zylbersztejn et al. 2020). In addition, the completeness of hospital admissions dataset and accuracy of administrative coding are known to vary over time and by hospital. As a consequence, direct comparisons of rates, frequency and LOS of hospitalisation between studies conducted in different settings/ countries were not always possible. Therefore, this review has focused on the important patterns and trends of anomaly-associated hospitalisation and their

implications. A further limitation is that the existing hospitalisation studies have mainly focused on a few major anomaly subgroups such as CHD, Down syndrome, congenital diaphragmatic hernia and gastroschisis. More hospitalisation and morbidity studies are needed in order to further assess the full disease burden for infants affected by a wide range of congenital anomalies.

7.5 Conclusions

This structured literature review has examined and summarised the contemporary evidence on hospitalisation and morbidity of infants with and without congenital anomalies. This review has shown that infants affected by congenital anomalies are consistently associated with a significantly greater risk of morbidity and hospitalisation compared to infants without an anomaly. Anomaly-associated complications and respiratory-related conditions are the most common morbidities and causes of hospitalisation of infants with congenital anomalies. These findings have therefore highlighted the significant impact of congenital anomalies on infant morbidity. In addition, preterm birth, disease severity and comorbidity are shown to be significant determinants of excess hospitalisation of infants with a congenital anomaly. This review has also identified research gaps in which the existing literature has focused mainly on a few major anomaly subgroups such as CHD, Down syndrome, congenital diaphragmatic hernia and gastroschisis. Further population-based hospitalisation studies of a wider range of congenital anomalies are needed in order to assess the full burden of related hospitalisation and morbidity, and monitor the outcomes and care for the affected infants.

Table 7.3: What this structured literature review adds

- This is the first literature review to investigate morbidity and hospitalisation of infants with congenital anomalies conducted in high-income countries.

- The admission rate of infants with a major congenital anomaly has generally increased over time which is most likely due to improved survival of these infants, who require regular inpatient investigations and interventions; whilst many surgical procedures for minor anomalies were performed as day cases as a result of medical and surgical advances.

- Infants with a major congenital anomaly have a significantly increased risk of morbidities and hospitalisation, compared to infant without an anomaly.

- Anomaly-related complications and respiratory-related conditions are the most common causes for hospitalisation of infants with congenital anomalies.

- Infants with a complex or syndromal/ chromosomal anomaly are admitted for a longer hospital stay due to comorbidities and complications, compared to infants without an anomaly, or with a less complex or non-syndromal anomaly.

- Preterm birth, disease severity and comorbidity are significantly associated with an increased risk of excess hospitalisation among infants with an anomaly.

- Heterogeneity is a major study limitation. Future hospitalisation and morbidity studies focusing on a wider range of congenital anomaly subgroups are needed.

Chapter 8: An Investigation Into The Patterns, Reasons For And Outcomes Of Hospitalisation Comparing Infants With And Without Congenital Anomalies.

8.1 Introduction

Congenital anomalies are a leading cause of morbidity and hospitalisation in infancy (Billet et al. 2008; McCandless et al. 2004; Yoon et al. 1997). As highlighted in the structured literature review in Chapter 7, infants and children with a major congenital anomaly such as CHD, Down syndrome and congenital diaphragmatic hernia have a significantly increased risk of morbidity and hospitalisation due to short- and long-term sequelae and complications associated with the anomaly compared to infants and children without an anomaly. The review also identified a major research gap in which the existing hospitalisation and morbidity studies have mainly focused on a few major anomaly groups including CHD, Down syndrome, congenital diaphragmatic hernia and gastroschisis. In the UK, there have been only a few population-based studies investigating the hospitalisation of infants affected by anomalies including CHDs (Billett et al. 2008), orofacial clefts (Fitzsimons et al. 2013), gastroschisis (Bradnock et al. 2011) and eye anomalies (Dharmasena et al. 2017). Epidemiological evidence from hospitalisation and morbidity studies on wider anomaly groups is lacking.

As survival of infants with congenital anomalies has greatly improved over time (Colvin and Bower 2009; Bloemer et al. 2007; Hilton et al. 1999), further population-based hospitalisation studies on a wider range of congenital anomalies are needed in order to monitor the full burden of anomaly-related hospitalisation and morbidity patterns and outcomes, and to inform clinicians about causes of hospitalisation and anomaly-specific complications.

The main rationale of this study was to generate epidemiological findings and contribute new knowledge from a UK based population-based study investigating the impact of a wide range of congenital anomalies and rare diseases on infant hospitalisation and morbidity.

8.2 Aims

The overall aims of the analyses of this study were to investigate the patterns, reasons for and outcomes of hospitalisation for infants with congenital anomalies compared to infants without congenital anomalies.

Specific objectives

8a. To compare the rates of hospitalisation in the first year after birth between infants with and without congenital anomalies;

8b. To describe the patterns of hospitalisation in the first year after birth in infants with and without congenital anomalies;

8c. To examine the risk factors for hospitalisation in the first year after birth among infants with congenital anomalies.

8.3 Methods

8.3.1 Data sources

This study was conducted using data from the Patient Episode Database for Wales (PEDW), CARIS and ONS. The data sources from CARIS and ONS were described in Chapter 5.

PEDW records all Wales hospitals' inpatient and day case activities within the NHS and for some Welsh residents treated in the other countries within the UK. These include elective and emergency admissions, minor and major operations, and hospital stay for giving birth. Hence, PEDW is representative of the healthcare received by the whole population of Wales.

The PEDW dataset was generated by the Secure Anonymised Information Linkage (SAIL) Databank at the University of Swansea. The PEDW dataset for this study consisted of four tables: the SPELL,

EPISODE, DIAGNOSIS and OPERATION tables contained spell level records, finished consultant episode level records, diagnostic details and operation information respectively (Table 8.1).

PEDW contains demographic, clinical and administrative data, such as age, sex and week of birth, which are collected and coded at each hospital. Diagnostic information recorded during an inpatient episode is transcribed and coded using ICD-10. Data are collected from patients' consultant episode. If the patient is transferred to the care of another consultant, either in the same or another specialty or they are transferred to another NHS provider for continuing in-patient care, another consultant episode is started and results in another PEDW record.

Table 8.1: Patient Episode Database for Wales (PEDW) tables provided by SAIL for this study (1999-2015 Birth cohort).

Table	Descriptions	Key data items
PEDW Spell	Information about each individual's spell (i.e. total continuous inpatient stay using a bed on premises controlled by the health care provider) over a given period.	Personal characteristics of all treated inpatient and day case admissions e.g. sex; and clinical information relating to each admission e.g. dates of admission/ discharge, length of spell, the methods of admission/ discharge etc.
PEDW Episode	Records at a finished consultant episode (FCE) level.	Personal characteristics of all treated inpatient and day case episodes e.g. age at start of episode; and clinical information relating to each episode e.g. dates of episode started/ ended, length of episode etc.
PEDW Diagnosis	Diagnosis information specific to an individual's episode of care in hospital over a given period.	Up to 14 diagnoses can potentially be recorded for a given hospital episode, with the order of the diagnoses assigned, e.g. primary, secondary diagnosis etc.
PEDW Operation	Operation information specific to an individual's episode of care in hospital.	Up to 12 operations can potentially be recorded for a given hospital episode.

Data quality of PEDW

PEDW has been implemented since April, 1991, and managed by the NHS Wales Information Service (NWIS), previously known as Health Solution Wales (HSW). The PEDW dataset represents

the primary information source relating to all inpatient and day case activities in NHS Wales hospitals.

Data about hospital inpatient admissions for Wales are coded by clinical coders and electronically transferred by each NHS Health Board and validated by NWIS/ HSW prior to transferring and merging into the main database. Data are continually updated; and all ICD diagnostic and Operating Procedure Codes (OPCS) classifications are revised regularly to account for newly emerging conditions and revised definitions. Therefore, the PEDW records are considered to be a robust and high-quality data source and are widely used by various health bodies throughout Wales.

Approximately 100,000 episodes of inpatient care are processed each month. With the size and complexity of the dataset, variable amount of missing data and coding errors and disparities can potentially occur in the PEDW records from year to year (Williams et al. 2003); however, only a relatively small proportion of PEDW data is affected. In addition, with new cleaning and derivation rules are being implemented by the data providers to check the validity and format of the data fields, the quality of hospital inpatient data within the PEDW dataset has improved over time.

Regarding the data quality of CARIS and ONS, see Chapter 5: Sections 5.1 and 5.2, and Chapter 6: Section 6.3.8.

8.3.2 Linkage of datasets

To conduct the hospitalisation analyses, I had to link the data tables provided together. At the beginning of the dataset linkage, I found a considerable number of linkage mismatches between PEDW tables (i.e. Episode, Spell, Diagnosis and Operation), which were subsequently proven to be due to an incorrect anonymised linking field (ALF) given by the SAIL databank. To resolve the problem, I worked closely with data scientists from the SAIL databank to revise and correct all the linking fields errors, before I was able to successfully join the PEDW tables together and collate all

available information about each individual infant's stay in hospital. I was then able to perform the rest of the dataset linkages such that the PEDW dataset was linked to the CARIS (i.e. Mother Townsend quintile, Mothers, Pregnancies, Baby/Fetus and Anomaly) and ONS (i.e. Births and deaths) datasets in order to collate the necessary data for the analyses of the specific objectives in this study. The outcomes of the joined dataset and linkages were checked and validated by the SAIL data scientists prior to analysis. Figures 8.1 and 8.2 show the study population, the datasets and merging method for this study.

Figure 8.1: Flow chart of the study population.

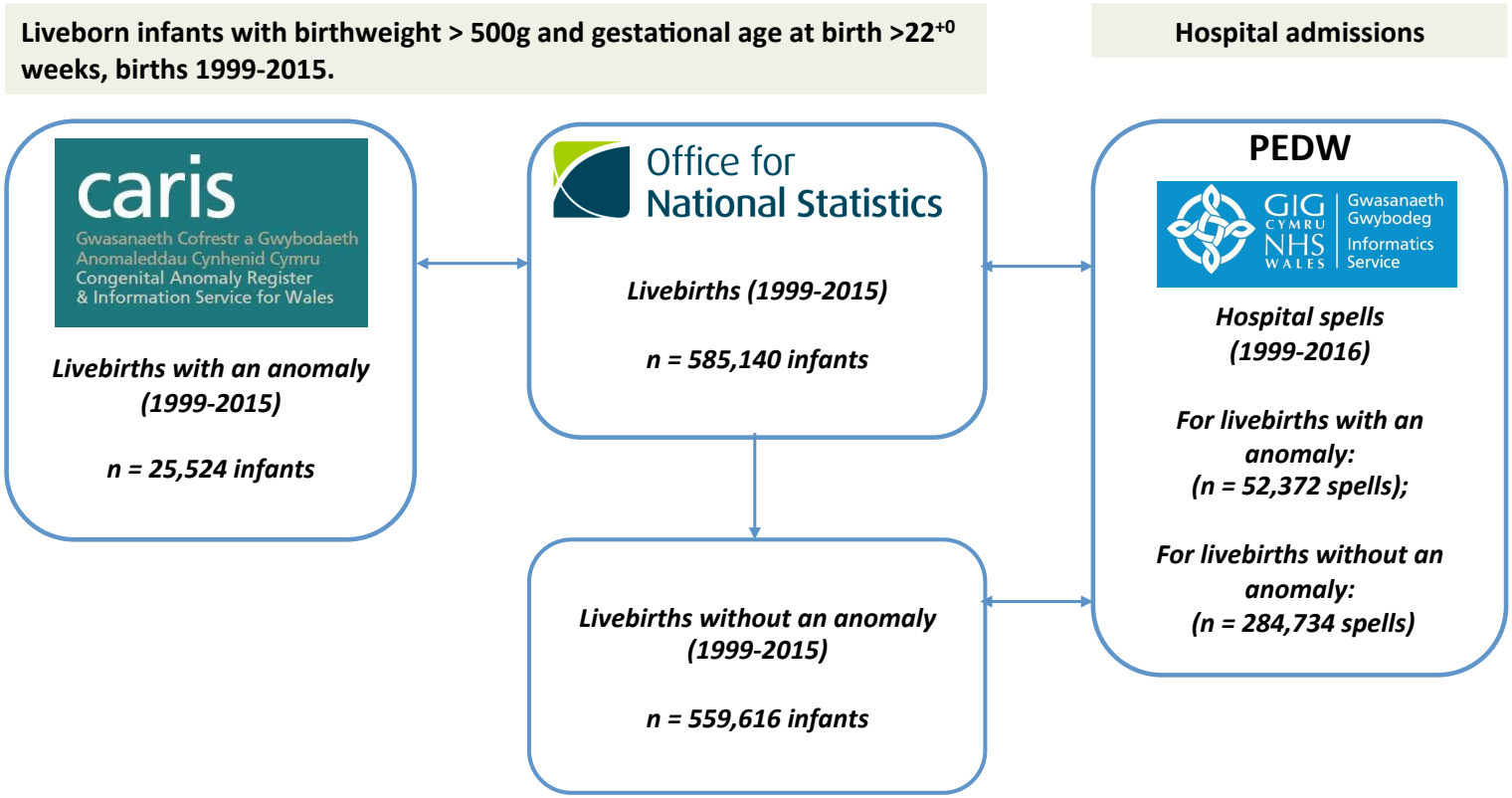
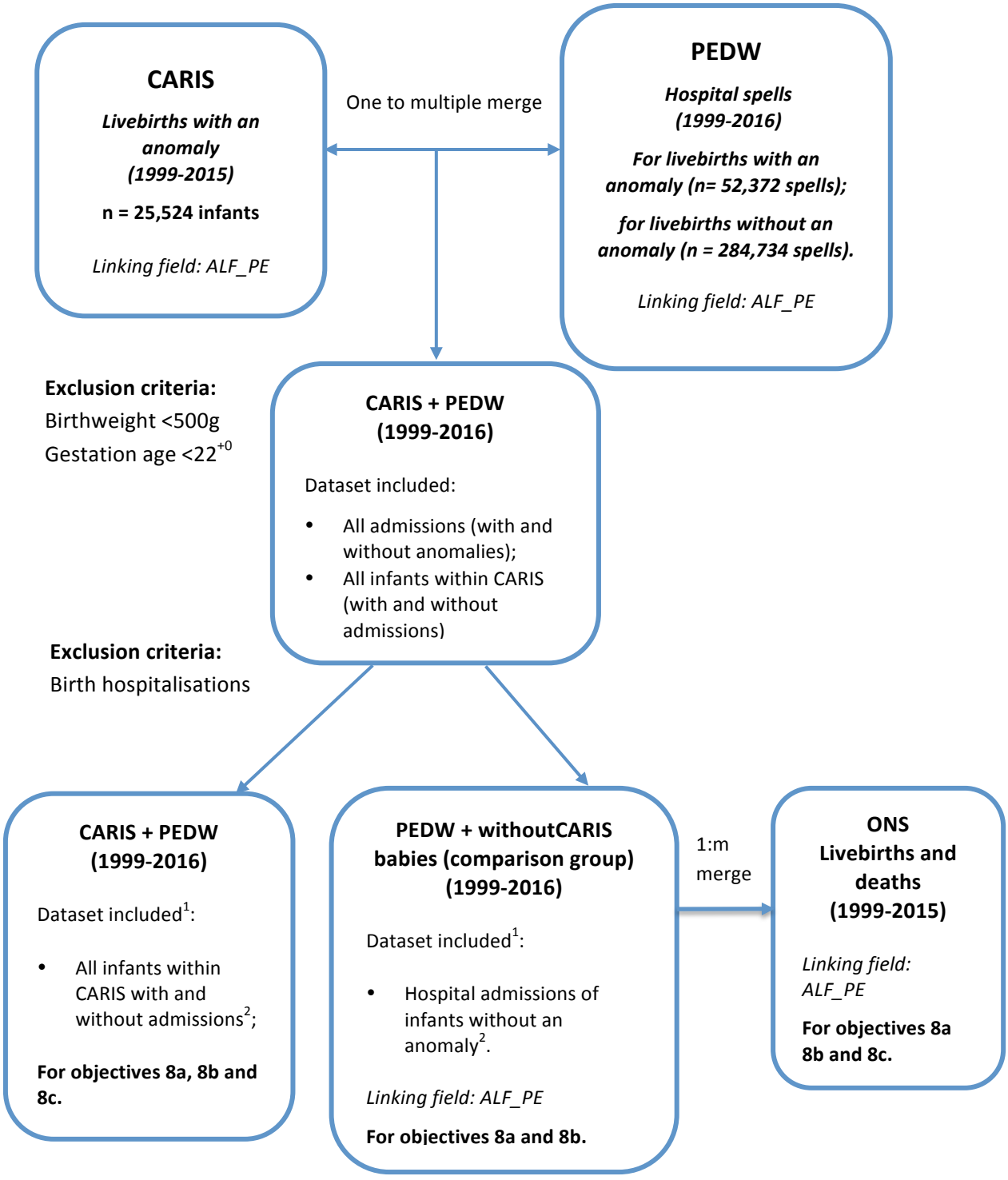


Figure 8.2: Flow diagram showing datasets and merging method using the anonymised linking fields.



[1]*Spells were the unit of analysis in the dataset.*

[2]*Transfers were excluded for the analysis of primary causes of hospital admissions, but were included for the estimates of total number of admissions (i.e. transfers being counted as additional admissions), admission rates and total length of stay.*

8.3.3 Inclusion and exclusion criteria

The following inclusion and exclusion criteria were applied to the analyses of study objectives 8a, 8b and 8c.

All livebirths between 1.1.1999 and 31.12.2015 (birth cohort), who were followed up to their first birthday (i.e. until 31.12.2016 at the latest), were included in the analysis. This study period excluded the years of 1998 (when CARIS registry was newly established), and 2017 (patients' records were incomplete for 2017 at the time when the PEDW dataset was released for this study), in which the recorded number of admissions among infants with an anomaly was extremely low.

Consistent with the mortality study in Chapter 6: Section 6.3.2, infants born at a gestational age $<22^{+0}$ and/or with a birthweight <500g were excluded from the analysis in this study. As there were no validation checks in birthweight within the NHS system prior to 2015, some cases of implausible birthweights were recorded and found in the dataset. Therefore, birthweight > 99.6^{th} centile up to 42^{+0} gestational weeks were treated as missing values, i.e. the cut-off birthweight for male infants was taken as 5300g, and the cut-off birthweight for females was taken as 4900g (Norris et al. 2018).

Admissions of healthy babies solely for birth in hospital (i.e. birth hospitalisation) were excluded from the analysis in this study (Figure 8.3). By excluding birth hospitalisation, well-babies admissions were separated from the burden of hospitalisation that infants with congenital anomalies might experience in order to avoid artificial inflation of the estimate of paediatric hospital admission due to well babies born in hospital (MacFaul and Werneke 2001).

Cases with an isolated minor anomaly (as described in Appendix 1.2: EUROCAT Minor Anomalies and other condition for Exclusion) were excluded from the analysis. Isolated minor anomalies are

considered to be of lesser medical, functional or cosmetic consequences. In addition, their definitions, diagnoses and reporting vary considerably in practice (EUROCAT 2019a).

Duplicate records were identified and excluded as appropriate. Further specific inclusion and exclusion criteria are described under specific objectives as appropriate.

Coding issues

A small proportion (<1%) of coding errors in the 'admission methods' were found in the dataset, in which infants' admissions were misclassified as maternal admissions. To resolve the coding errors, I performed further checks and revisions. The misclassified maternal admissions due to prematurity, respiratory distress, feeding problems and hypoglycaemia of infants were identified, and these admissions were subsequently corrected as infants' admissions, and included in all the analyses. In addition, admissions of infants solely due to postpartum maternal problems (i.e. babies who were admitted just to stay with their mothers in hospital) were excluded from all the analyses. A possible explanation for their original inclusion in the dataset is that these babies were admitted to a postnatal ward and these admissions were classed as maternal admissions for costing reasons.

An estimate of <5% of the episodes of admissions and their primary diagnoses were either missing or miscoded. To explore this, I performed a further investigation into the hospital episodes of infants with abdominal wall defects and congenital diaphragmatic hernia with missing admission data, and found that these infants were residents in North Wales. A likely explanation for the admissions and primary diagnoses being missing or miscoded is that these infants who reside in Mid- or North Wales received treatment in a specialist centre outside the catchment area of NHS Wales care providers e.g. in Birmingham Children's Hospital or Alder Hey Children's hospital in Liverpool, and consequently the reporting of these admission data was delayed, not

followed up or not made available in PEDW for various reasons. The method by which these missing or miscoded episodes and diagnoses were dealt with is described in Sections 8.3.4 – 8.3.6.

8.3.4 Rates of hospitalisation (objective 2a)

All spells, including emergency, elective and transfer hospital spells, were included in this analysis in order to assess the overall burden of hospitalisation.

A spell was defined as the total continuous stay of a patient using a bed on premises controlled by one healthcare provider (NHS Wales Digital Health and Care Wales, 2021). Each spell was used as the unit of analysis in this study objective. Hence, all (single and multiple) spells of infants were taken into account with the corresponding person time in the estimate for the rate of hospitalisation in infancy.

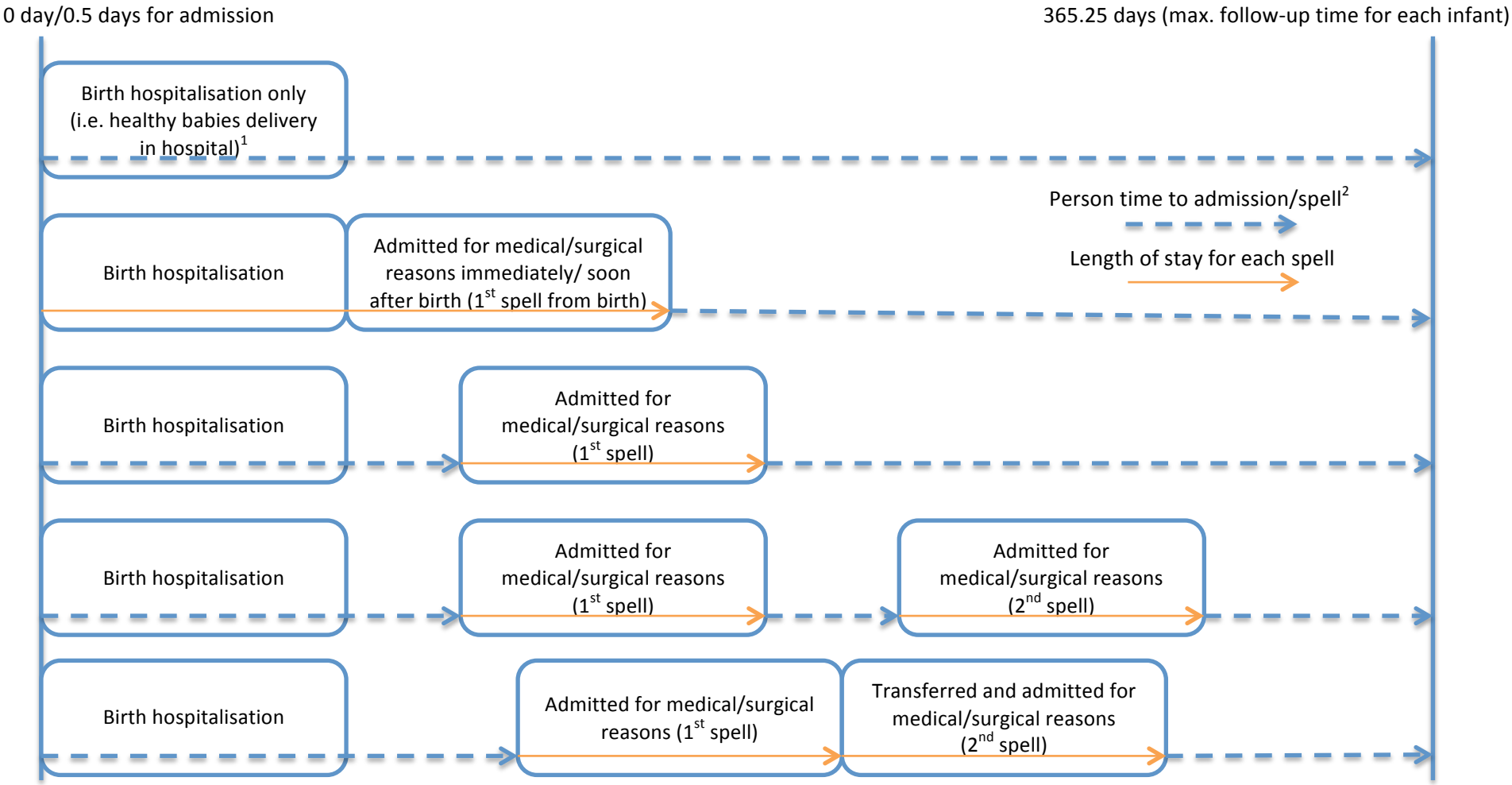
The rate of hospitalisation was defined as the total number of spells divided by total person-time to admission in infancy. Person time was calculated from week of birth (i.e. the Monday prior to the actual date of birth) to the date of admission for the first spell. This was because only information about the week of birth was given in the SAIL dataset by Health Information Research Unit (HIRU), as date of birth is an identifiable data; SAIL only contains anonymised information. Hence, all age calculations were accurate to +/- 7 days (see Section 8.5.3: Limitations). For the second and subsequent spells, person time was calculated from the discharge date of the prior spell to the admission date of the current spell. Censoring occurred at date of death or when data were missing. Person time (in days) of less than one day, which was shown as '0' (this represented 7.25% of all spells of infants with and without an anomaly in the dataset), was converted to 0.5 days in the analysis (See Table II and Figure 8.3 for person time). Figure 8.3 describes follow up time and common scenarios for hospital spells in the analysis.

Rates of hospitalisation were estimated for infants with and without anomalies, and for specific anomaly groups using the Stata command "strate [anomaly_group]". Crude rate ratios with 95%

CIs were estimated to compare infants with an anomaly (or specific anomalies) versus infants without an anomaly.

Figure 8.3: Follow up time and common scenarios for hospital spells in the analysis.

[1]Birth hospitalisation only were excluded from the analysis.[2]Person time (in days) to admission: for the 1st spell, person time was calculated from date of the admission minus the date of the Monday prior to the actual date of birth; for 2nd spell onwards was calculated from the current admission date minus the discharge date of the prior admission.



8.3.5 Patterns of hospitalisation (objective 8b)

The primary causes, frequency and length of hospitalisation were examined in this analysis.

Primary causes of hospitalisation

All emergency and elective hospital spells were included in the analysis of primary causes of hospital admissions. Transfer hospital spells were excluded in order to avoid double counting of the recorded primary diagnosis from the 'transfer' hospital records, or inclusion of other secondary diagnoses or complications (e.g. hospital-acquired complications as the main reason for transfer) in this analysis.

Each spell was the unit of analysis, and hence all (single and multiple) spells of the infants in the first year after birth were taken into account as appropriate. This study objective particularly focused on the primary diagnoses designated to the first episode of each spell, as this has been shown to be a standard approach in previous studies (Billet et al. 2008). All the ICD-10 coded primary diagnoses associated with each spell were categorised according to ICD-10 chapters headings. Using this approach, the top five most common causes of hospital admissions were examined and presented, stratified by anomaly subgroup. Using the same methods, inclusion and exclusion criteria, the top five most common causes of hospital admissions were presented for infants without an anomaly as the comparison group.

Frequency of hospitalisation

All spells (emergency, elective and transfer hospital spells) were included in the analysis of the frequency of hospitalisation in order to assess the overall burden of hospitalisation.

The frequency of hospitalisation was defined as the total number of spells per infant admitted. The distribution of the number of spells per infant admitted was found to be positively skewed (i.e. mean > median). Therefore, median number of spells per infant admitted was estimated.

Results are presented and stratified by anomaly subgroup. Using the same methods and criteria, frequency of hospitalisation was examined for infants without an anomaly as the comparison group.

Hospital length of stay (LOS)

All spells (emergency, elective and transfer hospital spells) were included in the analysis of the LOS in order to assess the overall burden of hospitalisation. Estimates for hospital LOS excluded any incomplete spells in which the first episodes were missing (i.e. this was likely due to coding errors or infants who were admitted outside the catchment area of NHS Wales providers as discussed in Section 8.3.3).

LOS of a hospital spell was calculated as the period of time (in days) between start date and discharge date of the provider spell. For infants who were admitted from birth, LOS was calculated from the discharge date minus the date of the Monday that occurred prior to the actual date of birth (Table II and Figure 8.3). In such cases, the LOS of the first spell was to within +/- 7 days accuracy. For infants whose discharge date and admission date were on the same date, spell duration was set to be 0.5 days to represent some extent of stay.

Total LOS of an infant was calculated by the sum of duration (in days) of all the hospital spells across all admissions in the first year after birth, using the Stata command 'collapse (sum), patient_id'. Distributions of the hospital LOS per spell (in days) and total LOS per admitted infant (in days) were found to be positively skewed (i.e. mean > median). Therefore, median hospital LOS per spell (in days) and median total LOS per admitted infants (in days) were estimated. Results are presented and stratified by anomaly subgroup. Using the same methods and criteria, hospital LOS was examined for infants without an anomaly as the comparison group.

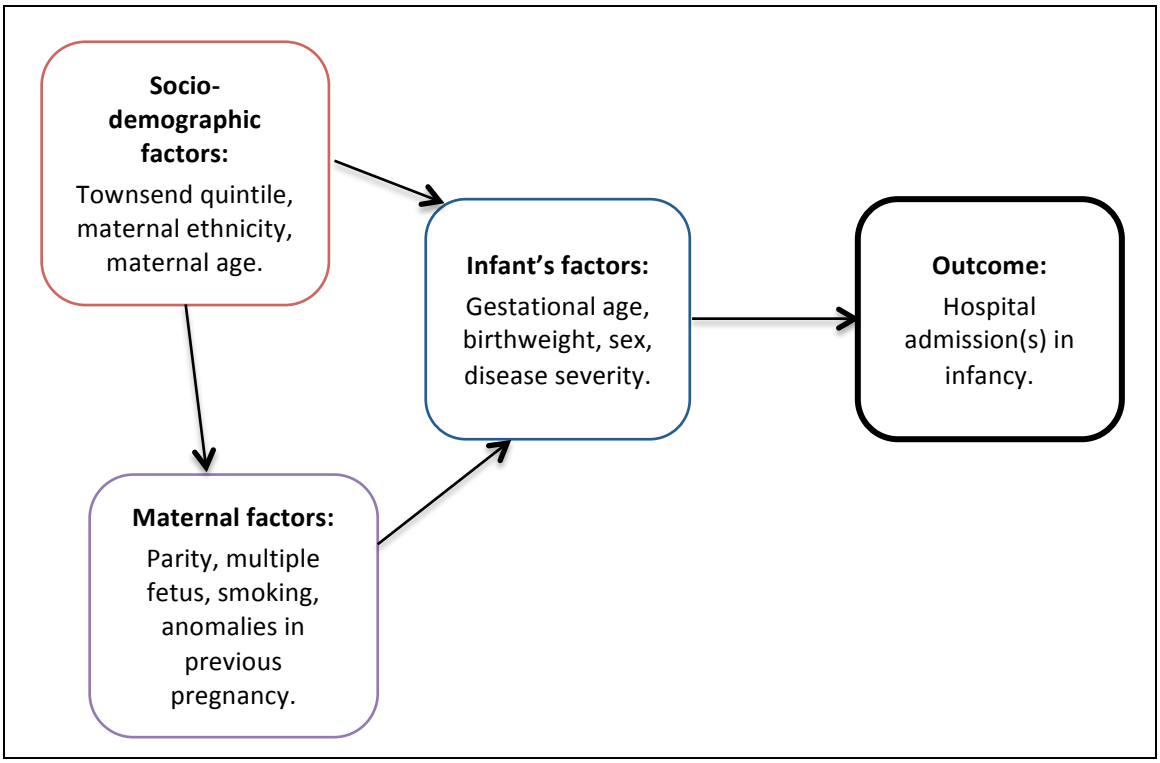
8.3.6 Risk factors for increasing numbers of hospital admissions (objective 8c)

All spells (emergency, elective and transfer hospital spells) were included in the analysis.

Here the analysis focused on identifying factors associated with increasing numbers of hospital admissions. Each infant was categorised as having 0, 1 or 2+ admissions. All analyses were conducted using multinomial logistic regression models with the Stata commands "mlogit" to estimate the relative risk ratios (RRR) of hospital spell and the corresponding 95% CI, comparing infants with one admission in infancy versus infants with no admission (no admission as the comparison group), and also comparing infants with repeated (2+) admissions in infancy versus infants with no admission. The RRR were estimated according to the categories of socio-demographic, maternal and infant using the conceptual framework shown in Figure 8.4. These variables were selected based on evidence from the literature review in Chapter 7, and 'missingness' of the variables in the dataset. The descriptions and categorisations of the included variables for the analysis of study objective 8c are summarised in Chapter 6: Table 6.1.

For all analyses, infant sex and gestational age at birth were selected as *a priori* variables as they are known determinants of infant morbidity and hospitalisation according to the literature (Butler and Behrman 2007; Stevenson et al. 2000). In addition, for the subgroup analysis of cardiovascular anomalies, disease severity (based on the EUROCAT severity classification for CHDs: Table 6.1) was also selected as an *a priori* variable, as previous studies have shown that disease severity is a determinant of infant hospitalisation. Infants with the most severe CHDs use inpatient resource more intensively compared to infants with a less severe CHD (Islam et al. 2016; Islam et al. 2016a; Mackie et al. 2017; Marston et al. 2019).

Figure 8.4: Conceptual framework showing a hypothesised relationship between socio-demographic, maternal and infant's factors used in this analysis, in relation to hospital admission(s) of an infant born with an anomaly.



Note: This conceptual framework is adopted from the mortality study (Chapter 6: Figure 6.2).

Descriptive statistics

Characteristics of all infants with any congenital anomaly were examined, stratified by the number of hospital admissions (0, 1 and 2+). Infants with an anomaly who had no hospital admission were classified as the comparison group.

Univariable analysis

Univariable multinomial regression was performed to obtain the crude RRR with corresponding 95% CI for each explanatory variable. Post-estimation of the regression analysis was performed using the Stata command 'testparm' to obtain the overall p value for the Wald test for each variable at all hospital admission outcome categories. Variables with $p < 0.1$ from Wald test were included in the multivariable analysis.

Multivariable analysis

All *a priori* variables (where appropriate) and significant variables from the univariable analysis (i.e. $p < 0.1$ from Wald test) were simultaneously fitted together in the same (full) model for the multivariable multinomial regression. Variables were removed from the full model if all of the categories of the variable yielded a $p \geq 0.05$. Explanatory variables remained in the final models if any of their categories yielded a Wald test result of $p < 0.05$ after adjustment for other variables in the multivariable analysis. Any category of a variable with $p < 0.05$ in the final model was considered as statistically significant. The multinomial logistic regression was conducted using complete case analysis.

All analyses were performed separately for the following anomalies/ subgroups as they contributed the greatest number of hospital admissions of the study population (Table 8.2).

1. All (Isolated and multiple) anomalies;
2. All isolated anomalies;
3. All multiple anomalies;
4. Cardiovascular anomalies;
5. Genitourinary anomalies.

Further subgroup analysis

In order to investigate further whether the risk factors were different between infants with anomaly-specific admissions and infants with other-cause admissions, a further subgroup analysis was conducted. Characteristics of infants with anomaly-specific admissions and those with other-cause admissions were identified (from Results: Table 8.3) and described. Univariable logistic regression was performed to obtain the crude odds ratio with corresponding 95% CI and p-values for each explanatory variable comparing infants with anomaly-specific admissions to those with other-cause admissions. Significant variables from the univariable analysis (i.e. $p < 0.1$ from

LR test) were included in the multivariable analysis using a 'backward stepwise approach' for the same reasons as those outlined in Chapter 6: section 6.3.7.

The analysis was carried out as follows:

First, significant variables from univariable analysis were fitted together in the same (full) model. Using LR test, variables were tested for removal from the full model one at a time. Variables with LRT $p < 0.05$ were retained in the model and carried forward until all variables in the full model had been removed and/or replaced. To check the robustness of the final model, the variables which had been removed (i.e. LRT $p \geq 0.05$) were individually put back to re-check their fit in the final model. Finally, the LRT was performed in order to assess the independent effect (i.e. adjusted OR) for each variable in the final model. $P < 0.05$ was considered as statistically significant.

8.4 Results

8.4.1 Overview of hospitalisation characteristics

Of 585,140 livebirths, there were 25,524 (4.4%) liveborn infants diagnosed and registered with an isolated or multiple anomalies in the 1999-2015 birth cohort (Figure 8.5). Among all spells of infants with isolated anomalies, the largest number of spells was for cardiovascular anomalies (n = 4,366 spells), which represented 8.3% of the total spells in all babies with anomalies. This was followed by babies with gastrointestinal anomalies (n = 4,079 spells), which represented 7.8% of the total spells; and babies with genitourinary anomalies (n = 3,332 spells), which represented 6.4% of the total spells (Figures 8.6 and 8.7).

Figure 8.5: Overview of anomaly status and spells.

**Estimates included transfer hospital spells and spells which began with a second episode (i.e. missing first episodes were likely due to coding errors or patients who were admitted outside Welsh NHS providers).*

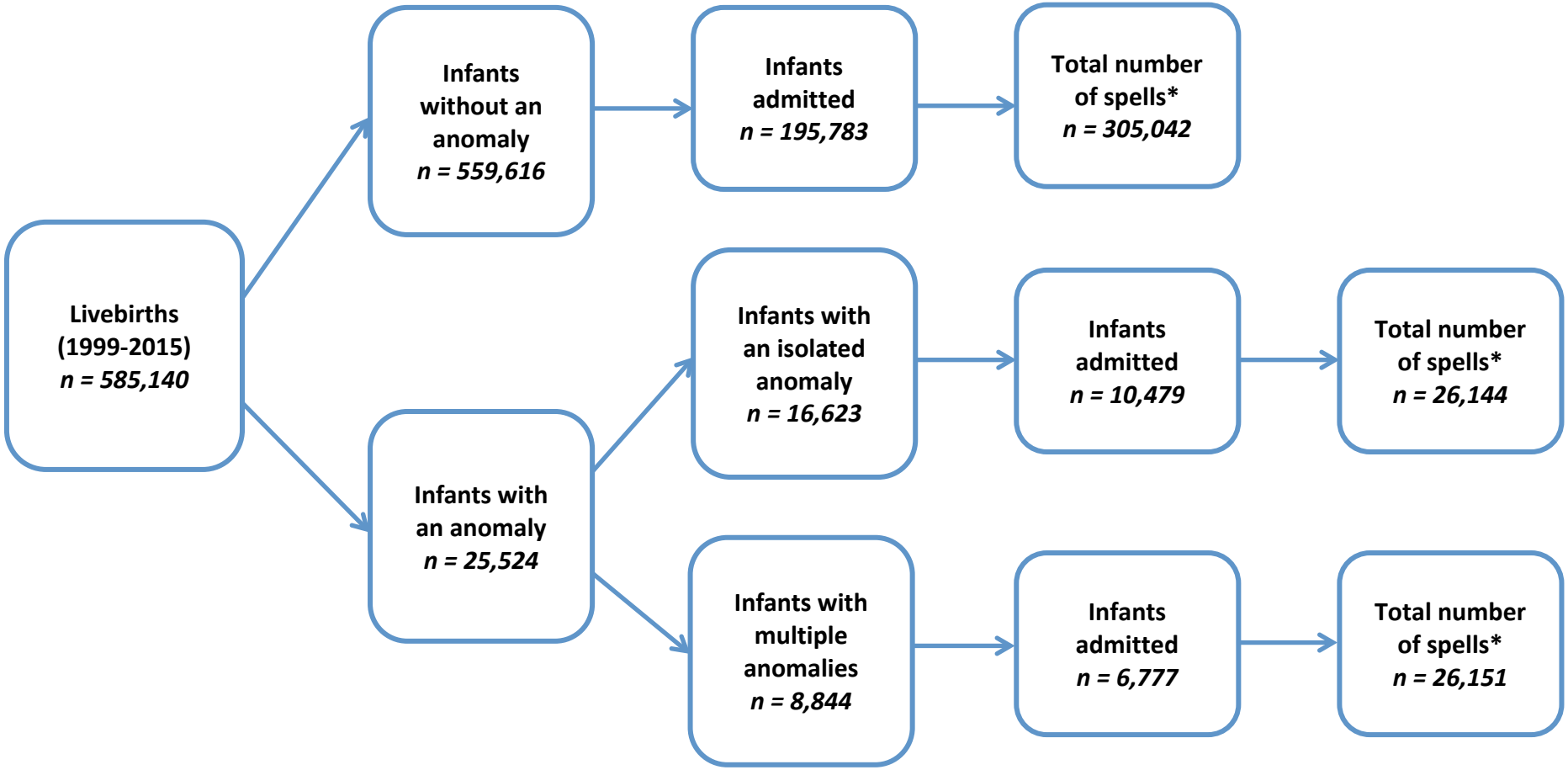
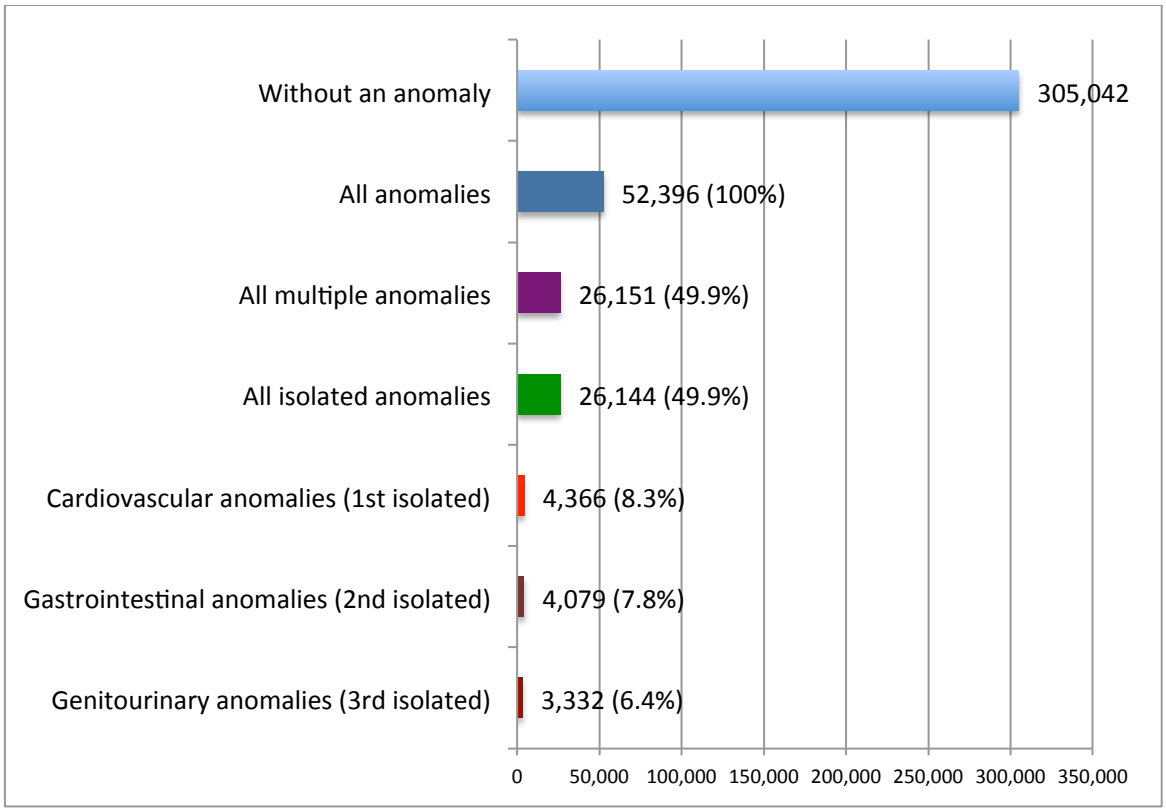
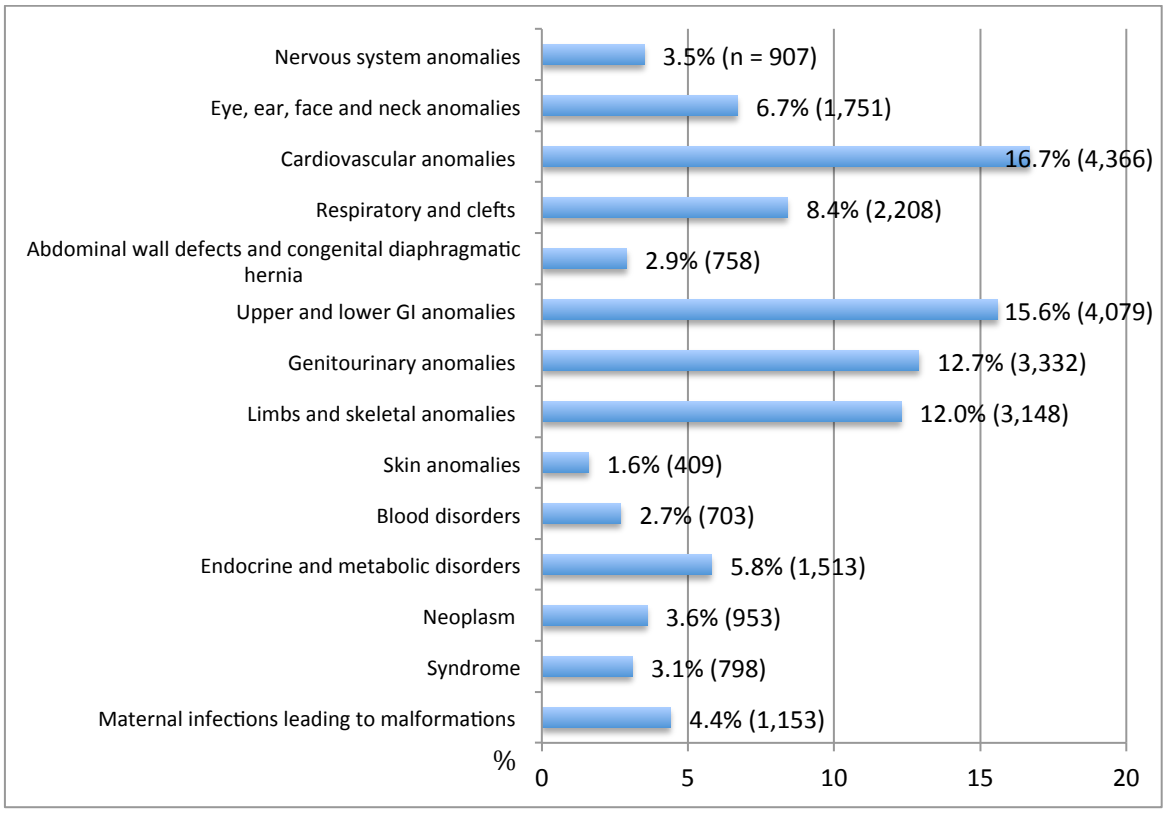


Figure 8.6: Total number of spells by anomaly status.



Note: only the three most common isolated anomalies related hospital spells are shown.

Figure 8.7: Distribution of hospital spells by isolated congenital anomaly subgroup (n = 26,144).



Note: All spells (i.e. across all admissions, including transfers) were included in the estimates.

Table 8.2: Rate and rate ratio of all hospitalisation in infancy of infants with and without congenital anomalies, births 1999 to 2015.

	No. of infants[1,2]	No. of infants admitted[1,2]	Total no. of spells[1,2]	Total person-time (years)[1,2,3.]	Hospitalisation rate[1,2] (no. of spell per person year), 95% CI	Rate ratio[1,2] (95% CI)
Without anomalies	559,616	195,783	305,042	410,677.6	0.70 (0.70-0.72)	1
All anomalies	25,524	16,829	50,705	14784.4	3.51 (3.48-3.54)	5.01 (4.96-5.06)
Multiple anomalies	8,844	6,613	25,293	4,928.1	5.10 (5.04-5.17)	7.28 (7.19-7.38)
Isolated anomalies	16,624	10,188	25,314	9856.3	2.70 (2.67-2.73)	3.85 (3.80-3.90)
Isolated anomaly subgroup						
Nervous system	503	284	865	293.9	3.01 (2.82-3.22)	4.30 (4.03-4.59)
Eye, ear, face and neck	1,468	721	1,724	967.9	1.84 (1.76-1.93)	2.63 (2.51-2.75)
Cardiovascular	2,606	1,609	4,162	1482.7	3.00 (2.91-3.09)	4.28 (4.15-4.41)
Respiratory and clefts	916	790	2,150	494.2	4.41 (4.23-4.60)	6.29 (6.03-6.56)
Abdominal wall defects and diaphragmatic hernias	318	253	671	99.5	6.64 (6.16-7.17)	9.48 (8.78-10.23)
Upper and lower GI	1,472	1,290	4,013	439.1	9.62 (9.33-9.91)	13.72 (13.31-14.14)
Genitourinary	3,559	1,686	3,217	2,459.1	1.39 (1.34-1.44)	1.98 (1.92-2.05)
Limbs and skeletal	2,504	1,593	3,078	1,613.9	2.02 (1.95-2.09)	2.88 (2.78-2.98)
Skin	326	178	399	226.4	1.95 (1.77-2.14)	2.78 (2.54-3.06)
Blood	227	153	693	126.5	5.45 (5.06-5.87)	7.78 (7.22-8.38)
Endocrine and metabolic	763	497	1,489	473.6	3.28 (3.12-3.44)	4.67 (4.45-4.91)
Neoplasm	397	243	945	237.4	3.95 (3.71-4.21)	5.64 (5.29-6.01)
Syndrome	798	358	769	616.8	1.55 (1.45-1.65)	2.21 (2.08-2.36)
Maternal infections leading to malformations	682	499	1,074	275.5	3.95 (3.73-4.20)	5.64 (5.31-5.99)

Table 8.2 (continued): Rate and rate ratio of all hospitalisation in infancy of infants with and without congenital anomalies, births 1999 to 2015.

[1]Each spell was used as the unit of analysis, hence all single and multiple spells (i.e. across all admissions, *including transfers*) were included in the estimates for the rate of hospitalisation. [2]Estimates excluded any spells in which the first episodes were missing due to coding errors. [3]Person time or follow up time (in day) of less than 1 day to admission was converted to 0.5 day in the analysis. For the first spell, person time (in days) to admission was the difference (in days) between the admission date and the date of the Monday prior to the actual date of birth. For the second spell onwards, person time was calculated from the admission date minus the discharge date of the prior admission. *Note: Birth hospitalisations were excluded from the analysis. Observations in the sub-categories may not add up to the total, as some of the categories are not shown due to small number or risk of statistical disclosure.*

8.4.2 Hospitalisation rates (study objective 8a)

Infants with any subgroup of congenital anomaly had a consistently higher hospitalisation rate compared to infants without an anomaly (Table 8.2). Infants with any congenital anomalies had an overall hospitalisation rate at 3.51 spells per person year, which was five times higher than that of infants without an anomaly (rate of 0.70; rate ratio, RR = 5.01, 95% CI: 4.96-5.06). Infants with multiple anomalies had a hospitalisation rate at 5.10 spells per person year, which was seven times higher than that of infants without an anomaly (RR = 7.28, 95% CI: 7.19-7.38); and infants with an isolated anomaly had a hospitalisation rate at 2.70 spells per person year, which was almost four times higher than that of infants without an anomaly (RR = 3.85, 95% CI: 3.80-3.90). Among infants with isolated anomalies, infants with structural anomalies had the highest hospitalisation rates. For example, infants with gastrointestinal anomalies had the highest hospitalisation rate at 9.62 spells per person year among all anomaly subgroups, which was almost 14 (95% CI: 13.31-14.14) times higher than that of infants without an anomaly (Table 8.2). This was followed by infants with abdominal wall defects and congenital diaphragmatic hernias (6.64 spells per person year), which was 9.5 (95% CI: 8.78-10.23) times higher than that of infants without an anomaly. In addition, infants with respiratory or clefts anomalies, cardiovascular anomalies and anomalies of the nervous system had hospitalisation rates which were between four to six times higher than that of infants without an anomaly (Table 8.2).

Infants with anomalies represented about 15% of total spells (52,396/357,438) among all infants hospitalised prior to their first birthday. A greater proportion of infants with an anomaly were hospitalised (66.3%, 16,829/25,254), compared to infants without an anomaly (35.0%, 195,783/559,616) (Table 8.2). Among infants with anomalies, a greater proportion of infants with multiple anomalies were hospitalised (74.8%; 6,613/8,844), compared to infants with isolated anomalies (61.3%; 10,188/16,624).

8.4.3 Patterns of hospitalisation (study objective 8b)

Primary cause of hospitalisation

The top five most common, primary causes of hospital admission in infancy of infants with various subgroups of congenital anomalies, and those without congenital anomalies are summarised in Figures 8.8-8.25, Tables 8.4 and 8.5.

For infants born with a congenital anomaly, the anomaly and associated diseases or complications were the most common primary cause of hospital admissions, contributing more than a quarter of all admissions (Figures 8.8-8.11 and Table 8.3). Apart from admissions due to congenital and chromosomal anomalies, the most common primary causes of hospitalisation in infancy between infants with and without congenital anomalies were similar, with diseases of the respiratory system and conditions originating in the perinatal period represented the leading causes of hospital admissions. This was followed by abnormal symptoms, signs and laboratory findings, and certain infectious and parasitic diseases (Table 8.3, Figures 8.8 and 8.9). Consistently, among different isolated anomaly subgroups, the top five most common primary causes of hospital admissions in infancy followed a similar pattern, with congenital anomalies and associated diseases/ complications, diseases of the respiratory system, and conditions originating in the perinatal period being the most common primary causes of admissions (Figures 8.12-8.25 and Table 8.4).

Table 8.3: Top five primary causes of hospital admissions in infancy of infants with and without congenital anomalies, births 1999 to 2015.

	Hospital admissions (spells[1]) frequency (%)[2]			
Primary cause[3] of hospital admission	**All anomalies (n = 49,312)[2]**	**All isolated anomalies (n = 24,758)[2]**	**All multiple anomalies (n = 24,459)[2]**	**Without an anomaly (n = 284,734)**
Congenital and chromosomal abnormalities	13,609 (27.6)	6,453 (26.6)	7,142 (29.2)	
Diseases of the respiratory system	7,006 (14.2)	3,426 (13.8)	3,557 (14.5)	72,323 (25.4)
Conditions originating in the perinatal period	5,960 (12.1)	3,463 (14.0)	2,486 (10.2)	60,507 (21.3)
Symptoms, signs and abnormal laboratory findings	5,550 (11.3)	2,648 (10.7)	2,886 (11.8)	40,099 (14.1)
Certain infectious and parasitic diseases	3,429 (7.0)	1,823 (7.4)	1,597 (6.5)	43,268 (15.2)
Diseases of digestive system				21,167 (7.4)
Other[4]	12,205 (24.8)	6,261 (25.3)	5,924 (24.2)	35,950 (12.6)
Missing/ unknown	1,553 (3.2)	684 (2.8)	867 (3.5)	11,420 (4.0)

[1]Spell was defined as the total continuous stay of a patient using a bed on premises controlled by the healthcare provider. [2]All spells were included in the estimate; *transfer hospital spells were excluded* in order to avoid double counting of the recorded primary diagnosis from the 'transfer' hospital records or inclusion of other secondary diagnoses or complications (e.g. hospital-acquired complications as the reason for transfer) in this analysis. [3]Causes of hospitalisation were categorised by ICD chapter headings. [4]Other included observations from other causes of hospital admissions categorised by all other ICD 10 Chapters Headings A to Z (excluding the top five commonest causes shown). Empty cell = Causes that were not in the top five most common causes and/or at risk of statistical disclosure, in which cases were added to 'Other'. *Note: Birth hospitalisations were excluded from the analysis.*

Table 8.4: Top five primary causes of all hospital admissions in infancy of infants with isolated congenital anomalies, births 1999 to 2015.

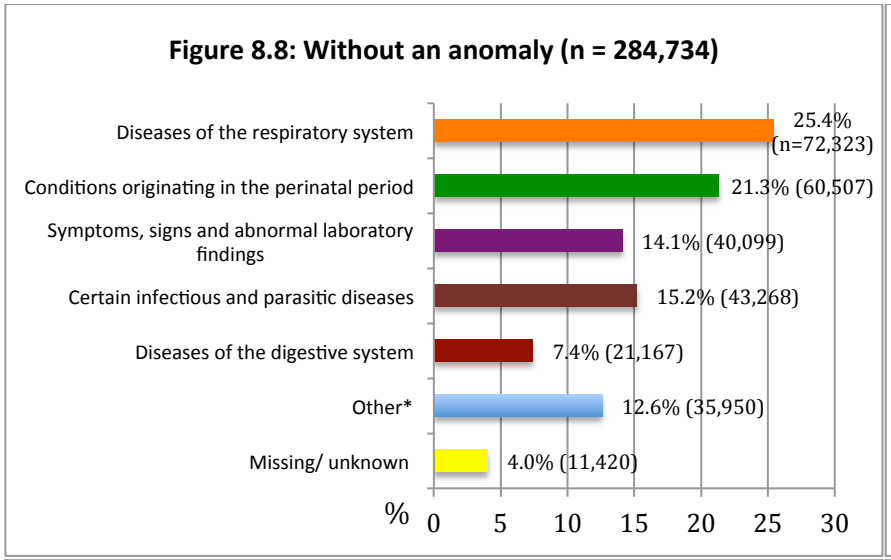
	Hospital admissions/ spells[1], frequency[2] (%) by isolated anomaly subtype						
Primary cause[3] of admission	**Nervous system anomalies (n = 837)**	**Eye, ear, face and neck anomalies (n = 1,695)**	**Cardiovascular anomalies (n = 4,051)**	**Respiratory anomalies and clefts (n = 2,121)**	**Upper and lower GI anomalies (n = 3,843)**	**Abdominal wall defects & congenital diaphragmatic hernias (n = 615)**	**Genitourinary anomalies (n = 3,198)**
Congenital malformations, deformations and chromosomal abnormalities	138 (16.5)	247 (14.6)	879 (21.7)	1,001 (47.2)	1,833 (47.7)	239 (38.9)	458 (14.3)
Diseases of the digestive system					402 (10.5)	88 (14.3)	
Diseases of the respiratory system	107 (12.8)	318 (18.8)	754 (18.6)	320 (15.1)	272 (7.1)	61 (9.9)	543 (17.0)
Certain conditions originating in the perinatal period	106 (12.7)	310 (18.3)	722 (17.8)	181 (8.5)	427 (11.1)	46 (7.5)	472 (14.8)
Diseases of the genitourinary system							354 (11.07)
Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	130 (15.5)	195 (11.5)	492 (12.2)	210 (9.9)	376 (9.8)	61 (9.9)	347 (10.9)
Diseases of the nervous system	104 (12.4)						
Certain infectious and parasitic diseases			344 (8.5)	107 (5.0)			
Diseases of the eye, adnexa, the ear and mastoid process		141 (8.3)					
Other[4]	228 (27.2)	425 (25.1)	723 (17.9)	253 (11.9)	444 (11.6)	99 (16.1)	925 (28.9)
Missing/ unknown	24 (2.9)	59 (3.5)	137 (3.4)	49 (2.3)	89 (2.3)	21 (3.4)	99 (3.1)

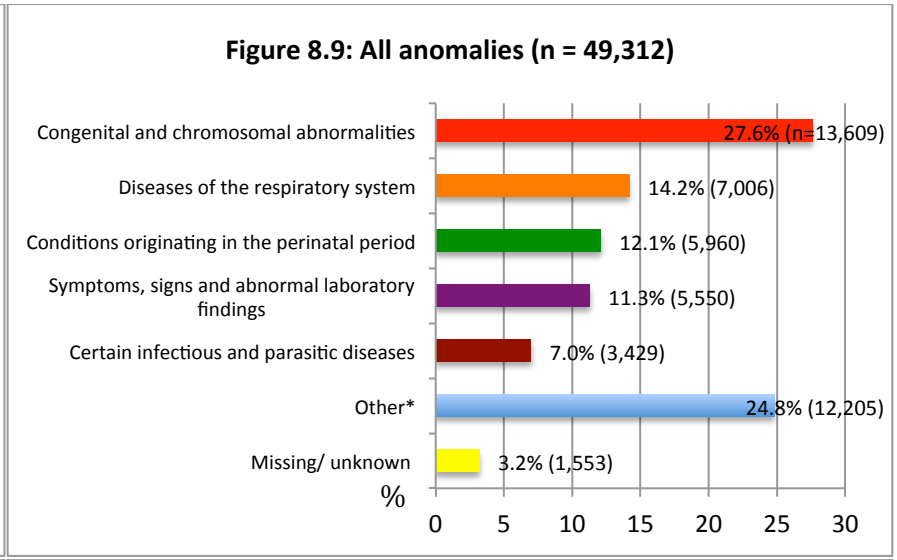
[1]Spell was defined as the total continuous stay of a patient using a bed on premises controlled by the healthcare provider. [2]All spells were included in the estimate; *transfer hospital spells were excluded* in order to avoid double counting of the recorded primary diagnosis from the 'transfer' hospital records or inclusion of other secondary diagnoses or complications (e.g. hospital-acquired complications as the reason for transfer) in this analysis. [3]Causes of hospitalisation were categorised by ICD chapters headings. [4]Other included observations from other causes of hospital admissions categorised by all other ICD 10 Chapters Headings A to Z (excluding the top five commonest causes shown). Empty cell = Causes that were not in the top five most common causes and/or at risk of statistical disclosure, in which cases were added to 'Other'. *Note: Birth hospitalisations were excluded from the analysis.*

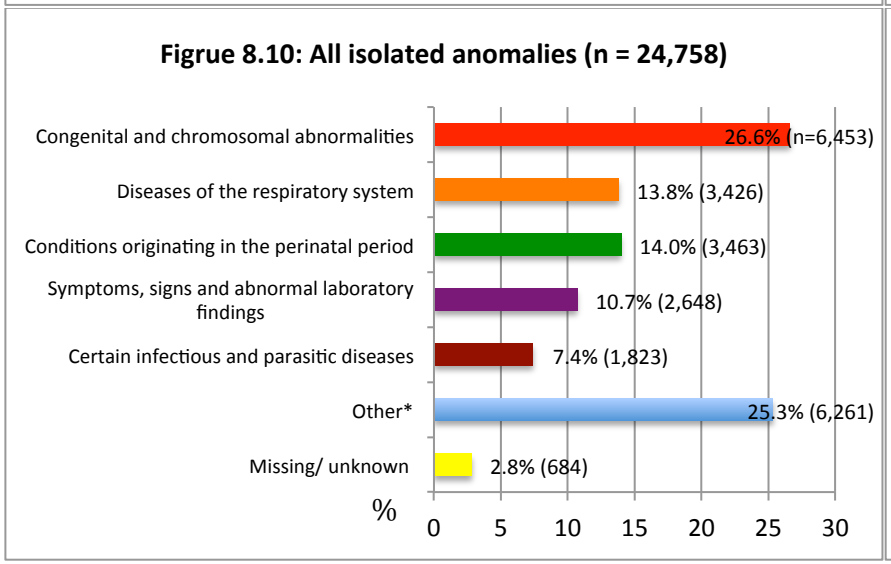
Table 8.4 (continued): Top five primary causes of all hospital admissions in infancy of infants with isolated congenital anomalies, births 1999 to 2015.

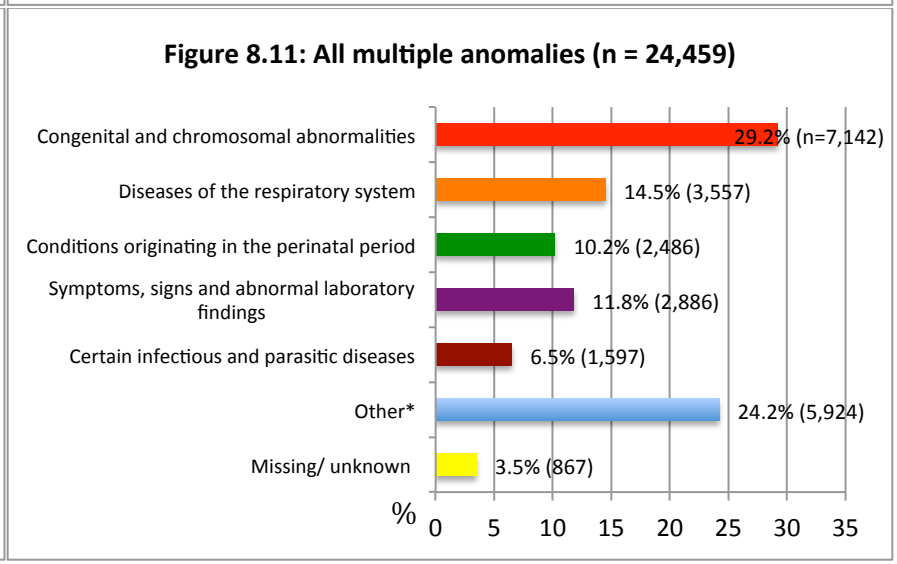
	Hospital admissions/ spells[1], frequency[2] (%) by isolated anomaly subtype						
Primary cause[3] of admission	**Limbs and skeletal anomalies (n = 3,059)**	**Skin (n = 396)**	**Blood disorders (n = 683)**	**Endocrine and metabolic (n = 1,467)**	**Neoplasm (n = 932)**	**Syndrome (n = 759)**	**Maternal infections leading to malformations (n = 1,037)**
Congenital malformations, deformations and chromosomal abnormalities	1,399 (45.73)	86 (21.72)					78 (7.52)
Diseases of the respiratory system	299 (9.77)	67 (16.92)	58 (8.49)	204 (13.91)	74 (7.94)	198 (26.09)	146 (14.08)
Certain conditions originating in the perinatal period	293 (9.58)	47 (11.87)	39 (5.71)	150 (10.22)	61 (6.55)	112 (14.76)	489 (47.16)
Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified		45 (11.36)	59 (8.64)	191 (13.02)	87 (9.33)	142 (18.71)	88 (8.49)
Certain infectious and parasitic diseases	214 (7.00)	38 (9.60)	28 (4.10)	135 (9.20)		74 (9.75)	64 (6.17)
Factors influencing health status and contact with health services	283 (9.25)				41 (4.40)		
Neoplasms and Diseases of the blood and blood-forming organs			405 (59.30)		500 (53.65)		
Endocrine, nutritional and metabolic diseases				500 (34.08)			
Diseases of the digestive system						48 (6.32)	
Other[4]	505 (16.51)	102 (25.76)	74 (10.83)	242 (16.50)	155 (16.63)	171 (22.53)	137 (13.21)
Missing	66 (2.16)	11 (2.78)	20 (2.93)	45 (3.07)	14 (1.50)	14 (1.84)	35 (3.38)

Figures 8.8-8.11: Primary cause of hospital admissions of infants with and without congenital anomalies in infancy, births 1999 to 2015.









Figures 8.12-8.25: Primary causes of hospital admissions of infants with isolated congenital anomalies in infancy, births 1999 to 2015.

Figure 8.12: Nervous system anomalies (n = 837)

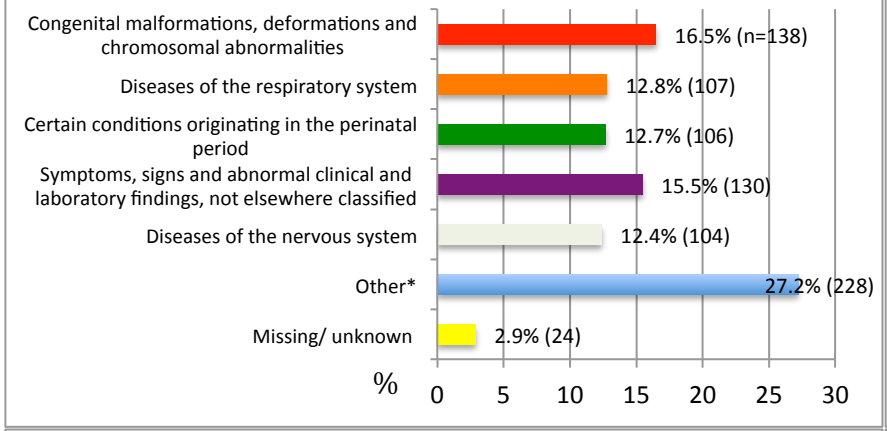


Figure 8.13: Eyes, ears, face and neck anomalies (n = 1,695)

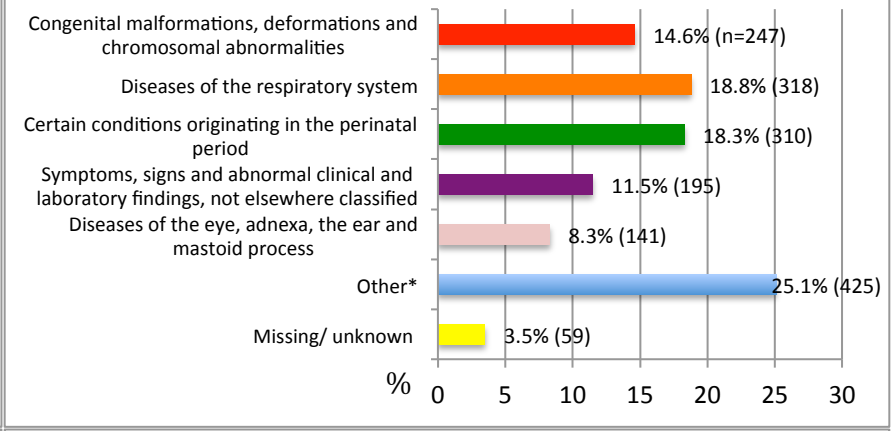


Figure 8.14: Cardiovascular anomalies (n = 4,051)

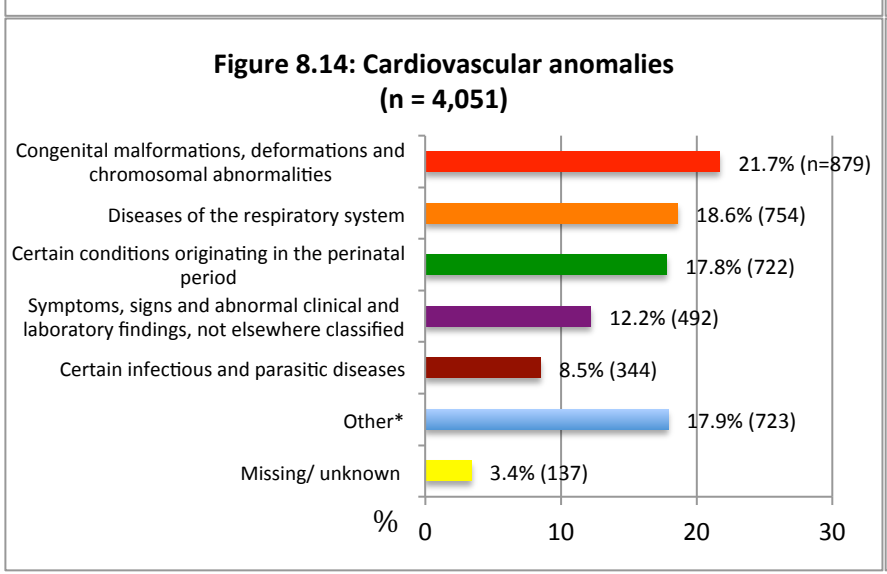


Figure 8.15: Respiratory and clefts (n = 2,121)

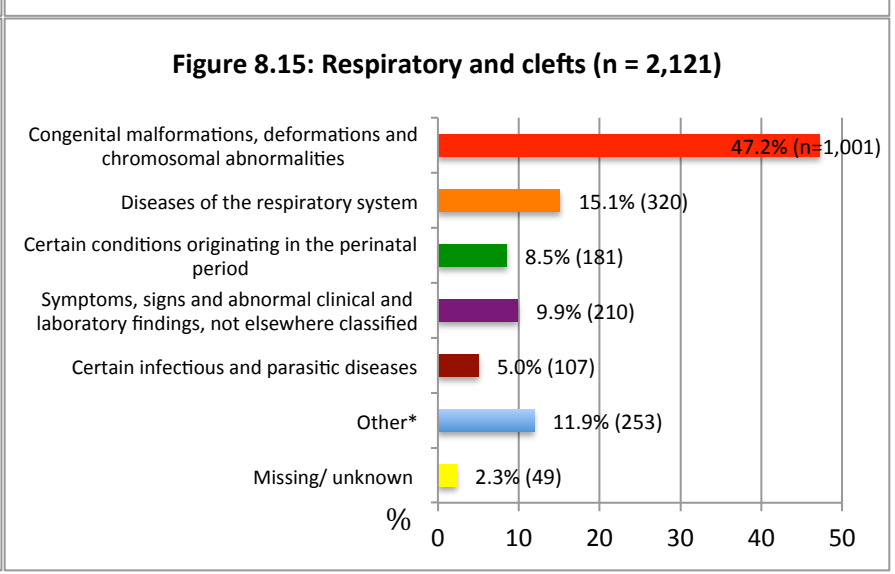


Figure 8.16: Upper and lower GI anomalies (n = 3,843)

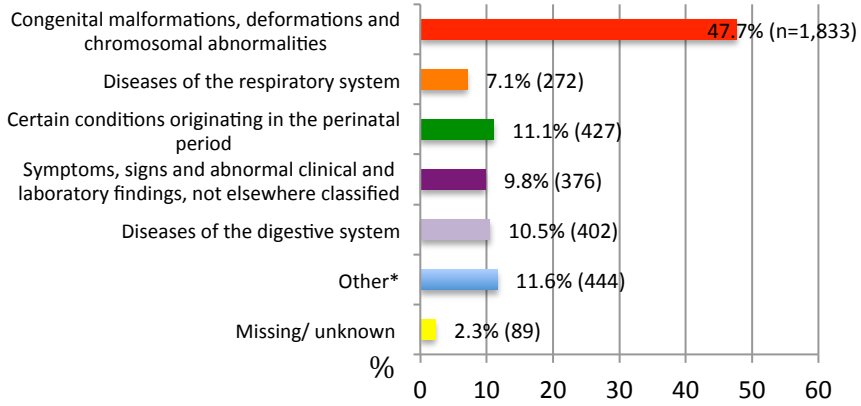


Figure 8.17: Abdominal wall defects and congenital diaphragmatic hernia (n = 615)

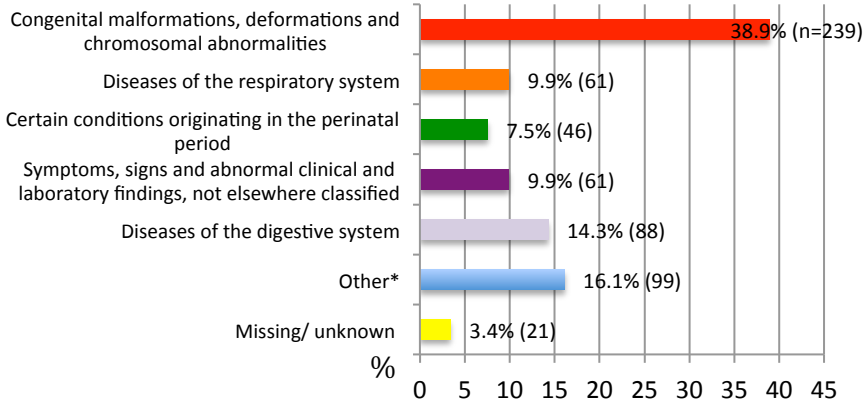


Figure 8.18: Genitourinary anomalies (n = 3,198)

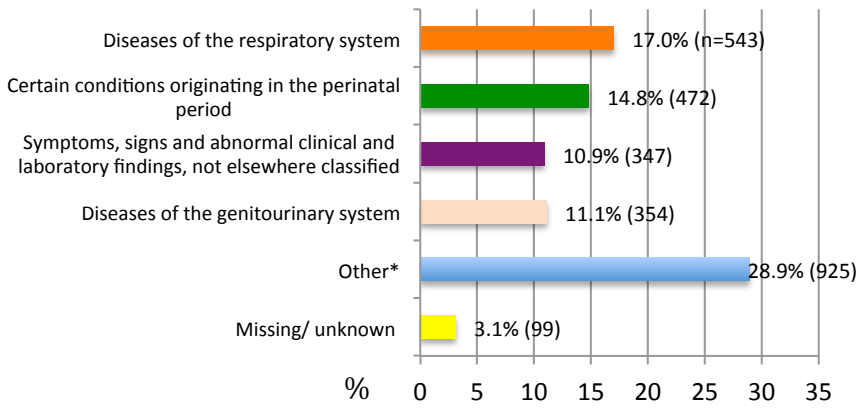


FIgure 8.19: Limbs and skeletal anomalies (n = 3,059)

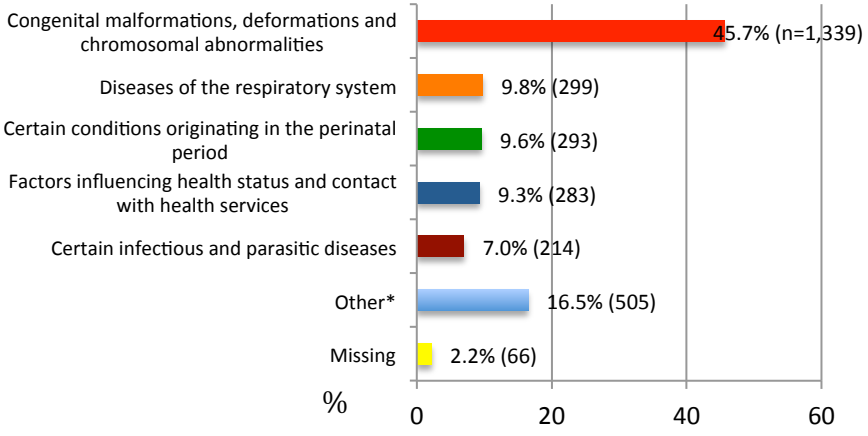


Figure 8.20: Skin (n = 396)

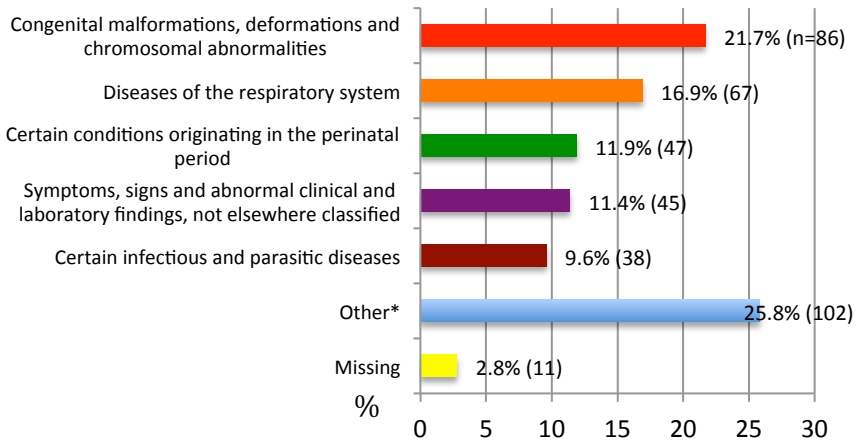


Figure 8.21: Blood disorders (n = 683)

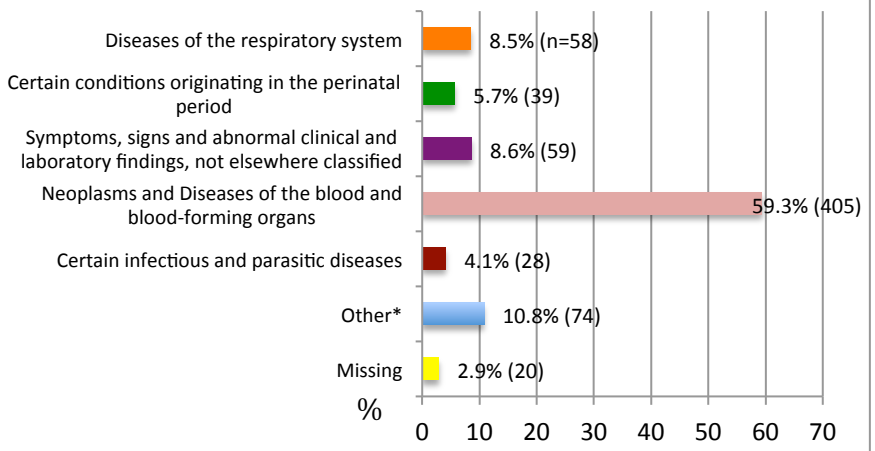


Figure 8.22: Endocrine and metabolic (n = 1,467)

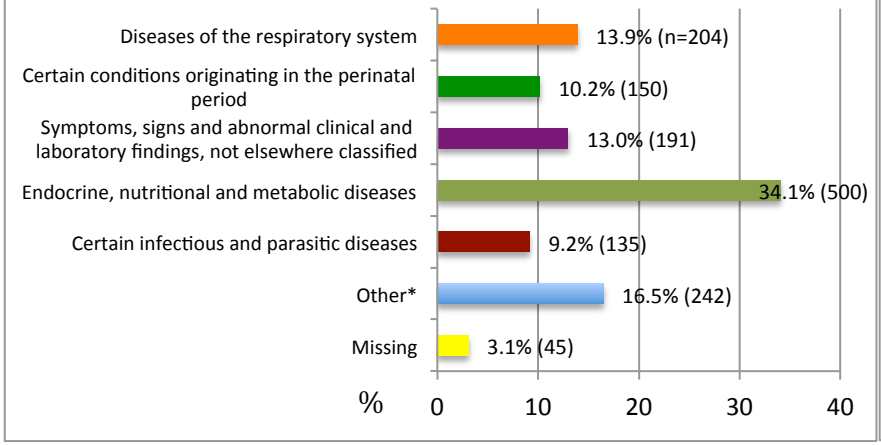


Figure 8.23: Neoplasm (n = 932)

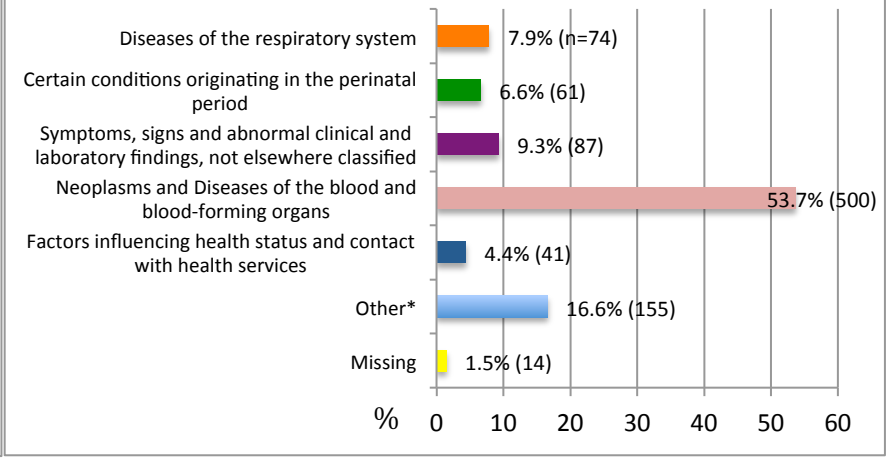


Figure 8.24: Syndrome (n = 759)

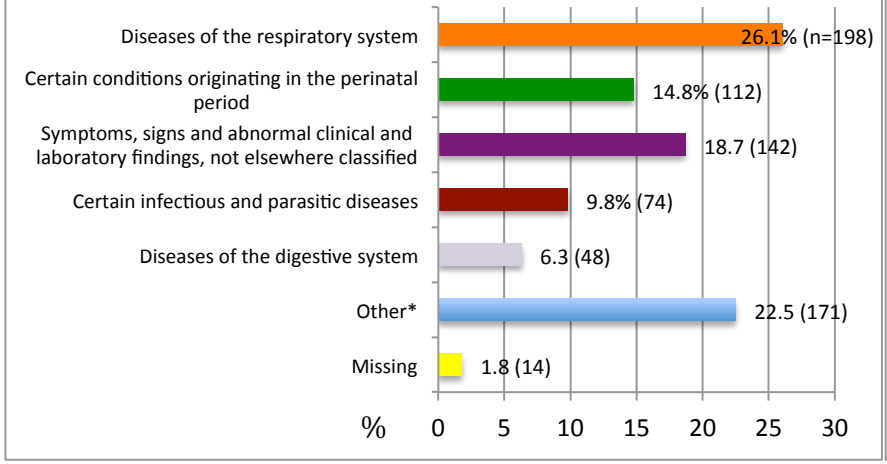
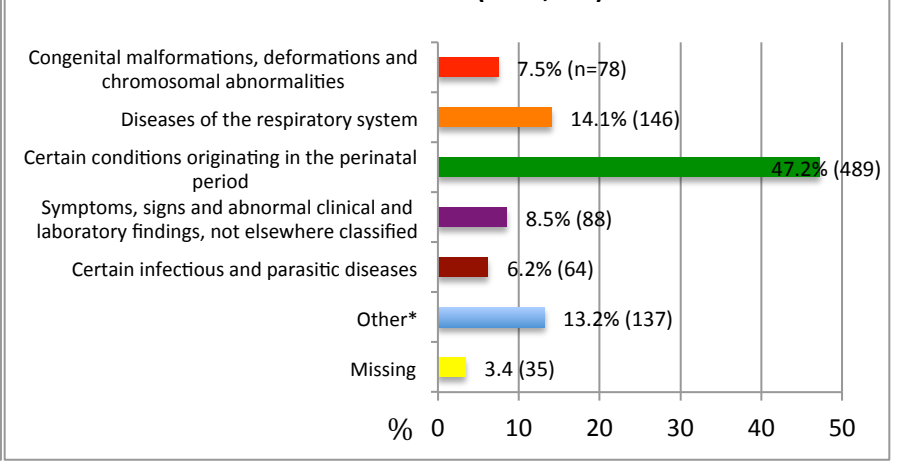


Figure 8.25: Maternal infections leading to malformations (n = 1,037)



Frequency of hospitalisation

The frequencies of hospitalisation for infants with and without anomalies were positively skewed (i.e. mean > median), with many infants having only one or two spells (i.e. spells), and a few infants having many more spells in infancy.

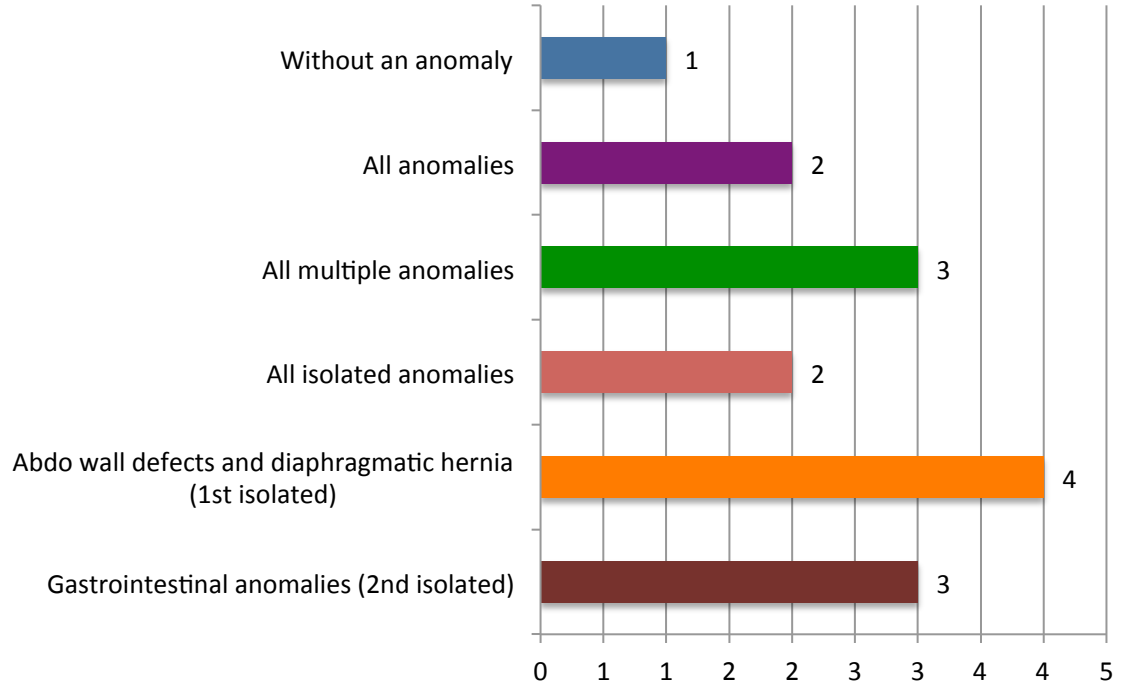
Infants with an anomaly had a higher median number of hospital spells (median = 2; interquartile range, IQR: 1-4) per infants admitted, compared to infants without an anomaly (median = 1, IQR: 1-2). Infants with multiple anomalies had a higher median number of spells (median = 3, IQR: 2-6), compared to infants with isolated anomalies (median = 2, IQR: 1-3) (Table 8.5 and Figure 8.26). Among infants with isolated anomalies, infants with abdominal walls defects and congenital diaphragmatic hernias had the largest median number of spells (median = 4, IQR: 2-5) per infant admitted; this was followed by gastrointestinal anomalies (median = 3, IQR: 2-4) (Table 8.5 and Figure 8.26). In addition, infants in the anomaly subgroups of gastrointestinal anomalies, respiratory anomalies and orofacial clefts, and abdominal wall defects and congenital diaphragmatic hernias had the highest proportions of the affected infants with at least one spell (88.0%, 87.0% and 86.5% respectively) (Table 8.5 and Figure 8.27).

Table 8.5: Distribution of all hospital spells by congenital anomaly subgroup, births 1999 to 2015.

	No. of infants[1]	No. admitted[1], n (%)	Total no. of spells[1,2], n (%)	Median (IQR[3]) of spells per infants admitted
Without an anomaly	559,616	195,783 (35.0)	305,042	1 (1-2)
All anomalies	25,523	17,284 (67.7)	52,396 (100)	2 (1-4)
Multiple anomalies	8,844	6,777 (76.6)	26,151 (49.9)	3 (2-6)
Isolated anomalies	16,623	10,479 (63.0)	26,144 (49.9)	2 (1-3)
Isolated anomalies subgroup				
Nervous system	504	294 (58.3)	907 (1.7)	2 (1-4)
Eye, ear, face and neck	1,466	727 (49.6)	1,751 (3.3)	2 (1-3)
Cardiovascular	2,606	1,685 (64.7)	4,366 (8.3)	2 (1-4)
Respiratory and clefts	916	797 (87.0)	2,208 (4.2)	2 (1-4)
Abdominal wall defects & congenital diaphragmatic hernias	318	275 (86.5)	758 (1.4)	4 (2-5)
Upper and lower GI	1,473	1,304 (88.0)	4,079 (7.8)	3 (2-4)
Genitourinary	3,560	1,742 (48.9)	3,332 (6.4)	1 (1-3)
Limbs and skeletal	2,503	1,628 (65.0)	3,148 (6.0)	2 (1-3)
Endocrine and metabolic	763	502 (65.8)	1,513 (2.9)	2 (1-4)
Syndrome	798	366 (45.9)	798 (1.5)	1.5 (1-3)
Maternal infections leading to malformations	681	544 (79.9)	1,153 (2.2)	2 (1-3)

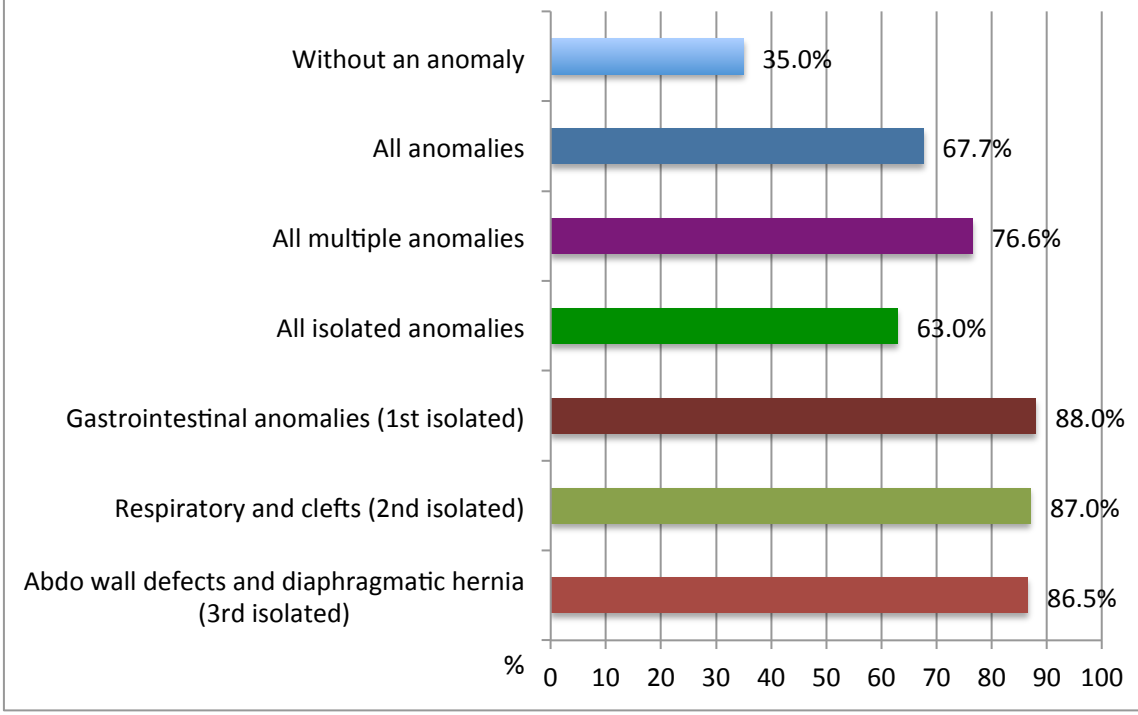
[1]Estimates included spells which could begin with any episodes. [2]All spells (i.e. across all admissions, *including transfers*) were included in the estimates. [3]IQR = Interquartile range. *Note: Birth hospitalisations were excluded from the analysis. Observations in the sub-categories may not add up to the total, as some of the categories are not shown due to small number or risk of statistical disclosure.*

Figure 8.26: Median number of spells per infant admitted.



Note: Only two isolated anomalies with the longest median LOS per infant admitted are shown due to risk of statistical disclosure.

Figure 8.27: Proportion of infants admitted.



Note: Only three isolated anomalies with the highest proportions of infants admitted are shown.

Hospital length of stay

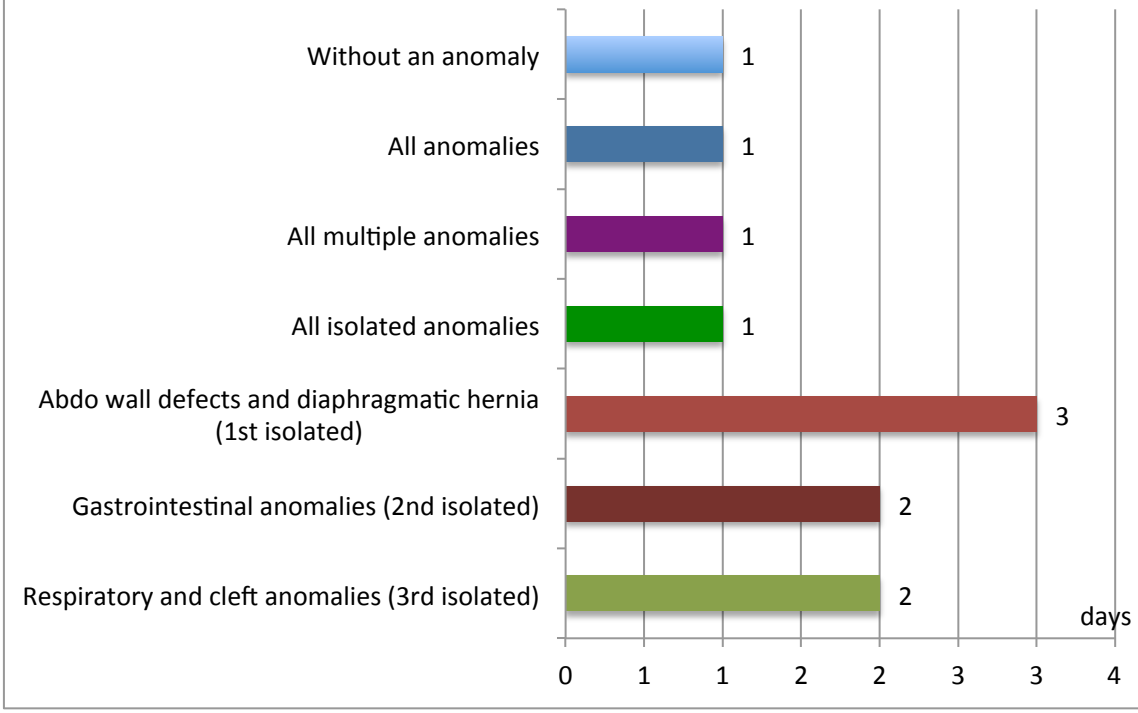
The hospital LOS for infants with and without anomalies were positively skewed (mean > median), with many infants staying for only one or a few days in hospital, and with a few infants staying in hospital for a prolonged period of time in infancy. Infants with an anomaly had a longer median total LOS per infant across all admissions in infancy (5 days, IQR: 1-14 days), compared to infants without an anomaly (1 day, IQR: 0.5-3 days) (Figures 8.29 and Table 8.6). Infants with multiple anomalies had a longer median total LOS (7.5 days, IQR: 2-24.5 days), compared to infants with an isolated anomaly (3.5 days, IQR: 1-9 days). Among infants with isolated anomalies, abdominal wall defects and congenital diaphragmatic hernias had the longest LOS per spell (3 days, IQR: 0.5-12 days) and the longest median total LOS per admitted infant (21.5 days, IQR: 7-33.5 days) in infancy. Infants with a gastrointestinal anomaly had the second longest LOS per spell (2 days, IQR: 1-4 days) and per admitted infant (6.5 days, IQR: 4.5-11 days). This was followed by cardiovascular (median total LOS = 5 days, IQR: 1-15 days), nervous system (median total LOS = 5 days, IQR: 1-14.25 days), and respiratory and clefts (median total LOS = 5 days, IQR: 2-8.5 days) anomalies (Figure 8.29 and Table 8.6).

Table 8.6: Length of hospital spells in infancy by congenital anomaly subgroup, births 1999 to 2015.

Anomaly subgroup	No. of infants admitted[1]	Total no. of spells[1,2]	Median[3] (IQR[3,4]) LOS[4] per spell (days)[e]	Median[3] (IQR[3,4]) total LOS[4] per admitted infant (days)[1,2]
Without an anomaly	195,783	305,042	1 (0.5-2)	1 (0.5-3)
All anomalies	16,829	50,705	1 (0.5-4)	5 (1.5-14)
Multiple anomalies	6,613	25,293	1 (0.5-5)	7.5 (2-24.5)
Isolated anomalies	10,188	25,314	1 (0.5-3)	3.5 (1-9)
Isolated anomalies subgroup				
Nervous system	284	865	1 (0.5-5)	5 (1-14.25)
Eye, ear, face and neck	721	1,724	1 (0.5-3)	2.5 (1-8)
Cardiovascular	1,609	4,162	1 (0.5-5)	5 (1-15)
Respiratory and clefts	790	2,150	2 (0.5-3)	5 (2-8.5)
Abdominal wall defects & congenital diaphragmatic hernias	253	671	3 (0.5-12)	21.5 (7-33.5)
Upper and lower GI	1,290	4,013	2 (1-4)	6.5 (4.5-11)
Genitourinary	1,686	3,217	1 (0.5-2)	1.5 (1-4)
Limbs and skeletal	1,593	3,078	1 (0.5-2)	1.5 (0.5-5)
Endocrine and metabolic	497	1,489	1 (0.5-4)	3.5 (1-13.5)
Syndrome	358	769	1 (0.5-2)	2 (1-5.5)
Maternal infections leading to malformations	499	1,074	2 (0.5-5)	4 (2-10)

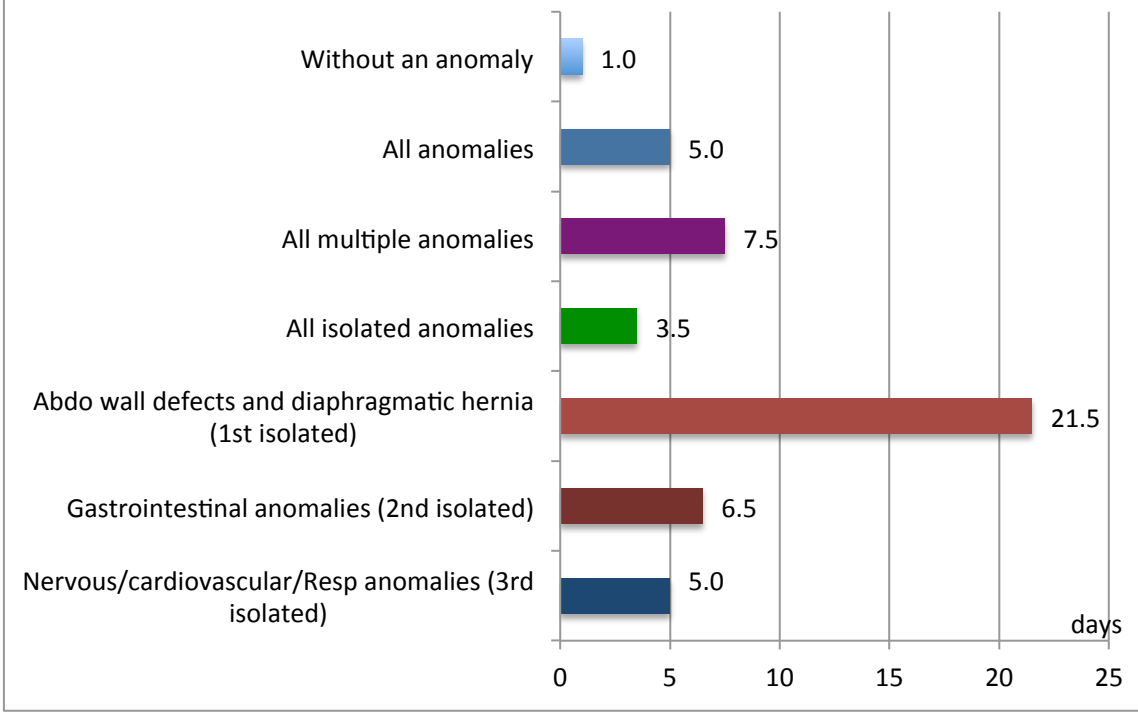
[1]Estimates excluded any spells in which the first episodes were missing, e.g. due to coding errors. [2]All spells (i.e. across all admissions, *including transfers*) were included in the estimates. Total LOS was the sum of all spells across all admissions (in days). [3]Median and IQR were estimated based on all spell duration, "0" day was converted to 0.5 days to include some extent of stay. [4]IQR = interquartile range; LOS = Length of stay (including transfers). *Note: Birth hospitalisations were excluded from the analysis. Observations in the sub-categories may not add up to the total, as some of the categories are not shown due to small number or risk of statistical disclosure.*

Figure 8.28: Median length of stay (days) per spell.



Note: Only three isolated anomalies with the longest median LOS per spell are shown.

Figure 8.29: Median total length of stay (days) across all admissions.



Note: Only three isolated anomalies with the highest median total per admitted infant across all admissions are shown.

8.4.4 Risk factors for increasing numbers of hospital admissions among infants with an anomaly (study objective 8c)

Table 8.7 shows the characteristics of infants with any anomaly, stratified by whether the infant had 0, 1 and 2+ admissions in total. Overall, there were more infants who had repeated (2+) admissions (42.3%) than those who had single (1) admissions (23.7%) or no (0) admission (34.1%) in infancy. In general, those with 2+ admissions tended to have a slightly higher risk profile than those with 0 admissions. For example, infants with 2+ admissions were more likely to live in the most deprived quintile (30.6%) than infants with 1 (28.6%) or 0 (26.7%) admissions. Maternal ethnicity did not vary substantially according to number of admission, with the proportion non-White ranging between 5.0% and 6.2%. Maternal age was slightly younger in those with 2+ admissions (27.8 years) than those with 0 admission (28.6 years). Infants with 2+ admissions were more likely to be born preterm (21.3%) than infants with 1 (14.0%) or 0 admissions (9.1%).

Table 8.7: Factors associated with 0, 1 and 2+ admissions among infants with any anomaly.

Characteristics	Number of admissions		
	2+ **No. of infants (%)[1]**	**1** **No. of infants (%)[1]**	**0** **No. of infants (%)[1]**
Socio-demographic factors			
Townsend quintile	*n = 10,785*	*n = 6,043*	*n = 8,695*
1 (least deprived)	1,542 (14.3)	991 (16.4)	1,272 (16.3)
2	1,645 (15.3)	956 (15.8)	1,316 (16.9)
3	1,928 (17.9)	1,102 (18.3)	1,571 (20.1)
4	2,351 (21.8)	1,257 (20.8)	1,558 (20.0)
5 (most deprived)	3,296 (30.6)	1,727 (28.6)	2,080 (26.7)
Not known/ missing	23	10	898
Maternal ethnicity	*n = 10,785*	*n = 6,043*	*n = 8,695*
White	6,729 (94.5)	3,547 (93.8)	4,252 (95.0)
Other	394 (5.5)	236 (6.2)	224 (5.0)
Not known/ missing	3,662	2,260	4,219
Maternal age at birth[2], years	*n = 10,781*	*n = 6,041*	*n = 8,695*
Mean (SD) (year)	*27.8 (6.3)*	*28.3 (6.2)*	*28.6 (6.2)*
Median (IQR)	*28 (23-32)*	*28 (24-33)*	*29 (24-33)*
≤ 24	3,596 (33.3)	1,768 (29.3)	2,204 (28.2)
25 – 29	2,880 (26.7)	1,697 (28.1)	2,096 (26.8)
30 – 34	2,585 (24.0)	1,526 (25.3)	2,046 (26.2)
≥ 35	1,720 (16.0)	1,050 (17.4)	1,468 (18.9)
Maternal factors			
Parity	*n = 10,785*	*n = 6,043*	*n = 8,695*
Nulliparous	4,572 (45.2)	2,454 (43.6)	3,029 (43.3)
≥ 1	5,535 (54.8)	3,173 (56.4)	3,973 (56.7)
Not known/ missing	678	416	1,693
Multiple fetus[2]	*n = 10,782*	*n = 6,041*	*n = 8,695*
Yes	417 (3.9)	175 (2.9)	185 (2.4)
No	10,365 (96.1)	5,866 (97.1)	7,640 (97.6)
Maternal smoking	*n = 10,785*	*n = 6,043*	*n = 8,695*
Smoker	2,200 (30.7)	1,036 (27.1)	1,136 (25.5)
Non/ Ex smoker	4,958 (69.3)	2,783 (72.9)	3,315 (74.5)
Not known / missing	3,627	2,224	4,244
Anomalies in previous pregnancies	*n = 10,785*	*n = 6,043*	*n = 8,695*
Yes	928 (12.0)	506 (12.2)	582 (12.0)
No	6,811 (88.0)	3,637 (87.8)	4,280 (88.0)
Not known / missing	3,046	1,900	3,833

Table 8.7 (continued): Factors associated with 0, 1 and 2+ admissions among infants with any anomaly.

Characteristics	2+ No. of infants (%)[1]	1 No. of infants (%)[1]	0 No. of infants (%)[1]
Infant factors			
Infant sex[2]	*n = 10,782*	*n = 6,040*	*n = 8,691*
Male	6,595 (61.2)	3,599 (59.6)	5,205 (59.9)
Female	4,187 (38.8)	2,441 (40.4)	3,486 (40.1)
Birthweight, grams	*n = 10,785*	*n = 6,043*	*n = 8,695*
Mean (SD)	*3,024 (810)*	*3,207 (697)*	*3,286 (660)*
Median (IQR)	*3,140 (2,610-3,570)*	*3,280 (2,860-3,660)*	*3,350 (2,950-3,710)*
< 2500 (low birthweight)	2,311 (21.5)	815 (13.5)	806 (10.1)
≥ 2500	8,441 (78.5)	5,209 (86.4)	7,166 (89.9)
Not known/ missing	32	19	723
Gestational age, week	*n = 10,785*	*n = 6,043*	*n = 8,695*
Mean (SD)	*37.9 (3.3)*	*38.6 (2.6)*	*39.0 (2.3)*
Median (IQR)	*39 (37-40)*	*39 (38-40)*	*39 (38-40)*
< 37^{+0} (preterm)	2,287 (21.3)	844 (14.0)	727 (9.1)
≥ 37^{+0} (term)	8,465 (78.7)	5,178 (86.0)	7,249 (90.9)
Not known/ missing	33	21	719

[1]Infants with birthweight <500g or gestational age at birth <22 completed weeks were excluded from the analysis. [2]Categories with observations n < 5 are not shown due to risk of statistical disclosure. Note: All spells (i.e. across all admissions, *including transfers*) were included in the estimates. Birth hospitalisations were excluded from the analysis.

Univariable analysis

Table 8.8 summarises which variables were significantly associated with number of admissions in univariable analyses by anomaly subgroups: all anomalies, isolated, multiple, cardiovascular and genitourinary anomalies.

Factors which were significantly associated with repeated (2+) admissions of infants compared with no admissions were area deprivation, maternal age, parity (except for cardiovascular anomalies), multiple fetus (except for multiple anomalies), active smoking during pregnancy (except for genitourinary anomalies), history of anomaly in previous pregnancy (for multiple anomalies only), infant sex (except for isolated anomalies), gestational age at birth, and disease severity (for cardiovascular anomalies only).

Factors which were significantly associated with single admissions of infants compared with no admission were maternal ethnicity (except for multiple and cardiovascular anomalies), maternal age, parity (except for cardiovascular and genitourinary anomalies), multiple fetus (except for multiple, cardiovascular and genitourinary anomalies), infant sex (multiple and genitourinary anomalies only), gestational age at birth, and disease severity (for cardiovascular anomalies only).

Table 8.8: Univariable analyses: factors associated with repeated (2+) and single (1) admissions by anomaly subgroup.

	2+ admissions			1 admission		
	Unadjusted RRR			Unadjusted RRR		
Factors	All[2]	Isolated[3]	Multiple[4]	All[2]	Isolated[3]	Multiple[4]
Townsend quintile						
1	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
2	1.03 (0.93-1.14)	1.04 (0.92-1.18)	1.06 (0.88-1.28)	0.93 (0.83-1.05)	0.88 (0.77-1.01)	1.09 (0.87-1.37)
3	1.01 (0.92-1.12)	1.06 (0.93-1.20)	0.93 (0.78-1.10)	0.90 (0.81-1.01)	0.88 (0.77-1.01)	0.92 (0.74-1.14)
4	1.24 (1.13-1.37)	1.23 (1.08-1.39)	1.24 (1.04-1.47)	1.04 (0.93-1.16)	1.02 (0.89-1.16)	1.08 (0.87-1.34)
5	1.31 (1.19-1.43)	1.32 (1.18-1.48)	1.28 (1.08-1.51)	1.07 (0.96-1.18)	1.02 (0.90-1.15)	1.17 (0.96-1.44)
Maternal ethnicity						
White	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Other	1.11 (0.94-1.32)	1.10 (0.88-1.38)	1.06 (0.82-1.39)	1.26 (1.05-1.52)	1.34 (1.06-1.69)	1.13 (0.82-1.56)
Maternal age at delivery, years						
≤ 24	1.19 (1.10-1.28)	1.16 (1.05-1.27)	1.23 (1.07-1.41)	0.99 (0.91-1.09)	0.97 (0.87-1.07)	1.05 (0.88-1.25)
25 – 29	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
30 – 34	0.92 (0.85-1.00)	0.89 (0.81-0.98)	0.94 (0.81-1.09)	0.92 (0.84-1.01)	0.93 (0.83-1.04)	0.90 (0.75-1.07)
≥ 35	0.53 (0.49-0.58)	0.50 (0.45-0.56)	0.55 (0.48-0.64)	0.55 (0.50-0.61)	0.54 (0.48-0.61)	0.58 (0.48-0.69)
Parity						
Nulliparous	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
≥ 1	0.73 (0.69-0.77)	0.73 (0.68-0.79)	0.76 (0.68-0.84)	0.78 (0.73-0.84)	0.78 (0.72-0.85)	0.80 (0.71-0.91)
Multiple fetus						
Yes	1.66 (1.39-1.98)	1.92 (1.53-2.39)	1.20 (0.89-1.60)	1.23 (1.00-1.52)	1.43 (1.11-1.84)	0.87 (0.60-1.27)
No	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Maternal smoking						
Smoker	1.30 (1.19-1.41)	1.32 (1.19-1.48)	1.24 (1.09-1.43)	1.09 (0.99-1.20)	1.06 (0.94-1.20)	1.14 (0.96-1.34)
Non/Ex smoker	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Anomalies in previous pregnancies						
Yes	1.00 (0.89-1.11)	1.04 (0.91-1.20)	0.81 (0.67-0.99)	0.98 (0.86-1.11)	1.00 (0.86-1.16)	0.90 (0.70-1.14)
No	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)

Table 8.8 (continued): Univariable analyses: factors associated with repeated (2+) and single (1) admissions by anomaly subgroup.

	2+ admissions			1 admission		
	Unadjusted RRR			Unadjusted RRR		
Factors	All[2]	Isolated[3]	Multiple[4]	All[2]	Isolated[3]	Multiple[4]
Infant sex[1]						
Male	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Female	0.95 (0.90-1.00)	0.94 (0.87-1.01)	0.88 (0.79-0.97)	1.01 (0.95-1.08)	1.07 (0.99-1.16)	0.86 (0.76-0.97)
Gestational age[1], week						
$< 37^{+0}$	2.95 (2.70-3.23)	3.25 (2.89-3.64)	2.15 (1.87-2.49)	1.79 (1.61-1.98)	1.91 (1.67-2.18)	1.48 (1.24-1.77)
$\geq 37^{+0}$	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)

[1]*a priori* variable. Note: P-value < 0.1 was considered as statistically significant for univariable analysis. [2]For all anomalies, Townsend quintile, maternal ethnicity, maternal age at delivery, parity, multiple fetus, maternal smoking, infant sex and gestational age were included for test in multivariable analysis. [3]For isolated anomalies, Townsend quintile, maternal ethnicity, maternal age at delivery, parity, multiple fetus, maternal smoking, infant sex and gestational age were included for test in multivariable analysis. [4]For multiple anomalies, Townsend quintile, maternal age at delivery, parity, maternal smoking, infant sex and gestational age were included for test in multivariable analysis.

Table 8.8 (continued): Univariable analyses: factors associated with repeated (2+) and single (1) admissions by anomaly subgroup.

	2+ admissions		1 admission	
	Unadjusted RRR		Unadjusted RRR	
Factors	Cardiovascular[2]	Genitourinary[3]	Cardiovascular[2]	Genitourinary[3]
Townsend quintile				
1	1 (reference)	1 (reference)	1 (reference)	1 (reference)
2	1.11 (0.80-1.53)	0.74 (0.56-0.99)	0.80 (0.56-1.12)	0.97 (0.73-1.28)
3	1.35 (0.99-1.85)	0.65 (0.49-0.87)	0.94 (0.68-1.31)	0.95 (0.72-1.24)
4	1.10 (0.81-1.50)	0.87 (0.66-1.15)	1.05 (0.77-1.43)	1.17 (0.89-1.53)
5	1.40 (1.05-1.85)	1.16 (0.90-1.49)	0.97 (0.72-1.30)	1.17 (0.91-1.52)
Maternal ethnicity				
White	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Other	0.82 (0.49-1.38)	1.42 (0.83-2.43)	0.91 (0.53-1.57)	1.91 (1.16-3.17)
Maternal age at delivery, years				
≤ 24	1.20 (0.95-1.53)	1.05 (0.84-1.30)	0.94 (0.72-1.23)	0.86 (0.69-1.06)
25 – 29	1 (reference)	1 (reference)	1 (reference)	1 (reference)
30 – 34	1.02 (0.80-1.31)	0.75 (0.60-0.95)	1.08 (0.83-1.41)	0.81 (0.65-1.01)
≥ 35	0.57 (0.43-0.75)	0.58 (0.45-0.75)	0.67 (0.51-0.90)	0.60 (0.47-0.77)
Parity				
Nulliparous	1 (reference)	1 (reference)	1 (reference)	1 (reference)
≥ 1	0.92 (0.76-1.11)	0.74 (0.62-0.88)	0.86 (0.70-1.05)	0.86 (0.73-1.01)
Multiple fetus				
Yes	1.86 (1.15-3.00)	1.65 (1.00-2.73)	1.55 (0.91-2.62)	0.86 (0.47-1.54)
No	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Maternal smoking				
Smoker	1.39 (1.07-1.79)	1.16 (0.89-1.51)	1.07 (0.81-1.42)	1.11 (0.85-1.46)
Non/Ex smoker	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Anomalies in previous pregnancies				
Yes	1.32 (0.94-1.86)	0.86 (0.62-1.21)	1.20 (0.84-1.71)	1.08 (0.76-1.53)
No	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Infant sex[1]				
Male	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Female	0.66 (0.55-0.79)	1.81 (1.43-2.30)	0.95 (0.78-1.15)	1.70 (1.35-2.14)

Table 8.8: Univariable analyses: factors associated with repeated (2+) and single (1) admissions by anomaly subgroup.

	2+ admissions		1 admission	
	Unadjusted RRR		Unadjusted RRR	
Factors	Cardiovascular[2]	Genitourinary[3]	Cardiovascular[2]	Genitourinary[3]
Gestational age[1], week				
$< 37^{+0}$	3.33 (2.55-4.35)	4.36 (3.31-5.73)	1.97 (1.46-2.65)	2.12 (1.57-2.87)
$\geq 37^{+0}$	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Disease Severity[1]				
Less severity	1 (reference)		1 (reference)	
Moderate severity	5.83 (4.19-8.11)	N/A	1.14 (0.75-1.75)	N/A
Most severe	2.67 (1.57-4.57)		0.38 (0.15-0.94)	
Other circulatory/PDA	1.39 (1.12-1.73)		0.91 (0.72-1.15)	

[1]*a priori* variable. Note: P-value < 0.1 was considered as statistically significant for univariable analysis. [2]For cardiovascular anomalies, Townsend quintile, maternal age at delivery, multiple fetus, maternal smoking, infant sex, gestational age and disease severity were included for test in multivariable analysis. [3]For genitourinary anomalies, Townsend quintile, maternal ethnicity, maternal age at delivery, parity, multiple fetus, infant sex and gestational age were included for test in multivariable analysis. N/A = not applicable.

Multivariable analysis

Table 8.9 shows which variables were significantly associated with number of admissions in multivariable multinomial regression analyses by anomaly subgroups: all anomalies, isolated, multiple, cardiovascular and genitourinary anomalies, after being adjusted in the final model. These summary results highlight that gestational age at birth was consistently shown to be a significant risk factor for single and repeated admissions of infants across all anomalies subgroups. In addition, infant sex was a significant factor for repeated admissions of infants across all anomalies subgroups investigated.

Table 8.9: Summary results of multivariable multinomial regression analyses on repeated (2+) and single (1) admissions by anomaly subgroup.

	2+					1				
Factors	All	Isolated	Multiple	CVS[1]	GU[2]	All	Isolated	Multiple	CVS[1]	GU[2]
Social deprivation					✔					
Maternal ethnicity										✔
Maternal age	✔		✔					✔		
Parity										
Multiple fetus										
Maternal smoking	✔	✔								
Anomaly in previous pregnancy										
Infant sex*	✔	✔	✔	✔	✔			✔		✔
Gestational age*	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Disease Severity*	n/a	n/a	n/a	✔	n/a	n/a	n/a	n/a	✔	n/a

✔ Statistical significance at $p < 0.05$ in multivariable analysis. [1]CVS = Cardiovascular anomalies; [2]GU = Genitourinary anomalies. **a priori* variable. n/a = not applicable.

Tables 8.10-8.14 show the detailed results of these multivariable multinomial regression analyses, and these are described as follows.

All (isolated and multiple) anomalies

Having adjusted for the factors in the final model (Table 8.10), the risk of repeated admissions decreased as maternal age increased. Infants with an anomaly born to mothers aged ≤ 24 years had a 17% increase in the risk of repeated admissions, compared to infants with an anomaly born to mothers aged 25-29 years (adjusted relative risk ratio aRRR = 1.17, 95% CI: 1.06-1.30). Infants with an anomaly born to mothers who were active smokers during pregnancy had a 20% increase in the risk of repeated admissions, compared to infants with an anomaly born to mothers who were ex- or non-smokers (aRRR = 1.20, 95% CI: 1.10-1.31). Preterm infants with an anomaly had a 67% increase in the risk of a single admission (aRRR = 1.67, 95% CI: 1.46-1.91) and a two-and-half fold increased risk of repeated admissions (aRRR = 2.52, 95% CI: 2.25-2.82), compared to term infants with an anomaly. Girls with an anomaly had a 16% decreased risk of repeated admissions, compared to boys with an anomaly (aRRR = 0.84, 95% CI: 0.78-0.91).

Table 8.10: Factors associated with 0, 1 and 2+ admissions among infants with any anomaly: Adjusted multinomial regression analysis[1,2]; births 1999-2015.

	Number of admissions vs. No admission *(n = 10,785)*	
	2+	**1**
	n = 10,785	***n = 6,043***
Risk factors	**Adjusted RRR[4]**	**Adjusted RRR[4]**
Socio-demographic factor		
Maternal age at birth[3], years		
≤ 24	1.17 (1.06-1.30)	1.00 (0.89-1.12)
25 – 29	1 (reference)	1 (reference)
30 – 34	0.99 (0.89-1.10)	0.94 (0.83-1.06)
≥ 35	0.93 (0.82-1.04)	0.95 (0.83-1.09)
Maternal factor		
Maternal smoking[3]		
Smoker	1.20 (1.10-1.31)	1.06 (0.96-1.17)
Non/ Ex smoker	1 (reference)	1 (reference)
Infant factors		
Infant sex[3,*]		
Male	1 (reference)	1 (reference)
Female	0.84 (0.78-0.91)	0.95 (0.87-1.04)
Gestational age[3,*], week		
$< 37^{+0}$ (preterm)	2.52 (2.25-2.82)	1.67 (1.46-1.91)
$\geq 37^{+0}$ (term)	1 (reference)	1 (reference)

[1]Infants with birthweight <500g or gestational age at birth $<22^{+0}$ completed weeks were excluded from the analysis. [2]Based on complete case analysis. [3]Variable had ≥ 1 category with $p < 0.05$ in the multivariable analysis and was hence included in the final model. [4]Mutually adjusted odds ratios for other factors in the table. **a priori* variable.

All isolated anomalies

After adjustment for the factors in the final model (Table 8.11), infants with an isolated anomaly born to mothers who were active smokers during pregnancy had a 27% increase in the risk of repeated admissions, compared to infants with an isolated anomaly born to mothers who were ex- or non-smokers (aRRR = 1.27, 95% CI: 1.13-1.41). Preterm infants with an isolated anomaly had nearly a three-fold increased risk of repeated admissions (aRRR = 2.83, 95% CI 2.42-3.31) and an almost two-fold increased risk of a single admission (aRRR = 1.85, 95% CI: 1.55-2.20), compared to term infants with an isolated anomaly. Girls with an isolated anomaly had an 18% decreased risk of repeated admissions, compared to boys with an isolated anomaly (aRRR = 0.82, 95% CI: 0.74-0.90).

Table 8.11: Factors associated with 0, 1 and 2+ admissions among infants with isolated anomalies: Adjusted multinomial regression analysis[1,2]; births 1999-2015.

	Number of admissions vs. No admission *(n = 6,436)*	
	2+	**1**
	n = 5,976	***n = 4,211***
Risk factors	**Adjusted RRR[4]**	**Adjusted RRR[4]**
Maternal factor		
Maternal smoking[3]		
Smoker	1.27 (1.13-1.41)	1.04 (0.92-1.17)
Non/ Ex smoker	1 (reference)	1 (reference)
Infant factors		
Infant sex[3,*]		
Male	1 (reference)	1 (reference)
Female	0.82 (0.74-0.90)	1.01 (0.91-1.13)
Gestational age[3,*], week		
< 37^{+0} (preterm)	2.83 (2.42-3.31)	1.85 (1.55-2.20)
≥ 37^{+0} (term)	1 (reference)	1 (reference)

[1]Infants with birthweight <500g or gestational age at birth <22^{+0} completed weeks were excluded from the analysis. [2]Based on complete case analysis. [3]Variable had ≥ 1 category with $p < 0.05$ in the multivariable analysis and was hence included in the final model. [4]Mutually adjusted odds ratios for other factors in the table. **a priori* variable.

All multiple anomalies

After adjustment for the factors in the final model (Table 8.12), the risk of repeated admissions in infants with multiple anomalies declined as maternal age increased. Infants with multiple anomalies born to mothers aged ≤24 years had a 22% increased risk of repeated admissions, compared to infants with multiple anomalies born to mothers aged 25-29 years (aRRR = 1.22, 95% CI: 1.06-1.41); while infants with multiple anomalies born to mothers aged ≥35 years had a 46% decreased risk of repeated admissions (aRRR = 0.54, 95% CI: 0.47-0.63). Furthermore, infants with multiple anomalies born to mothers aged ≥35 years had a 42% decreased risk of a single admission, compared to infants with multiple anomalies born to mothers aged 25-29 years (aRRR = 0.58, 95% CI: 0.48-0.69).

Preterm infants with multiple anomalies had a two-fold increased risk of repeated admissions (aRRR = 2.19, 95% CI: 1.90-2.53) and a 1.5 fold increased risk of a single admission (aRRR = 1.50, 95% CI: 1.26-1.79), compared to term infants with multiple anomalies. Girls with multiple anomalies had a 13% and 10% decreased risk of single (aRRR = 0.87, 95% CI: 0.77-0.99) and repeated (aRRR = 0.90, 95% CI: 0.81-1.00) admissions respectively, compared to boys with multiple anomalies.

Table 8.12: Factors associated with 0, 1 and 2+ admissions among infants with multiple anomalies: Adjusted multinomial regression analysis[1,2]; births 1999-2015.

	Number of admissions vs. No admission *(n = 2,231)*	
	2+	**1**
	n = 4,791	***n = 1,822***
Risk factors	**Adjusted RRR[4]**	**Adjusted RRR[4]**
Maternal factors		
Maternal age at birth[3], years		
≤ 24	1.22 (1.06-1.41)	1.04 (0.88-1.24)
25 – 29	1 (reference)	1 (reference)
30 – 34	0.94 (0.81-1.09)	0.90 (0.75-1.07)
≥ 35	0.54 (0.47-0.63)	0.58 (0.48-0.69)
Infant factors		
Infant sex[3,*]		
Male	1 (reference)	1 (reference)
Female	0.90 (0.81-1.00)	0.87 (0.77-0.99)
Gestational age[3,*], week		
$< 37^{+0}$ (preterm)	2.19 (1.90-2.53)	1.50 (1.26-1.79)
$\geq 37^{+0}$ (term)	1 (reference)	1 (reference)

[1]Infants with birthweight <500g or gestational age at birth $<22^{+0}$ completed weeks were excluded from the analysis. [2]Based on complete case analysis. [3]Variable had ≥ 1 category with $p < 0.05$ in the multivariable analysis and was hence included in the final model. [4]Mutually adjusted odds ratios for other factors in the table. **a priori* variable.

Cardiovascular anomalies

After adjustment for the factors in the final model (Table 8.13), preterm infants with a cardiovascular anomaly had an almost two-fold increased risk of a single admission (aRRR = 1.97, 95% CI: 1.46-2.66), and an almost four-fold increased risk of repeated admissions (aRRR = 3.76, 95% CI 2.86-4.93), compared to term infants with a cardiovascular anomaly. Girls with a cardiovascular anomaly had a 25% decreased risk of repeated admissions, compared to boys with a cardiovascular anomaly (aRRR = 0.75, 95% CI: 0.62-0.91).

Infants with the most severe CHD had a 61% decreased risk of a single admission (aRRR = 0.39, 95% CI: 0.16-0.96) but an almost three-fold increased risk of repeated admissions (aRRR = 2.72, 95% CI: 1.58-4.71), compared with infants with the least severe CHD. In addition, infants with a moderately severe CHD had a six-fold increased risk of repeated admissions, compared with infants with the least severe CHD (aRRR = 6.25, 95% CI: 4.47-8.74). Furthermore, infants with a

patent ductus arteriosus (PDA) or another unclassified CHD had a 38% increased risk of repeated admissions, compared with infants with the least severe CHD (aRRR = 1.38, 95% CI: 1.11-1.73).

Table 8.13: Factors associated with 0, 1 and 2+ admissions among infants with a cardiovascular anomaly: Adjusted multinomial regression analysis[1,2]; births 1999-2015.

	Number of admissions vs. No admission *(n = 997)*	
	2+	**1**
	n = 910	***n = 699***
Risk factors	**Adjusted RRR[5]**	**Adjusted RRR[5]**
Infant factors		
Infant sex[3,*]		
Male	1 (reference)	1 (reference)
Female	0.75 (0.62-0.91)	0.95 (0.78-1.15)
Gestational age[3,*], week		
< 37^{+0} (preterm)	3.76 (2.86-4.93)	1.97 (1.46-2.66)
≥ 37^{+0} (term)	1 (reference)	1 (reference)
CHD severity*		
Less severity	1 (reference)	1 (reference)
Moderate severity	6.25 (4.47-8.74)	1.18 (0.77-1.81)
Most severe	2.72 (1.58-4.71)	0.39 (0.16-0.96)
PDA[4] and other CHDs unclassified	1.38 (1.11-1.73)	*0.91 (0.72-1.15)*

[1]Infants with birthweight <500g or gestational age at birth <22^{+0} completed weeks were excluded from the analysis. [2]Based on complete case analysis. [3]Variable had ≥ 1 category with p < 0.05 in the multivariable analysis and was hence included in the final model. [4]PDA = Patent ductus arteriosus. [5]Mutually adjusted odds ratios for other factors in the table. **a priori* variable.

Genitourinary anomalies

After adjustment for the factors in the final model (Table 8.14), infants with a genitourinary anomaly born to mothers of non-White ethnicity had an almost two-fold increased risk of a single admission, compared to infants with a genitourinary anomaly born to mothers of White ethnicity (aRRR = 1.88, 95% CI: 1.13-3.14). Preterm infants with a genitourinary anomaly had an almost two-fold increased risk of a single admission (RRR = 1.72, 95% CI: 1.11-2.67), and an almost four-fold increased risk of repeated admissions (aRRR = 3.90, 95% CI: 2.67-5.70), compared to term infants with a genitourinary anomaly. Girls with a genitourinary anomaly had a 61% increased risk of single (aRRR = 1.61, 95% CI: 1.19-2.18) and repeated (aRRR = 1.61, 95% CI: 1.19-2.19) admissions, compared to boys with a genitourinary anomaly.

Table 8.14: Factors associated with 0, 1 and 2+ admissions among infants with a genitourinary anomaly: Adjusted multinomial regression analysis[1,2]; births 1999-2015.

	Number of admissions vs. No admission *(n = 1,873)*	
	2+	**1**
	n = 794	***n = 892***
	Adjusted RRR[4]	**Adjusted RRR[4]**
Socio-demographic factors		
Townsend quintile[3]		
1 (least deprived)	1 (reference)	1 (reference)
2	0.74 (0.49-1.13)	1.13 (0.73-1.75)
3	0.51 (0.33-0.77)	1.03 (0.69-1.56)
4	0.74 (0.50-1.09)	1.25 (0.84-1.86)
5 (most deprived)	1.00 (0.71-1.41)	1.26 (0.87-1.84)
Maternal ethnicity[3]		
White	1 (reference)	1 (reference)
Other	1.37 (0.79-2.36)	1.88 (1.13-3.13)
Infant factors		
Infant sex[3,*]		
Male	1 (reference)	1 (reference)
Female	1.59 (1.17-2.16)	1.63 (1.20-2.20)
Gestational age[3,*], week		
$< 37^{+0}$ (preterm)	3.91 (2.67-5.72)	1.72 (1.11-2.66)
$\geq 37^{+0}$ (term)	1 (reference)	1 (reference)

[1]Infants with birthweight <500g or gestational age at birth $<22^{+0}$ completed weeks were excluded from the analysis. [2]Based on complete case analysis. [3]Variable had ≥ 1 category with $p < 0.05$ in the multivariable analysis and was hence included in the final model. [4]Mutually adjusted odds ratios for other factors in the table. **a priori* variable.

Further subgroup analysis

A further subgroup analysis was conducted to investigate whether risk factors were different between infants with anomaly-specific admissions and infants with other-cause admissions. After adjustment for the factors in the final model, preterm birth and a history of anomalies in a previous pregnancy were significant and protective factors for other-cause admissions in infants with an anomaly. However, there were no statistically significant difference in relationships between social deprivation, maternal ethnicity, maternal age, parity, multiple fetus, maternal smoking or infant sex and anomaly-specific hospital admissions versus other-cause specific admissions among infants with any anomalies (Tables 8.15 and 8.16).

Table 8.15: Factors associated with cause-specific admissions among infants with any anomaly (isolated or multiple): Univariable analysis[1].

	Anomaly-specific admissions, Frequency (%)	Other-cause admissions, Frequency (%)	Unadjusted OR (95% CI)[2]	P-value[3]
Socio-demographic factors				
Townsend quintile	*n = 5,003*	*n = 11,435*		
1 (least deprived)	772 (15.4)	1,709 (14.9)	1 (reference)	0.253
2	767 (15.3)	1,780 (15.6)	0.95 (0.85-1.08)	
3	932 (18.6)	2,042 (17.9)	1.01 (0.90-1.13)	
4	1,093 (21.8)	2,432 (21.3)	0.99 (0.89-1.11)	
5 (most deprived)	1,439 (28.8)	3,472 (30.4)	0.92 (0.83-1.02)	
Maternal ethnicity	*n = 3,292*	*n = 7,377*		
White	3,101 (94.2)	6,948 (94.2)	1 (reference)	0.978
Other	191 (5.8)	429 (5.8)	1.00 (0.84-1.19)	
Maternal age at birth, years *(n = 29,400)*	*n = 5,015*	*n = 11,456*		
Mean +/- SD (year)	*28.0 +/- 6.2*	*27.9 +/- 6.3*		
≤ 24	1,570 (31.3)	3,680 (32.1)	0.97 (0.89-1.06)	0.712
25 – 29	1,363 (27.1)	3,103 (27.1)	1 (reference)	
30 – 34	1,251 (24.9)	2,782 (24.3)	1.02 (0.93-1.22)	
≥ 35	831 (16.6)	1,891 (16.5)	1.00 (0.90-1.11)	
Maternal factors				
Parity	*n = 5,015*	*n = 11,456*		
Nulliparous	2,101 (41.9)	4,782 (41.7)	1 (reference)	0.856
≥ 1	2,914 (58.1)	6,674 (58.3)	0.99 (0.93-1.06)	
Multiple fetus	*n = 5,015*	*n = 11,456*		
Yes	153 (3.1)	427 (3.7)	0.81 (0.67-0.98)	0.028
No	4,862 (96.9)	11,029 (96.3)	1 (reference)	
Maternal smoking	*n = 3,376*	*n = 7,365*		
Smoker	946 (28.0)	2,218 (30.1)	0.90 (0.83-0.99)	0.027
Non/ Ex smoker	2,430 (72.0)	5,147 (69.9)	1 (reference)	
Anomalies in previous pregnancies	*n = 3,605*	*n = 8,009*		
Yes	374 (10.4)	1,028 (12.8)	1.27 (1.12-1.44)	<0.001
No	3,231 (89.6)	6,981 (87.2)	1 (reference)	
Infant factors				
Infant sex	*n = 5,012*	*n = 11,453*		
Male	3,013 (60.1)	6,964 (60.8)	1 (reference)	0.405
Female	1,999 (39.9)	4,489 (39.2)	1.03 (0.96-1.10)	
Birthweight, grams	*n = 5,015*	*n = 11,456*		
Median (IQR)	*3220 (2858-3645)*	*3038 (2615-3590)*		
< 2500 (low birthweight)	598 (11.9)	2,448 (21.4)	0.50 (0.45-0.55)	<0.0001
≥ 2500	4,417 (88.0)	9,008 (78.6)	1 (reference)	
Gestational age, week	*n = 5,015*	*n = 11,456*		
Median (IQR)	*39 (38-40)*	*38 (37-40)*		
< 37^{+0} (preterm)	577 (11.5)	2,470 (21.6)	0.47 (0.43-0.52)	<0.0001
≥ 37^{+0} (term)	4,438 (88.5)	8,986 (78.4)	1 (reference)	

[1]Infants with birthweight <500g or gestational age at birth <22^{+0} completed weeks were excluded from the analysis. [2]P-value of the univariable analysis was obtained from the LR test. P value < 0.1 was considered as statistically significant.

Table 8.16: Factors associated with cause-specific admissions among infants with any anomaly (isolated or multiple): The final model.

Risk factors	Crude OR (95% CI)	P-value[1]	aOR (95% CI)[2] in final model	P-value[3]
Anomalies in previous pregnancies				
Yes	1.27 (1.12-1.44)	<0.001	1.26 (1.11-1.43)	<0.001
No	1 (reference)		1 (reference)	
Gestational age, week				
< 37^{+0} (preterm)	0.47 (0.43-0.52)	<0.0001	0.47 (0.42-0.52)	<0.0001
≥ 37^{+0} (term)	1 (reference)		1 (reference)	

[1]P-value of the univariable analysis was obtained from LR test. P value < 0.1 was considered as statistically significant. [2]Mutually adjusted odds ratios for other factors in the table. [3]P-value of the multivariable analysis was obtained from LR test. P value < 0.05 was considered as statistically significant.

8.5 Discussion

8.5.1 Summary of results

This study was the first population-based cohort study to investigate the impact of all congenital anomalies and rare diseases on infant hospitalisation as an indicator of morbidity in the UK. In the 1999-2015 birth cohort, 4.4% of infants were born with at least one anomaly; they represented 15% of all hospital spells of all infants in Wales in this period. Infants born with any anomaly had an overall hospitalisation rate (3.51 spells per person year) which was five times higher compared to that of infants born without an anomaly (0.70 spells per person year); and infants born with multiple anomalies had a hospitalisation rate (5.10 spells per person year) which was almost twice as high compared to that of infants with isolated anomalies (2.70 spells per person year). Among all isolated anomalies, infants with structural anomalies had the highest hospitalisation rates. For example, infants born with a gastrointestinal anomaly had the highest hospitalisation rate which was 13 times higher compared to that of infants born without an anomaly, and the highest proportion (88%) of anomaly-specific admissions; while infants with cardiovascular anomalies had the largest number of spells representing 8.3% of the total spells of infants with any anomaly.

The most common primary cause of hospitalisation of infants with any anomaly was the anomaly itself and its associated diseases or complications, which represented more than a quarter of all their hospital admissions in infancy. With the exception of causes associated with the anomaly, the other leading causes of hospitalisation of infants with and without an anomaly were similar. Diseases of the respiratory system, conditions originating in the perinatal period, and symptoms, signs and abnormal laboratory findings represented 14.2%, 12.1% and 11.3% of all hospital admissions of infants with an anomaly in infancy respectively. Infants with an anomaly were admitted more frequently and had a median of 2 spells per infant admitted, which was twice as high compared to that of infants without an anomaly. Infants with abdominal wall defects and congenital diaphragmatic hernias had the highest median number of spells (4 spells) per infant

admitted, followed by multiple and gastrointestinal anomalies (3 spells per infant admitted). The median LOS per spell was one day in infants with and without anomalies. However, because infants with a congenital anomaly tended to have more admissions compared to infants without an anomaly, so infants with an anomaly had a significantly longer total LOS across all admissions (median total LOS per admitted infant = 5 days) compared to those without an anomaly (median total LOS per admitted infant = 1 day). Among all anomalies, infants with an abdominal wall defect or a congenital diaphragmatic hernia had the longest LOS per spell (median = 3 days) and total LOS across all admissions (median = 21.5 days).

This study was the first to investigate risk factors separately for single and repeated hospital admissions of infants with congenital anomalies and rare diseases, with a hypothesis that the characteristics determining single and repeated hospital admissions of infants with congenital anomalies were different. In general, those with repeated admissions tended to have a higher risk profile than those with single or no admissions. For example, infants with repeated admissions were more likely to live in the most deprived quintile, have younger mothers and more likely to be born preterm compared to those with single or no admissions. The risk factors significantly associated with repeated admissions of infants with any anomalies were younger maternal age ≤24 years, maternal smoking during pregnancy and preterm birth. In addition, girls born with an anomaly were less likely to have repeated admissions than boys born with an anomaly, except for genitourinary anomalies in which girls were more likely to be admitted than boys. Factors significantly associated with a single admission for infants with any anomalies were preterm birth.

8.5.2 Comparison with evidence from literature

Rates of hospitalisation

This study has found that infants with congenital anomalies had an overall hospitalisation rate of 3.51 admissions per person year in Wales between 1998 and 2016, which was higher than that in

Western Australia between 1980 and 1998 (1.05 admissions per person year) (Colvin and Bower 2009). This could be due to several reasons. First, there were methodological differences related to the definition of an admission, as well as inclusion criteria for congenital anomalies between this study and the study by Colvin and Bower (2009). This study included all emergency, elective and transfer hospital admissions in the analysis of the rate of hospitalisation in order to assess the full burden of hospitalisation, whereas the study by Colvin and Bower (2009) merged transfer admissions with the primary admissions which would partly account for the lower hospitalisation rate compared to this study. In addition, this study included a wider group of congenital anomalies (as defined by CARIS) involving structural, metabolic, endocrine, or genetic defects and rare diseases; whereas the study by Colvin and Bower (2009) in Western Australia included major anomalies (as defined by the U.S. Centers for Disease Control and Prevention, CDC) which mainly focused on structural and functional abnormalities (CDC 2019a) (Appendix 8.1). Given the wider definition and inclusion of anomalies and rare diseases in this study, it would be reasonable to anticipate that there would be a higher overall admission rate for infants affected by any anomaly. Second, as highlighted in the literature review (Chapter 7), the improved survival of infants born with major congenital anomalies due to advances in medical and perioperative care, surgical interventions and neonatal intensive care has led to an increase in hospital admissions for preventive procedures, new investigations and interventions over time (Leonard et al. 2000; Slack-Smith et al. 2009; Larsen et al. 2017; Meyers et al. 2015). Therefore, the difference in the year of study cohorts can partly explain the higher rate of hospitalisation shown in this current study (births, 1999-2015) compared to that in the earlier study (births, 1980-1999) by Colvin and Bower (2009).

This study has shown that cardiovascular, gastrointestinal and genitourinary anomalies contributed the largest numbers of hospital admissions; while blood disorders and anomalies of the nervous system contributed the largest numbers of admissions per infant. Similarly, the study by Colvin and Bower (2009) showed that ventricular septal defects, pyloric stenosis, undescended

testis and vesico-ureteral reflux contributed the largest numbers of admissions; and thalassaemia, congenital hydrocephalus, microcephaly and spina bifida contributed the largest numbers of admissions per child. These findings suggest that the general contributions of certain anomaly groups in relation to the overall hospitalisation found in this study are consistent with the existing literature, and have generally remained unchanged over time.

Patterns of hospitalisation

The overall patterns of hospitalisation of infants with anomalies in this study are consistent with the findings in the literature. These included the causes, frequency and LOS of hospitalisation, and are discussed as follows.

Causes of hospitalisation

This study has found that the most common primary cause of hospital admissions of infants with any anomaly was the anomaly itself and associated diseases or complications of the anomaly, which represented more than a quarter of all hospital admissions of infants with an anomaly in infancy. These findings have highlighted the significant impact of congenital anomalies as a leading cause of morbidity and hospitalisation of infants affected by congenital anomalies. In addition, this study has shown that respiratory-related conditions were a leading cause of morbidity and hospitalisation for infants with an anomaly. The relationship between congenital anomalies and respiratory complications such as asthma, non-suppurative otitis media, acute upper respiratory infections and bronchiolitis has been previously investigated and shown especially in infants with Down syndrome and congenital heart diseases (Bloemers et al. 2007; Medrano et al. 2007; Glezen et al. 1986; López et al. 2010; Kristensen et al. 2009; So et al. 2007; Zachariah et al. 2012). Possible mechanisms involve abnormal development of the lungs and decreased airway branching in infants with Down syndrome (Schloo et al. 1991). Consequently, abnormal cilia, anatomy of the upper respiratory tract and bronchial reactivity increase the

susceptibility of these infants to respiratory illness (Medrano et al. 2007; Hilton et al. 1999). In addition, infants with Down syndrome are susceptible to an increased risk of respiratory infections due to associated comorbidities such as neuromuscular disorders, swallowing disorders, gastro-oesophageal reflux and impairment of T and B lymphocytes leading to impairment of the immune system (Medrano et al. 2007; Schloo et al. 1991; Kristensen et al. 2009; de Hingh et al. 2005; Scotese et al. 1998). Perinatal conditions were the third most common cause of hospital admissions of infants with congenital anomalies overall; these were likely attributed by those with serious anomalies (e.g. metabolic and endocrine disorders, blood disorders and neoplasms) and comorbidities (e.g. extreme prematurity) needing critical and emergency treatment for the conditions or their complications soon after birth.

Frequency of hospital admission

Infant with a congenital anomaly were more frequently admitted to hospital compared to infants without an anomaly. For example, this study has shown that the median number of hospital spells among infants born with a cardiovascular anomaly (2 days) was twice as that of infants without an anomaly (1 day). Previous studies have shown that infants with a CHD were admitted more frequently and used inpatient care resource more intensively than infants without a CHD (Frid et al. 2002); in particular, infants who underwent CHD surgery were at a significantly increased risk of respiratory, renal and infectious complications requiring frequent hospitalisation (Dyamenahalli et al. 2000; Kongon et al. 2019). In addition, this study has shown that the median number of hospital spells among infants born with a syndromal defect was 50% higher than that of infants without an anomaly. The CIVIC study has shown that infants with Down syndrome were admitted more frequently due to RSV-related infections compared to infants without Down syndrome (Medrano et al. 2007), as well as other comorbidities such as CHDs, neuromuscular disorders, haematological malignancies and immunity-related disorders which predispose these infants to short and long term illnesses (Medrano et al. 2007; Hilton et al. 1999; Shott 2006). Similarly,

infants with abdominal wall defects and congenital diaphragmatic hernias were admitted more frequently due to long-term gastrointestinal, pulmonary and neurological morbidities compared to infants without an anomaly (Wynn et al. 2013; Bagolan and Morini 2007). These findings suggest that infants with anomalies are overall admitted more than infants without anomalies; the difference is largely due to needing admissions for conditions and complications relating to their anomaly.

Hospital length of stay (LOS)

This study has shown that when admitted, infants with an anomaly had a longer median total hospital stay across all admissions (5 days) compared to infants without an anomaly (1 day); however, the median total hospital LOS varied markedly ranging from 1.5 to 21.5 days depending on the number and complexity of the anomaly. For example, infants with multiple anomalies had a doubling in the median total LOS compared to infants with an isolated anomaly (7.5 days versus 3.5 days respectively). This is likely due to case complexity and an increased risk of requiring multiple operations and experiencing comorbidities and complications especially for multiple anomalies compared to other anomalies (Dawson et al. 2014; Zhu et al. 2013; Hilton et al. 1999; Frid et al. 2002; So et al. 2007). Those with abdominal wall defects and congenital diaphragmatic hernias had the longest median hospital LOS per spell (3 day) and the longest median total hospital LOS across all admissions (21.5 days), followed by infants with gastrointestinal, cardiovascular, and nervous system anomalies. This finding is consistent with the study by Colvin and Bower (2009). Previous studies have shown that infants with a congenital diaphragmatic hernia are susceptible to multiple and long-term gastrointestinal, pulmonary and neurological morbidities such as gastro-oesophageal reflux disease, feeding problems, pulmonary hypertension and oxygen dependence which often require frequent and prolonged hospital readmissions (Putnam et al. 2016; Wynn et al. 2013; Bagolan et al, 2007; Bevilacqua et al. 2014; Valfrè et al. 2011; Safavi et al. 2012; Bairdain et al. 2015). For infants who underwent surgery for a

CHD, post-operative infections and pleural effusion are common causes for prolonged hospital readmissions (Smith et al. 2015; Saharan et al. 2014; Dyamenahalli et al. 2000). In addition, the study by Medrano et al. (2007) has shown that up to 16% of the admitted children with a CHD required paediatric intensive care and approximately 5% of admitted children required mechanical ventilation. These findings have demonstrated that the burden of hospitalisation for infants with an anomaly (especially for those with multiple and structural anomalies) is much greater than their peers without an anomaly.

Risk factors for hospitalisation

This study investigated risk factors separately for single and repeated hospital admissions among infants with congenital anomalies.

Maternal age

Increased maternal age was inversely associated with the risk of repeated admissions of infants with an anomaly. This finding of the effect of maternal age is consistent with the UK Millennium Cohort study, which showed that in a general population of children, the risk of hospital admissions decreased with increasing maternal age after adjusting for socio-demographic, maternal and child factors (Sutcliffe et al. 2012). Evidence suggests that younger maternal age is associated with higher risks of adverse neonatal outcomes and preterm birth due to increased risks of genital tract infections, obstetric complications, inadequate antenatal care and social support, and other behavioural determinants such as maternal smoking, alcohol and recreational drug misuse (Harper et al. 2011; Torfs et al. 1994). In addition, infants born to older mothers tend to have a reduced risk of unintentional injuries and an increased uptake of routine immunisation in childhood, which may explain the protective effect of older maternal age in relation to general childhood hospitalisation. Genetics and differences in parenting have also been suggested as possible mechanisms (Sutcliffe et al. 2012).

A further subgroup analysis in this study found no significant difference in the relationship between maternal age and anomaly-specific admissions, and maternal age and other-cause admissions. This finding suggests that the mechanisms by which maternal age is a risk factor for hospitalisation of infants with an anomaly are similar for infants with anomaly-specific admissions and infants with other-cause admissions.

Maternal smoking

Infants with an anomaly born to mothers who were active smokers during pregnancy had a 20% increased risk of repeated hospitalisation, compared to infants born to mothers who did not smoke. Active smoking during and after pregnancy has been shown to increase the risk of respiratory infectious diseases, bacterial meningitis and necrotising enterocolitis in infants (DiFranza et al. 2004; Cook and Strachan 1999; Håberg et al. 2007; Yusuf et al. 1999; Stuart et al. 2010). The study by Metzger et al. (2013) has further demonstrated a significant dose-response relationship between maternal smoking and all types of respiratory infections (except croup) in infants after adjusting for other socio-demographic and infant factors. Possible mechanisms include intrauterine stress due to nicotine substances which trigger the neuroenteric components of, for example, the gastrointestinal tract, which may manifest clinically during infancy (Weinsheimer et al. 2008).

The subgroup analysis found no significant difference in the relationship between maternal smoking and anomaly-specific admissions, and maternal smoking and other-cause admissions. This suggests that the mechanisms by which maternal smoking is a risk factor for hospitalisation of infants with an anomaly are similar for infants with anomaly-specific admissions and for infants with other-cause admissions.

Preterm birth

Infants with an anomaly who were born preterm had a two-fold increased risk of single and repeated hospitalisation compared to infants with an anomaly born at term. Preterm birth has been shown to be a significant factor associated with an increased risk of morbidities and hospitalisation among infants with a congenital anomaly in the literature. For example, in a large multi-centre cohort study, Hardy et al. (2019) found that extremely preterm infants (<24 gestation weeks) with a congenital anomaly had a significantly increased risk of comorbidities and complications including respiratory distress syndrome, sepsis, apnoea, hyperbilirubinaemia and any infectious disease, compared to term infants with a congenital anomaly. The study by Weinsheimer et al. (2008) showed that moderately preterm infants (<36 weeks) born with a gastroschisis were significantly more likely to have intestinal necrosis, compared to term infants born with a gastroschisis. Possible mechanisms include a lower physiologic reserve and a higher susceptibility to infections among preterm infants compared to term infants (Björ and Bråbäck 2003). Furthermore, clinicians may be more cautious and having a lower threshold for admission of preterm infants with a congenital anomaly when complications arise (Mackie et al. 2008).

The subgroup analysis demonstrated that preterm birth was a significant and protective factor for other-cause admissions in infants with an anomaly. This finding suggests that prematurity is a significant and predominant characteristics for infants with anomaly-specific admissions. Since having a major anomaly increases the risk of an infant being born preterm, prematurity can be considered as an important association pathway rather than a competing risk for many of the anomaly-specific admissions.

Infant sex

Girls with an anomaly were 16% less likely overall to have repeated hospital admissions than boys with an anomaly, with the exception of genitourinary anomalies in which girls were more likely to be admitted than boys.

Being male is generally associated with poorer short- and long- term disease outcomes compared to being female at every age (Melamed et al. 2010; Speakman 2013; Steen et al. 2014; Barford et al. 2006; O'Driscoll et al. 2018; Naeye et al. 1971). Previous twin studies have also shown that boys have an increased risk of intrauterine growth restriction, respiratory distress syndrome and overall morbidities (Lisi et al. 2005; Tennant et al. 2011; Zhao et al. 2017; Stevenson et al. 2000; Mulla et al. 2013; Peelen et al. 2016; Steen et al. 2014; Kent et al. 2012). The possible mechanisms of these sex-specific differences in morbidities are likely to be multifactorial, with genetic, immunological and hormonal differences likely to play an important role (O'Driscoll et al. 2017).

This study has found that boys with a genitourinary anomaly had a lower risk for hospitalisation compared with girls with a genitourinary anomaly. This is likely because undescended testis is the most common genitourinary anomaly in boys (Colvin and Bower 2009). The surgical treatment (i.e. orchidopexy) is nowadays typically planned and carried out as a day case rather than inpatient. The transfer from inpatient to day case procedures applies similarly to the surgical repair for hypospadias (Borer et al. 2001). This is in contrast to the surgery required by girls with genitourinary anomalies, which is likely to be complex and require an inpatient procedure (Edmonds 2003; Kachhawa and Kriplani 2017).

Severity of anomaly

Infants with the most severe CHD had a two-third decreased risk of single admission but an almost three-fold increased risk of repeated admissions, compared to infants with a less severe CHD. In addition, infants with a moderately severe CHD or a patent ductus arteriosus (PDA) had a

1.4-6.3 fold increased risk of repeated admissions, compared to infants with a less severe CHD. A likely explanation is that infants with the most severe CHD (e.g. single ventricle, tricuspid atresia and stenosis, Ebstein's anomaly and hypoplastic left/ right heart) often experience acute and life-threatening events and required surgical interventions during infancy; mortality risk among these infants is considerably higher during neonatal and infancy period compared to infants with a less severe CHD (e.g. isolated VSD, ASD and pulmonary valves stenosis) regardless of surgical interventions (Billet et al. 2008; Gandhi and Sreekantam 2011; Dyamenahalli et al. 2000; van Dongen et al. 2003; Best and Rankin 2016; Desai et al. 2017). For those infants with a moderate to severe CHD who survive, the aetiology and pathophysiology of their anomaly are complex; they are likely to experience long-term morbidities which would require repeated hospitalisation for ongoing investigations, medical treatment, surgical interventions and treatment for postoperative complications (Smith et al. 2015; Dyamenahalli et al. 2000; Duppenthaler et al. 2004; Marston et al. 2019). In addition, this finding is consistent with previous studies which showed that infants with a more severe CHD used inpatient resources more intensively, compared to infants with a less severe CHD (Islam et al. 2016; Islam et al. 2016a; Mackie et al. 2017).

Of note, a widely used classification of anomaly according to severity is uncommon and currently limited to a few anomaly groups such as CHDs (EUROCAT 2016; EUROCAT 2013). Hence, the analysis of the effect of anomaly severity on hospitalisation could not be performed for most other anomaly subgroups in this and previous studies.

8.5.3 Strengths and limitations

Strengths

This is the first population-based cohort study to investigate the impact of a wide group of congenital anomalies and rare diseases on infant hospitalisation as a proxy for morbidity in the UK.

The main strengths of this study include the use of routinely collected data from PEDW with a national coverage of all hospital admissions in Wales and the robust study design. Hospital episode data has been widely recognised and used for health services research, and are particularly advantageous for examining patterns of hospitalisation due to the large size of the dataset and long period of routine data collection. The large sample size and long time span in this study have made it possible to precisely estimate the rate, patterns and outcomes of hospitalisation of infants with congenital anomalies. The findings in this study are representative of the whole population in Wales.

Another strength relates to the study inclusion criteria of a wide group of congenital anomalies. This study has uniquely included congenital anomalies and rare diseases involving structural, metabolic, endocrine and genetic defects collected and reported by CARIS, which are beyond those normally included in EUROCAT congenital anomaly subgroups. Consequently, it was possible to generate robust findings and assess the full impact of congenital anomalies and rare diseases on infant hospitalisation as an index of morbidity.

A further strength is that the high quality of data was assured by rigorous additional checks and revisions where necessary. For example, all the infants' admissions that had been misclassified as mothers' admissions were revised. In addition, efforts were made by working with the SAIL team to optimise the quality of data linkage and outcomes prior to the analysis.

Finally, in order to robustly assess the burden of hospitalisation of infants with congenital anomalies, this study included all spells (emergency, elective and transfer admissions) in the estimates of rate, frequency and LOS of hospitalisation, while birth hospitalisation was excluded from all the analyses to avoid artificial inflation of the estimate resulting from 'well-babies' admissions. In addition, in the analysis of hospital LOS, this study excluded any incomplete spells in which the first episodes were missing due to coding errors. Therefore, this approach aimed to

accurately assess the full burden of hospitalisation of infants with any anomaly, and minimise the potential for misclassification bias that was highlighted in the literature.

Limitations

As PEDW is a hospital administrative dataset rather than a database established for research purposes, data on admissions and primary diagnoses were not always complete; and missing data varied over time and by region. The causes of the missing episodes were investigated and discussed with SAIL and CARIS. For example, about 5% of admission episodes and their primary diagnoses were missing or miscoded. Following discussion, it appeared that this was likely in part due to infants being treated in a specialist centre outside the catchment area of NHS Wales care providers. Thus it seemed likely that the missing data were missing completely at random (i.e. the missing observations are a random subset of all observations, and the missing and observed values are likely to have a similar distribution), hence multiple imputation was not justified (Bhaskaran and Smeeth 2014). The missing data were dealt with in the analysis by one of several ways; for example, any spells with missing first episodes were excluded from the analyses of the primary cause of hospital admission to minimise misclassification bias, and from the estimates of hospital length of stay to minimise underestimation. As the missingness of the first admission episodes in the dataset was trivial (< 5%) and an estimate that 90% of spells consisted of just one episode, it is unlikely that this level of missingness would have had a significant effect on the findings in relation to the causes and length of infant hospitalisation.

Another limitation relates to the unavailable data about infant's date of birth; instead, the week of birth i.e. the Monday prior to actual date of birth was made available in accordance to the NWIS protocol. Consequently, all the age calculations were accurate to +/- 7 days and hence it was possible that these calculations could have limited the accuracy of the estimates of follow-up time to the first admission and hospital LOS for infants who were admitted from birth. This was thus likely to have underestimated the absolute hospital admission rates (where the week rather

than date of birth was used to calculate the person time for the first admission) and overestimated the absolute hospital LOS of infants with anomalies (where the week rather than date of birth was used to calculate the LOS for those infants admitted from birth). In addition, this was likely to have underestimated the hospitalisation rate ratios, as infants with congenital anomalies were more likely to be admitted to hospital compared to infants without congenital anomalies.

In addition, it is possible that factors other than those available in the dataset are also important determinants of hospitalisation of infants with congenital anomalies. For example, these include institutional factors such as outpatient resource availability, which may have an impact on the hospitalisation especially among infants with less severe anomalies and those who can be treated as day cases.

Finally, due to methodological differences in the inclusion criteria for congenital anomalies and study populations, classifications and definitions of congenital anomalies and admissions, as well as different healthcare systems (UK has a government funded National Health System with universal access to healthcare compared to private health insurance system in some high-income countries) and study periods, direct comparisons of rates, frequency and LOS of hospitalisation between studies can be challenging and are not always informative. Therefore, the literature comparisons with this study mainly focused on the overall findings and patterns, and the results were largely consistent.

8.5.4 Implications for clinical practice and population health

The findings in this study have important implications for clinical practice and population health. From a primary prevention perspective, this study has advanced our knowledge about risk factors for hospitalisation of infants affected by an anomaly. Primary prevention measures such as promoting smoking cessation, good prenatal health among women of reproductive age, and

ensuring easy access to antenatal care and support particularly for younger mothers may help reduce morbidity and hospitalisation of all infants including those with an anomaly.

Regarding secondary prevention, this study has investigated the patterns of infant hospitalisation for selected anomaly subgroups. This information can be used to assess the burden of hospitalisation for infants with anomalies, and inform parental counseling about the expected hospitalisation and prognosis. Having general information on the likely causes, frequency and length of hospital stay of infants with a congenital anomaly may help to alleviate potential anxiety felt by their parents and other carers.

In relation to tertiary prevention, this study has identified the common primary causes of hospitalisation of infants affected by anomalies. This information has important implications for health service commissioners to plan resources effectively in order to improve the care for the infants affected by congenital anomalies, especially for those with complex needs; and for clinicians to manage anomaly-related infant morbidity and hospitalisation according to their general causes and patterns.

Table 8.17: What this hospitalisation study adds

- This is the first population-based cohort study to investigate the impact of all congenital anomalies and rare diseases on infant hospitalisation as an index of morbidity in the UK.

- The most common primary causes of hospital admissions of infants with an anomaly are the anomaly itself and associated disease or complications, followed by respiratory conditions, and conditions originating in the perinatal period.

- Infants with congenital anomalies (especially multiple and structural anomalies) are more frequently admitted to hospital and have a longer LOS due to a greater risk of comorbidities, case complexity and associated complications, compared to infants without an anomaly.

- Younger maternal age, maternal smoking, preterm birth and male sex (with the exception of genitourinary anomalies) are significantly associated with an increased risk of repeated admissions of infants with an anomaly.

- The mechanisms by which maternal age and smoking increase the risk of hospitalisation of infants with an anomaly are similar for infants with anomaly-specific admissions and infants with other-cause admissions. Preterm birth is an important association pathway for many of the anomaly-specific admissions.

Chapter 9: Overarching Discussion, Recommendations For Future Research and Conclusions

9.1 Main findings of this study

Congenital anomalies have a significant impact on infant morbidity and mortality. They contributed almost one-third of all infant deaths, and represented an infant mortality rate (IMR) of 16.5 deaths per 10,000 livebirths in the 1998-2016 birth cohort in Wales. Infants with multiple and structural anomalies had the highest IMRs (up to 11.3 deaths per 10,000 livebirths) and case fatality (up to 8.2%). Among infants with congenital anomalies who died, the congenital anomalies themselves and associated complications were the most common main and underlying causes of neonatal and post-neonatal deaths respectively. Preterm birth was found to be the single strongest factor significantly and consistently associated with almost or more than a four-fold increased risk of excess infant case fatality across all anomaly subgroups, compared to term birth. The effects of maternal ethnicity, maternal smoking, parity, infant sex, anomaly severity and surgery varied according to anomaly subgroups.

In regard to morbidity, congenital anomalies contributed about 15% of the total hospital admissions of all livebirths in infancy in the 1999-2015 birth cohort in Wales. Infants with multiple and complex anomalies were particularly admitted more frequently and for a longer hospital stay compared to infants without an anomaly or with isolated anomalies. Among infants with congenital anomalies who were admitted, the anomalies themselves and associated diseases or complications were the most common main causes of hospitalisation. Preterm birth was the strongest risk factor significantly and consistently associated with increased risks for single and repeated hospital admissions of infants across all anomaly groups. Younger mother, maternal smoking and male sex (except for genitourinary anomalies) were also independently associated with increased risks of anomaly-related infant hospitalisation.

9.2 What can be drawn from previous studies and literature reviews

Congenital anomalies are the second most frequent cause of infant death after prematurity, and a major cause of paediatric morbidity (Bishop et al. 2017; Colvin and Bower 2009; PHE 2019; CDC 2019). The impact of congenital anomalies on prognostic outcomes is particularly greater in infancy compared to other period in childhood (Agha et al. 2016; Dastgiri et al. 2003; Tennant et al. 2010; Schneuer et al. 2019; Berger et al. 2003). However, in-depth investigations of infant morbidity and mortality due to congenital anomalies have been limited, with the existing research mainly focused on congenital heart diseases (CHDs), neural tube defects (NTDs), Down syndrome and certain gastrointestinal anomalies such as gastroschisis and congenital diaphragmatic hernias.

Two systematic reviews were conducted in this thesis focusing specifically on NTDs as these serious anomalies of the nervous system contribute significantly to anomaly-related infant deaths. IMRs and case fatality due to spina bifida and encephalocele significantly declined over time in the past few decades in high-income countries (Wang et al. 2015; Wen et al. 2000; Liu et al. 2001; Laishram et al. 1993; Kalucy et al. 1994; Schneuer et al. 2019; Bakkar et al. 2019; Sutton et al. 2008; McDonnell et al. 2015). Advances in medical and surgical interventions (Laishram et al. 1993; Mitchell et al. 2004; Grivell et al. 2014; Date et al. 1993; Adzick et al. 2011); improved technology in and access to prenatal screening and diagnosis; access to termination of pregnancy (Kalucy et al. 1994; Riley et al. 1998; Boyd et al. 1998; RCOG 2010; Thompson 2009); the implementation of mandatory folic acid food fortification programmes (Atta et al. 2016; Christianson et al. 2006; Kancherla et al. 2018; Murphy et al. 2020; EUROCAT 2003; Crider et al. 2011); and the recommendation of periconceptional folic acid supplementation (MRC Vitamin Study Research Group 1991; Czeizel 1998; Berry et al. 1999) are likely the main causes for these declines.

Preterm birth, low birthweight, maternal black ethnicity, plurality, inadequate prenatal care, lesion severity/ complexity and the presence of multiple defects were found to be significant

determinants of excess case fatality due to spina bifida or encephalocele. However, the interplay of factors contributing to spina bifida/encephalocele associated infant mortality is complex and geographically dependent, with calendar time being a major source of heterogeneity. Other population-based studies have also shown a decline in infant deaths due to CHD (Best et al. 2016; Leonard et al. 2000; Sánchez-Luna et al. 2017; Bloemer et al. 2007; Thomas et al. 2011; Hilton et al. 1999) and Down syndrome (Slack-Smith et al. 2009; Nelson et al. 2012) in high-income countries over time. For many other anomaly groups and subtypes however, there have been few, or no population-based survival or mortality data published.

Infants with a major anomaly as defined by the CDC (such as CHD, Down syndrome and congenital diaphragmatic hernia) have an increasing burden of hospitalisation over time due to improved survival and their complex medical needs (Colvin and Bower 2009); these infants were admitted more frequently and for a longer hospital stay compared to infant without an anomaly (Slack-Smith et al. 2009; Nelson et al. 2012; Leonard et al. 2000; Sánchez-Luna et al. 2017; Bloemer et al. 2007; Thomas et al. 2011; Hilton et al. 1999; CDC 2019a). Respiratory-related conditions and anomaly-related complications were the most common causes for hospitalisation of infants with a major congenital anomaly (Kristensen et al. 2009; Medrano et al. 2007; So et al. 2007; Zachariah et al. 2012). Preterm birth, the presence of comorbidity, and severe/ complex anomaly were found to be significantly associated with excess hospitalisation among infants with a CHD, orofacial cleft, gastroschisis or Down syndrome. Study evidence on hospitalisation risk factors for other congenital anomaly groups is limited.

9.3 What this study adds

9.3.1 Mortality study

The CARIS data indicates that 4.8% of liveborn babies had an isolated or multiple congenital anomalies in the 1998-2016 birth cohort in Wales. A total of 1,044 infants in this study cohort died in infancy, which represented almost one-third of all infant deaths; and the overall case fatality was 3.4%. Survival outcome varied with the pattern of anomalies. As expected, IMRs are generally lower for babies with isolated anomalies involving non-vital organs such as anomalies of the eye, ear, face and neck (IMR = 0.19 deaths per 10,000 livebirths), and the limbs and skeletal system (IMR = 0.27 deaths per 10,000 livebirths). As the number and complexity of anomalies increase, the rate of infant deaths also increases. The most significant contribution of congenital anomalies to infant mortality were mainly driven by infants with multiple anomalies (IMR = 11.28 deaths per 10,000 livebirths), and structural anomalies of vital organs such as the cardiovascular system (IMR = 1.33 deaths per 10,000 livebirths), the nervous system (IMR = 0.60 death per 10,000 livebirths), the respiratory system (IMR = 0.46 death per 10,000 livebirths), and abdominal wall defects and congenital diaphragmatic hernias (IMR = 0.46 death per 10,000 livebirths), who experienced the highest IMRs and infant case fatality. This can be explained by the complex anatomy and potentially severe disease complications with which these anomalies are often associated (Springett et al. 2014). Indeed, congenital anomalies themselves and immaturity-related conditions contributed up to 56% and 23% respectively of the underlying/ main cause of death of infants with anomalies who died. Thus, these findings demonstrate that the majority of deaths of infants with congenital anomalies were anomaly- or immaturity- related, which in turns contributes significantly to the overall infant mortality in Wales.

Preterm birth was found to be the single strongest factor associated with an increased risk of excess infant mortality across all anomaly subgroups. Understanding the relationship between prematurity and congenital anomalies, and their contributions to infant mortality is complex.

Previous studies suggested that congenital anomalies and preterm birth are strongly correlated, and they share some common underlying risk factors such as maternal smoking, obesity and diabetes mellitus (Honein et al. 2009; Werler 1997; Weintrob et al. 1996). Fetuses with anomalies often have other developmental effects during gestation, which may lead to preterm birth (Dolan et al. 2007; Behrman and Butler 2007). Therefore, having a major anomaly significantly increases the risk of an infant being born preterm, both of which are independently associated with an increased risk of infant death with a likely synergistic effect (Honein et al. 2009; Kase and Visintainer 2007; Norman et al. 2020). In addition, a number of interrelated risk factors acting from the preconceptional period, through pregnancy and after birth were found to be significant contributors for excess anomaly-related infant deaths. These include socio-demographic and maternal factors such as maternal ethnicity, maternal age, maternal smoking during pregnancy and parity, which determine to some extent infant factors such as prematurity, low birthweight and anomaly severity which in turns determine intervention factors such as requiring surgery, and consequently influence the risk of excess mortality of infants with congenital anomalies. This finding suggests that anomaly-associated infant deaths can potentially be reduced by targeting distal and proximal factors such as reducing ethnic disparity in the access to health care service and improving maternal health during pregnancy (e.g. adequate prenatal care and smoking cessation advice) which can help minimising the risks of preterm birth and anomaly-/ immaturity-associated conditions and complications. Furthermore, among infants with a CHD, having surgery was found to be a protective factor which lowered the risk for infant death after adjusted for CHD severity. Indeed, the survival rates for children with a moderate CHD such as tetralogy of Fallot, transposition of great vessels, coarctation of the aorta and arterial truncus in the absence of other comorbidities have improved dramatically over the recent decades as suggested in the CARIS annual report; the majority of these infants successfully undergo surgery during infancy and their long-term cardiac function is generally excellent (CARIS 2020e).

This study defined infant case fatality as infant affected by a congenital anomaly who died from all causes in infancy. An alternative approach would be to include those who died from congenital anomalies only in the analysis. However, given that assigning the main/ underlying cause of neonatal and post-neonatal deaths of infants with a major anomaly on the death certificate is often very difficult due to other competing causes, and using 'all cause mortality' is a standard approach in which previous studies has adopted, therefore the current definition and approach in this study would minimise potential misclassification bias and allow comparison with other studies in a more systematic manner.

9.3.2 Generalisability and limitations

The findings of the mortality study reported here are based on the whole population of Wales between 1998 and 2016. The use of data from CARIS (the national anomaly registry of Wales with a high quality reporting system and own internal data checks) and ONS (the most complete national data source of births and deaths in the UK), and together with the researcher's (PH) additional checks on diagnostic coding and plausible ranges of values of the included variables across data sources optimised the internal validity of the study results. Therefore, the findings of the mortality study are considered to be representative of Wales. Given that the health care systems are similar, and the registration and reporting of extremely preterm births are standardised between the UK countries, it is reasonable to generalise the study findings to the whole of the UK population. It is important to note that however, Wales has a significantly lower proportion of non-White population compared to England overall (<5% vs. 25-30%) (ONS 2019a), and indeed, previous studies in England and Wales have shown that infants from an ethnic minority background had higher risks of adverse birth outcomes compared to White British infants (ONS 2015a); therefore, extrapolations of findings from this study should take into account the specific ethnic and socioeconomic characteristics of the populations being compared. As far as other countries with different health care systems are concerned, previous studies have

highlighted that comparison of IMRs is extremely difficult due to variations in neonatal practice for caring, registration and reporting of extremely preterm births, access to advanced care and surgical treatment, and the capacity to track all the anomaly cases and link with death registry over time and between different countries (Nath et al. 2020; Davis et al. 2018; ONS 2019c); therefore, the results of this study using historical data from Wales is unlikely to be fully generalisable for other countries beyond the UK without taking these variations in clinical practice and health care systems into account.

9.3.3 Hospitalisation study

Hospital admissions have been considered as an useful indicator of morbidity and quality of care to inform the health care system (Fitzsimons et al. 2013; Duppenthaler et al. 2004); thus, quantifying service utilisation can help planning and commissioning of health services as well as monitoring outcomes and improving care. This study found that infants with structural anomalies such as cardiovascular anomalies had the largest number of admissions representing 8.3% of the total admissions of infants with any anomaly, followed by infants with gastrointestinal (7.8% of total anomaly-related admissions) and genitourinary (6.4% of total anomaly-related admissions) anomalies in the 1999-2015 birth cohort in Wales. Whilst these major anomalies were also among the most prevalent congenital anomalies, advances in surgical treatment and improvements in neonatal care may lead to improved survival of many of the affected infants who now survive beyond infancy and may require regular hospital admissions for preventative procedures, further investigations and interventions (Thomas et al. 2011). The overall improved survival of infant with congenital anomalies over time may also partly explain the higher rate of hospital admissions shown in this study (Welsh birth cohort, 1999-2015) compared to the rates reported in the earlier Australian cohort study (1980-1999) by Colvin and Bower (2009), although the difference in results was also likely confounded by other factors such as variations in anomaly definitions, inclusion criteria and registration thresholds of extremely premature infants between the two

studies. Compared to infants without an anomaly, infants with congenital anomalies were admitted more often and for a longer hospital stay. The most likely explanation is that infants with congenital anomalies are predisposed to greater risks of anomaly-related comorbidities and complications due to various underlying pathophysiology. For example, infants who require surgery are susceptible to a range of respiratory, renal and infectious complications post surgery (Dyamenahalli et al. 2000; Kongon et al. 2019). Infants with Down syndrome have an increased risk of RSV-related infections, CHDs, endocrinological and developmental impairments (Medrano et al. 2007; Kristensen et al. 2009; de Hingh et al. 2005; Scotese et al. 1998). Infants with a congenital diaphragmatic hernia are susceptible to gastro-oesophageal reflux disease, feeding problems, pulmonary hypertension and oxygen dependence (Putnam et al. 2016; Wynn et al. 2013; Bagolan and Morini 2007; Bevilacqua et al. 2014; Valfrè et al. 2011; Safavi et al. 2012; Bairdain et al. 2015). The mechanism is likely to be multifactorial, with interaction of systemic pathologies, hormonal activation and prematurity playing an important role (Lui et al. 2017). These explanations are supported in this study which demonstrated that the congenital anomalies themselves and associated diseases or complications were the most common primary causes of hospital admissions of infants across different anomaly subgroups, and they represented more than a quarter of all hospital admissions of infants with an anomaly in infancy in the 1999-2015 birth cohort in Wales. These findings therefore have established the significant impact of congenital anomalies on infant morbidity, with important implications for clinical practice, planning of health care resource and services, and parental counseling. An understanding of the likely patterns and causes of hospitalisation helps to optimise the quality of care delivered to the affected infants (e.g. early specialised care) and alleviate potential anxiety and stress felt by their parents and other carers.

Studies of risk factors for hospital admissions of infants with anomalies are limited; previous studies mainly focused on 30-days readmission for infants who underwent surgery for certain anomalies including CHDs (Smith et al. 2015; Dyamenahalli et al. 2000; Saharan et al. 2014;

Mackie et al. 2008; Islam et al. 2018; Simic et al. 2009; Li et al. 2016; Kogon et al. 2019), choanal atresia (Marston et al. 2019), biliary atresia (Garcia et al. 2018) and hypospadias (Roth et al. 2018). This study sought to determine the extent to which the variations in hospital admissions of infants with anomalies could be explained by socio-demographic, maternal and clinical characteristics. Using multinomial logistic regression methods, this study found that preterm birth was the single strongest factor consistently associated with an increased risk of infants having single and repeated hospital admissions across all anomaly groups. By stratifying the cause-specific admissions, this study further demonstrated that prematurity was a significant and predominant factor for infants with anomaly-specific admissions versus other-cause admissions, thus suggesting that prematurity is an important pathway for anomaly-specific admissions. Indeed, as discussed, anomaly and prematurity may share some common risk factors e.g. maternal smoking, hypertension and diabetes, and hence potentially a common association pathway for hospitalisation of the affected infants. In addition, this study found that younger maternal age and maternal smoking are other significant risk factors for repeated admissions of infants with anomalies overall. From a public health perspective, these findings suggest that the excess in anomaly-associated infant hospitalisation can be reduced by optimising the care of preterm birth, as well as by the means of prenatal and social support for younger mothers especially those from a more deprived area having a baby affected by congenital anomalies. Finally, knowledge about specific risk factors for hospitalisation and repeated hospitalisation of infants with congenital anomalies helps to define a subset of these infants who are more likely to utilise health care resources. This information is important for service commissioning.

9.3.4 Generalisability and limitations

This is the first population-based cohort study to investigate hospitalisation as an index of morbidity of infants with a wide group of congenital anomalies and rare diseases in the UK. The findings of this study are based on generally high-quality hospital administrative records of the

whole population of Wales (birth cohort 1999-2015) with a relatively small proportion of missing data on admission episodes (i.e. < 5%), and hence are representative of the Welsh population.

However, as health care systems (e.g. public vs. privately funded) and resources (e.g. inpatient and outpatients) vary significantly between geographical regions, these are likely to have an influence on the patterns of hospitalisation such as admission threshold and length of stay (Smith et al. 2015; Hasan et al. 2010; Novotny and Anderson 2008; Robbins and Webb 2006). Thus, the findings of this study can be considered as a useful reference rather than generalisable beyond the UK to other countries with different health care systems.

Finally, the analyses in the hospitalisation and mortality studies were based on anomaly groups according to the EUROCAT classification, subgroup analyses of individual anomalies particularly those related to genetic and chromosomal defects were not possible due to their rarity in prevalence and low occurrence of anomaly-related infant deaths. Even with 18 years of data, the absolute reported numbers of infants with specific anomalies to CARIS is relatively small. Therefore, the results are representative of the infants with anomalies but not necessarily of an individual anomaly.

9.4 Novelty of this research

There are several novel aspects of this study that make it different from the previous studies. First, this study focused on livebirth prevalence of all congenital anomalies reported in Wales (i.e. excluding stillbirths and termination of pregnancy). As congenital anomalies are the leading cause of infant morbidity and mortality, it is imperative to estimate their burden among the affected liveborn infants since health care resource planning and service commissioning are mainly based on disease burden on livebirths. Second, unlike most previous mortality and morbidity studies which focused on a specific anomaly, this study included infants who were affected by a wide range of congenital anomalies and rare diseases beyond the EUROCAT and CDC classifications of congenital anomalies, and thus was able to robustly assess and establish the full impact of these conditions on infant hospitalisation and mortality using relatively recent birth cohorts (1999-2015 and 1998-2016 respectively). Third, this is the first UK population-based cohort study to investigate the primary causes of hospitalisation and the main/ underlying causes of death of infants across different anomaly subgroups; the results of which advance our knowledge about how significantly particular subgroup of congenital anomalies contributes to infant hospitalisation and mortality in the UK. Fourth, this study is the first to investigate comprehensively the extent to which socio-demographic, maternal and clinical factors independently contribute to hospitalisation and mortality of infants with congenital anomalies overall; and whether the risk factors are different between infants with anomaly-specific admissions and infants with other-cause admissions. Thus, the findings advance our understanding on a wide range of anomaly-related prognostic risk factors and the possible mechanisms.

9.5 Recommendations for future studies

Several recommendations follow from the findings of the studies reported in this thesis.

1. Future research should aim to use big data with a national total population study design in order to have large enough numbers to investigate infant hospitalisation and mortality associated with individual anomalies. For example, BINOCAR (1985-2012) or the National Congenital Anomaly and Rare Disease (2013-present) are large research network databases, which collect data about congenital anomaly outcomes from all regional English congenital anomaly registries and can be linked to Hospital Episodes Statistics (HES) in England and mortality data from ONS. This approach can minimise heterogeneity due to variations in health care system and between anomaly subtypes, which has been a challenge in prognostic studies.

2. As the survival of infants with congenital anomalies has improved over time, an emerging higher number of infants with an anomaly will live beyond infancy and childhood. Future research is necessary to investigate the long-term patterns of hospitalisation and the contributing risk factors in order to provide a benchmark to monitor and improve outcomes of hospital care for children of all ages affected by specific anomalies. Such knowledge is essential for the planning of long-term healthcare resources and targeted interventions for children affected by specific congenital anomalies.

3. Future research should aim to assess the effects of wider clinical and institutional factors e.g. disease severity, other comorbidities, intervention exposure and access to inpatient/outpatient resources etc., which are potentially important determinants of the impact of congenital anomalies on child morbidity and mortality.

9.6 Conclusions

This research has robustly investigated and reaffirmed the significant impact of congenital anomalies and rare diseases on infant hospitalisation (as a proxy for morbidity) and mortality in Wales. Congenital anomalies remain an important public health concern due to their significant contribution to the total infant deaths and a greater utilisation of hospitalisation among the affected infants over time as demonstrated in this study. While it is not surprising to find that infants with congenital anomalies have significantly higher risks for hospitalisation and case fatality compared to infants without an anomaly, the findings from this study have made it abundantly clear that the congenital anomalies themselves and associated complications are a major cause of infant hospitalisation and mortality. In addition, preterm birth, low birthweight, maternal black ethnicity, younger or parous mothers, maternal smoking, infant sex, severe CHDs are significant risk factors for excess infant hospitalisation or mortality; while having surgery is a protective factor for infant mortality in the case of CHDs after adjusted for severity.

This information provides a better understanding of the likely patterns and causes of hospitalisation and mortality, and their contributing factors which can help support resource planning and optimise the quality of care delivered to affected infants aiming to improve their prognostic outcomes.

However, heterogeneity is the main limitation of this study. Generalisability of the analytical findings beyond the UK may be limited due to variations in anomaly definitions, health care systems, admission thresholds, neonatal practices and registration of extremely premature births over time and between countries. Further studies are necessary and should aim at using big data with a national total population study design in order to have sufficient numbers to investigate individual anomaly subtypes, as well as using standardised protocols, anomaly definitions, inclusion criteria and data collection methods to minimise heterogeneity.

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Appendices

1.1: European Surveillance of Congenital Anomalies (EUROCAT) subgroups of congenital anomalies. (EUROCAT 2013)

EUROCAT Subgroups	ICD10-BPA	ICD9-BPA	Comments	Excluded minor anomalies post-2005	Excluded minor anomalies pre-2005	Subgroup binary variable number (al)
All anomalies *	Q-chapter, D215, D821, D1810^, P350, P351, P371	74, 75, 27910, 2281^, 76076, 76280, 7710, 7711, 77121		Exclude all minor anomalies as specified in Guide 1.4, section 3.2	Exclude all minor anomalies as specified in Guide 1.2 (ICD9 and ICD10)	al1
Nervous system	Q00, Q01, Q02, Q03, Q04, Q05, Q06, Q07	740, 741, 742		Q0461, Q0782		al2
Neural Tube Defects	Q00, Q01, Q05	740, 741, 7420				al3
Anencephalus and similar	Q00	740				al4
Encephalocele	Q01	7420	Exclude if associated with anencephalus subgroup			al5
Spina Bifida	Q05	741	Exclude if associated with anencephalus or encephalocele subgroups			al6
Hydrocephalus	Q03	7423	Exclude hydranencephaly 74232. Exclude association with NTD subgroup			al7
Severe microcephaly	Q02	7421	Exclude association with NTD subgroup			al8
Arhinencephaly / holoprosencephaly	Q041, Q042	74226				al9
Eye	Q10-Q15	743		Q101-Q103, Q105, Q135	74365	al10
Anophthalmos / microphthalmos	Q110, Q111, Q112	7430, 7431				al11
Anophthalmos	Q110, Q111	7430				al12
Congenital cataract	Q120	74332				al13
Congenital glaucoma	Q150	74320				al14
Ear, face and neck	Q16, Q17, Q18	744		Q170-Q175, Q179, Q180-Q182, Q184-Q187, Q1880, Q189	74411, 74412, 7443, 74491	al15
Anotia	Q160	74401				al16

1.1 (continued): EUROCAT subgroups of congenital anomalies. (EUROCAT 2013)

EUROCAT Subgroups	ICD10-BPA	ICD9-BPA	Comments	Excluded minor anomalies post-2005	Excluded minor anomalies pre-2005	Subgroup binary variable number (al)
Congenital Heart Defects	Q20-Q26	745, 746, 7470-7474	Exclude PDA with GA <37 weeks Exclude peripheral pulmonary artery stenosis with GA < 37 weeks	Q2111, Q250 if GA <37 weeks, Q2541, Q256 if GA<37 weeks, Q261	Q250, 7470 if GA <37 weeks **	al17
Severe CHD	Q200, Q201, Q203, Q204, Q212, Q213, Q220, Q224, Q225, Q226, Q230, Q232, Q233, Q234, Q251, Q252, Q262	74500, 74510, 7452, 7453, 7456, 7461, 7462, 74600, 7463, 7465, 7466, 7467, 7471, 74720, 74742	ICD9-BPA has no code for HRH and double outlet right ventricle			al97
Common arterial truncus	Q200	74500				al18
Double outlet right ventricle	Q201	No code				al109
Transposition of great vessels	Q203	74510				al19
Single ventricle	Q204	7453				al20
VSD	Q210	7454				al21
ASD	Q211	7455		Q2111		al22
AVSD	Q212	7456				al23
Tetralogy of Fallot	Q213	7452				al24
Triscuspid atresia and stenosis	Q224	7461				al25
Ebstein's anomaly	Q225	7462				al26
Pulmonary valve stenosis	Q221	74601				al27
Pulmonary valve atresia	Q220	74600				al28
Aortic valve atresia/stenosis	Q230	7463	ICD9-BPA has no code for atresia			al29
Mitral valve anomalies	Q232, Q233	7465, 7466				al110
Hypoplastic left heart	Q234	7467				al30
Hypoplastic right heart	Q226	No code				al31
Coarctation of aorta	Q251	7471				al32
Aortic atresia / interrupted aortic arch	Q252	74720				al111
Total anomalous pulm venous return	Q262	74742				al33
PDA as only CHD in term infants (GA +37 weeks)	Q250	7470	Livebirths only			al100
Respiratory	Q300, Q32-Q34	7480, 7484, 74850, 74852, 74858, 7486, 7488	Exclude Q336	Q320, Q331	Q309, 74819	al34
Choanal atresia	Q300	7480				al35
Cystic adenomatous malf of lung	Q3380	No code				al36

1.1 (continued): EUROCAT subgroups of congenital anomalies. (EUROCAT 2013)

EUROCAT Subgroups	ICD10-BPA	ICD9-BPA	Comments	Excluded minor anomalies post-2005	Excluded minor anomalies pre-2005	Subgroup binary variable number (al)
Oro-facial clefts	Q35-Q37	7490, 7491, 7492	Exclude association with holoprosencephaly or anencephaly subgroups			al101
Cleft lip with or without cleft palate	Q36, Q37	7491, 7492	Exclude association with holoprosencephaly or anencephaly subgroups			al102
Cleft palate	Q35	7490	Exclude association with cleft lip subgroup. Exclude association with holoprosencephaly or anencephaly subgroups			al103
Digestive system	Q38-Q45, Q790	750, 751, 7566		Exclude Q381, Q382, Q3850, Q400, Q401, Q4021, Q430, Q4320, Q4381, Q4382	Q381, Q401, 7500, 7506	al40
Oesophageal atresia with or without trachea-oesophageal fistula	Q390-Q391	75030-75031				al41
Duodenal atresia or stenosis	Q410	75110	Exclude if also annular pancreas subgroup			al42
Atresia or stenosis of other parts of small intestine	Q411-Q418	75111-75112				al43
Ano-rectal atresia and stenosis	Q420-Q423	75121-75124				al44
Hirschsprung's disease	Q431	75130-75133				al45
Atresia of bile ducts	Q442	75165				al46
Annular pancreas	Q451	75172				al47
Diaphragmatic hernia	Q790	75661				al48
Abdominal wall defects	Q792, Q793, Q795	75671, 75670, 75679				al49
Gastroschisis	Q793	75671				al50
Omphalocele	Q792	75670				al51
Urinary	Q60-Q64, Q794	75261, 753, 75672		Q610, Q627, Q633		al52
Bilateral renal agenesis including Potter syndrome	Q601, Q606	75300	Exclude unilateral			al53
Multicystic renal dysplasia	Q6140, Q6141	75316				al54
Congenital hydronephrosis	Q620	75320				al55
Bladder exstrophy and / or epispadia	Q640, Q641	75261, 7535				al56
Posterior urethral valve and / or prune belly	Q6420, Q794	75360, 75672				al57

1.1 (continued): EUROCAT subgroups of congenital anomalies. (EUROCAT 2013)

EUROCAT Subgroups	ICD10-BPA	ICD9-BPA	Comments	Excluded minor anomalies post-2005	Excluded minor anomalies pre-2005	Subgroup binary variable number (al)
Genital	Q50-Q52, Q54-Q56	7520-7524, 75260, 75262, 7527-7529		Q523, Q525, Q527, Q5520, Q5521	Q540, 75260#	al58
Hypospadias	Q54	75260			Q540, 75260	al59
Indeterminate sex	Q56	7527				al60
Limb	Q65-Q74	7543-7548, 755		Q653-Q656, Q662-Q669, Q670-Q678, Q680, Q6810, Q6821, Q683-Q685, Q7400	75432, 75452, 75460, 75473, 75481, 75560	al61
Limb reduction defects	Q71-Q73	7552-7554				al62
Club foot – talipes equinovarus	Q660	75450				al66
Hip dislocation and / or dyspasia	Q650-Q652, Q6580, Q6581	75430				al67
Polydactyly	Q69	7550				al68
Syndactyly	Q70	7551				al69
Other anomalies / syndromes						
Skeletal dysplasias	Q7402, Q77, Q7800, Q782-Q788,	No code				al104
Craniosynostosis	Q750	75600				al75
Congenital constriction bands / amniotic band	Q7980	76280				al76
Situs inversus	Q893	7593				al79
Conjoined twins	Q894	7594				al80
Congenital skin disorders	Q80-Q82	7571, 7573		Q825, Q8280	Q825, Q8280, Q8281, 75731, 75738	al81
VATER/VACTERL	Q8726	759895				al112
Vascular disruption anomalies	Q0435, Q411, Q412, Q418, Q710, Q712, Q713, Q720, Q722, Q723, Q730, Q793, Q795, Q7980, Q7982, Q8706	No code				al113
Laterality anomalies	Q206, Q240, Q3381, Q890, Q893	No code				al114
Teratogenic syndromes with malformations	Q86, P350, P351, P371	No code				al82
Fetal alcohol syndrome	Q860	76076				al83
Valproate syndrome	Q8680	No code				al84
Maternal infections resulting in malformations	P350, P351, P371	7710, 7711, 77121				al86

1.1 (continued): EUROCAT subgroups of congenital anomalies. (EUROCAT 2013)

EUROCAT Subgroups	ICD10-BPA	ICD9-BPA	Comments	Excluded minor anomalies post-2005	Excluded minor anomalies pre-2005	Subgroup binary variable number (al)
Genetic syndromes + microdeletions	Q4471, Q6190, Q7484, Q751, Q754, Q7581, Q87, Q936, D821	75581, 75601, 75604, 7598, 27910	Exclude Associations and sequences Exclude Q8703, Q8704, Q8706, Q8708, Q8724, Q8726 Exclude 759801, 759844, 759895			al105
Chromosomal	Q90-Q92, Q93 , Q96-Q99	7580-7583, 7585-7589	Exclude microdeletions Q936			al88
Down syndrome	Q90	7580				al89
Patau syndrome / trisomy 13	Q914-Q917	7581				al90
Edwards syndrome / trisomy 18	Q910-Q913	7582				al91
Turner syndrome	Q96	75860, 75861, 75862, 75869				al92
Klinefelter syndrome	Q980-Q984	7587				al93

1.2: European Surveillance of Congenital Anomalies (EUROCAT) minor congenital anomalies. (EUROCAT 2013)

	Specified ICD10-BPA – if present
Head	
Aberrant scalp hair patterning	
Bony occipital spur	
Brachycephaly	
Compression facies	Q671
Depressions in skull	Q6740
Dolichocephaly	Q672
Dysmorphic face	Q189
Facial asymmetry	Q670
Flat occiput	
Frontal bossing / wide forehead	
Plagiocephaly – head asymmetry	Q673
Macrocephalus	Q753
Metopic ridge	
Metopic suture synostosis	
Other congenital deformities of skull, face and jaw	Q674
Third fontanel	

1.2 (continued): EUROCAT minor congenital anomalies. (EUROCAT 2013)

Eyes	
Blue sclera	Q135
Congenital ectropion	Q101
Congenital entropion	Q102
Crocodile tears	Q0782
Downward slanting palpebral fissures	
Dystopia canthorum	
Epicanthic folds	
Epicanthus inversus	
Exophthalmos	
Hypertelorism	Q752
Hypotelorism	
Other congenital malformations of eyelid	Q103
Short palpebral fissures	
Stenosis or stricture of lacrimal duct	Q105
Synophrys	Q1880
Upward slanting palpebral fissures	
Ears	
Absent tragus	
Accesorry auricle, preauricular appendage, tag or lobule	Q170
Asymmetric size	Q173
Auricular pit	
Bat ear, prominent ear	Q175
Double lobule	Q170
Lack of helical fold	Q173
Low set ears	Q174
Macrotia	Q171
Microtia	Q172
Narrow external auditory meatus	
Posterior angulation	Q173
Preauricular sinus or cyst	Q181
Primitive shape	Q173
Protuberant ears	Q173
Unspecified and minor malformation of ear	Q179
Nose	
Anomalies of philtrum	
Broad nasal root, anomaly of nasal root	
Deviation of nasal septum	Q6741
Dysmorphic nose	Q189
Notched alas	
Small nares	
Oral regions	
Aberrant frenula	
Alveolar crest	
Borderline small mandible/ minor micrognathia	
Disturbances in tooth eruption	
Enamel hypoplasia	

1.2 (continued): EUROCAT minor congenital anomalies. (EUROCAT 2013)

Eyes	
Blue sclera	Q135
Congenital ectropion	Q101
Congenital entropion	Q102
Crocodile tears	Q0782
Downward slanting palpebral fissures	
Dystopia canthorum	
Epicanthic folds	
Epicanthus inversus	
Exophthalmos	
Hypertelorism	Q752
Hypotelorism	
Other congenital malformations of eyelid	Q103
Short palpebral fissures	
Stenosis or stricture of lacrimal duct	Q105
Synophrys	Q1880
Upward slanting palpebral fissures	
Ears	
Absent tragus	
Accesorry auricle, preauricular appendage, tag or lobule	Q170
Asymmetric size	Q173
Auricular pit	
Bat ear, prominent ear	Q175
Double lobule	Q170
Lack of helical fold	Q173
Low set ears	Q174
Macrotia	Q171
Microtia	Q172
Narrow external auditory meatus	
Posterior angulation	Q173
Preauricular sinus or cyst	Q181
Primitive shape	Q173
Protuberant ears	Q173
Unspecified and minor malformation of ear	Q179
Nose	
Anomalies of philtrum	
Broad nasal root, anomaly of nasal root	
Deviation of nasal septum	Q6741
Dysmorphic nose	Q189
Notched alas	
Small nares	
Oral regions	
Aberrant frenula	
Alveolar crest	
Borderline small mandible/ minor micrognathia	
Disturbances in tooth eruption	
Enamel hypoplasia	

1.2 (continued): EUROCAT minor congenital anomalies. (EUROCAT 2013)

Glossoptosis	
High arched palate	Q3850
Macrocheilia	Q186
Macroglossia	Q382
Macrostomia	Q184
Malformed teeth	
Microcheilia	Q187
Microstomia	Q185
Neonatal teeth	
Ranula	
Retrognathia	Q674
Thin lips	
Tongue tie or cyst of tongue	Q381
Neck	
Congenital malformation of face and neck, unspecified	Q189
Mild webbed neck	
Other branchial cleft malformations	Q182
Preauricular sinus or cyst	Q181
Sinus, fistula or cyst of branchial cleft	Q180
Torticollis	Q680
Hands	
Accessorry carpal bones	Q7400
Arachnodactyly	
Clinodactyly (5th finger)	Q6810
Duplication of thumbnail	
Enlarged or hypertrophic nails	Q845
Overlapping fingers	
Short fingers (4. 5. th finger)	
Single/abnormal palmar crease	Q8280
Small fingers	
Unusual dermatoglyphics	
Feet -Limb	
Clicking hip, subluxation or unstable hip	Q653-Q656
Clubfoot of postural origin - other cong deformities of feet	Q668
Congenital deformity of feet, unspecified	Q669
Congenital pes planus	Q665
Enlarged or hypertrophic nails	Q845
Gap between toes (1st-2nd)	
Hallux varus – other congenital varus deformities of feet	Q663
Metatarsus varus – other congenital valgus deformities of feet	Q666
Metatarsus varus or metatarsus adductus	Q662
Overlapping toes	
Pes cavus	Q667
Prominent calcaneus	
Recessed toes (4th, 5th)	
Short great toe	
Syndactyly (2nd-3rd toes)	

1.2 (continued): EUROCAT minor congenital anomalies. (EUROCAT 2013)

Talipes or pes calcaneovalgus	Q664
Skin	
Accessory nipples	Q833
Angioma	
Cafe-au-lait spot	
Depigmented spot	
Hemangioma if no treatment is required	
Heterochromia of hair	
Hypoplasia of toe nails	
Lymphangioma	
Mongoloid spot (whites)	Q8252
Neavus flammeus	Q8250
Persistent lanugo	
Pigmented naevus – congenital non-neoplastic naevus	Q825
Strawberry naevus	Q8251
Unusual placement of nipples/ wide spaced nipples	
Skeletal	
Abortive 12.th rib	
Absence of rib	Q7660
Accessory rib	Q7662
Cervical rib	Q765
Congenital bowing of femur	Q683
Congenital bowing of fibula and tibia	Q684
Congenital bowing of long bones of leg, unspecified	Q685
Congenital bowing of upper limb	
Congenital deformity of spine	Q675
Congenital lordosis, postural	Q7643
Cubitus valgus	
Depressed sternum	Q676
Fused rib, single	
Genu recurvatum	Q6821
Genua valgum	
Genua varum	
Prominent sternum	Q677
Sacral dimple	
Shieldlike chest, other congenital deformities of chest	Q678
Spina bifida occulta	Q760
Sternum bifidum	Q7671
Brain	
Anomalies of septum pellucidum	
Arachnoid cyst	
Choroid plexus cyst	
Periventricular leukomalacia	
Single congenital cerebral cyst	Q0461
Cardiovascular	
Absence or hypoplasia of umbilical artery, single umbilical artery	Q270
Functional or unspecified cardiac murmur	

1.2 (continued): EUROCAT minor congenital anomalies. (EUROCAT 2013)

Patent ductus arteriosus if GA < 37 weeks	Q250 if GA <37 weeks
Patent or persistent foramen ovale	Q2111
Peripheral pulmonary artery stenosis	Q256 if GA < 37 weeks
Persistent left superior vena cava	Q261
Persistent right aortic arch	Q2541
Pulmonary	
Accessory lobe of lung	Q331
Azygos lobe of lung	Q3310
Congenital laryngeal stridor	Q314
Hyperplasia of thymus	
Laryngomalacia	Q314, Q315
Pleural effusion	
Thymus involution	
Tracheomalacia	Q320
Vocal cord palsy	
Gastro-intestinal	
Abdominal cyst	
Anterior anus	
Congenital cholestasis	
Congenital mesenteric cyst	
Diastasis recti	
Functional gastro-intestinal disorders	Q4021, Q4320, Q4381, Q4382
Hiatus hernia	Q401
Inguinal hernia	
Meckel's diverticulum	Q430
Plica of anus	
Pyloric stenosis	Q400
Transient choledochal cyst	
Umbilical hernia	
Renal	
Hydronephrosis with a pelvis dilatation less than 10 mm	
Hyperplastic and giant kidney	Q633
Single renal cyst	Q610
Vesico-ureteral-renal reflux	Q627
External genitals	
Bifid scrotum	Q5521
Congenital malformation of vulva	Q527
Curvature of penis	
Cysts of vulva	
Deficient or hooded foreskin	
Developmental ovarian cyst	
Enlarged clitoris	
Fusion of labia	Q525
Hydrocele of testis	
Hymen imperforatum	Q523
Hypertrophia of hymen	
Hypoplasia of penis	

1.2 (continued): EUROCAT minor congenital anomalies. (EUROCAT 2013)

Phymosis	
Prominent labia minora	
Retractile testis	Q5520
Transient ovarian cyst	
Undescended testicle	Q53
Unspecified ectopic testis	
Vaginal skin tag	
Other	
Congenital malformation, unspecified	Q899
Chromosomal	
Balanced translocations or inversions in normal individuals	Q950, Q951

1.3: Congenital anomalies: classification of groups and their descriptions. (Feldkamp et al. 2017)

Group	
Aetiology	
Known	Genetic: a known genetic aetiology e.g. abnormal chromosomal number (such as Trisomy), structure (insertion, deletion such as del 22q) or a single gene mutation (such as Noonan syndrome) and expression (such as methylation-related Beckwith-Wiedemann syndrome). Environmental or teratogenic: a known teratogen e.g. medication (such as valproic acid), diabetes. Twinning: abnormalities in twinning included either acardiac or conjoined twins.
Unknown	No identifiable cause.
Morphology	
Isolated	A single birth defect (e.g. spina bifida).
Multiple	Two or more birth defects. (e.g. spina bifida and Trisomy 21).
Minor	Defect that is not clinically significant.
None	No defects were detected.
Pathogenesis	
Sequence	Pattern of related abnormalities due to a primary abnormality. A sequence can occur as an isolated anomaly (e.g. spina bifida sequence) or as multiple defects (e.g. spina bifida sequence with cleft lip).
Developmental field defect	Pattern of abnormalities due to abnormal development of an embryonic unit in early embryogenesis. Aetiology is typically heterogeneous e.g. DiGeorge anomaly is associated with abnormal development of neural crest cells leading to multiple structural anomalies potentially caused by different genetic abnormalities (such as 22q11 deletion) or environmental factors (such as retinoic acid).
Pattern	Non-random occurrence or pattern of multiple abnormalities without a known cause, e.g. VATER/VACTERL recurrent and variable pattern of anomalies.

1.4: Recommendations summary from NICE 2008 and PHE 2015 guidelines on antenatal screening on fetal anomalies for uncomplicated pregnancies. (NICE 2008; PHE 2015a)

Prenatal screening test	Recommended time (in gestational week) for test during pregnancy	Limitations
Down screening **Combined test for Down, Edward and Patau syndromes:** nuchal translucency (NT), free beta-human chorionic gonadotropin (free b-HCG), pregnancy-associated plasma protein-A (PAPP-A), together with maternal age and the gestation of the pregnancy **Triple or quadruple blood test (Second trimester):** AFP, uE3, free b-hCG (or total hCG), and inhibin-A together with maternal age (screening for Down syndrome for late bookers or when NT is not possible to measure) (As well as information about screen -positive and -negative result pathways)	Usually by 13 weeks 6 day, i.e. end of the first trimester, although provision can be made to allow later screening by 20 weeks 0 days for late bookers. Between 11 weeks 0 day and 13 weeks 6 days. Between 15 weeks 0 days and 20 weeks 0 days. (less effective than the combined test)	Screening does not provide a definitive diagnosis. NT may not possible to measure due to fetal position or raised maternal BMI.
Diagnostic tests: chorionic villus sampling or amniocentesis	Chorionic villus sampling: between 11th and 14th week (may be later if necessary) of pregnancy. Amniocentesis: between 15th and 20th weeks (may be later if necessary) of pregnancy. Tests if either the combined test or the quadruple blood test shows a higher risk result.	Relatively more invasive tests
Ultrasound for structural anomalies of fetus (as well as information about reproductive choice) Note: for NTDs, alpha-fetoprotein testing is not required when ultrasound is performed.	Between 18 weeks 0 days and 20 weeks 6 days – aims to identify abnormalities, which indicate that the baby may die shortly after birth, to plan delivery in an appropriate centre and/or to optimise treatment before or after the baby is born.	Detection rates and sensitivity vary by type of anomaly, maternal BMI and fetal position.

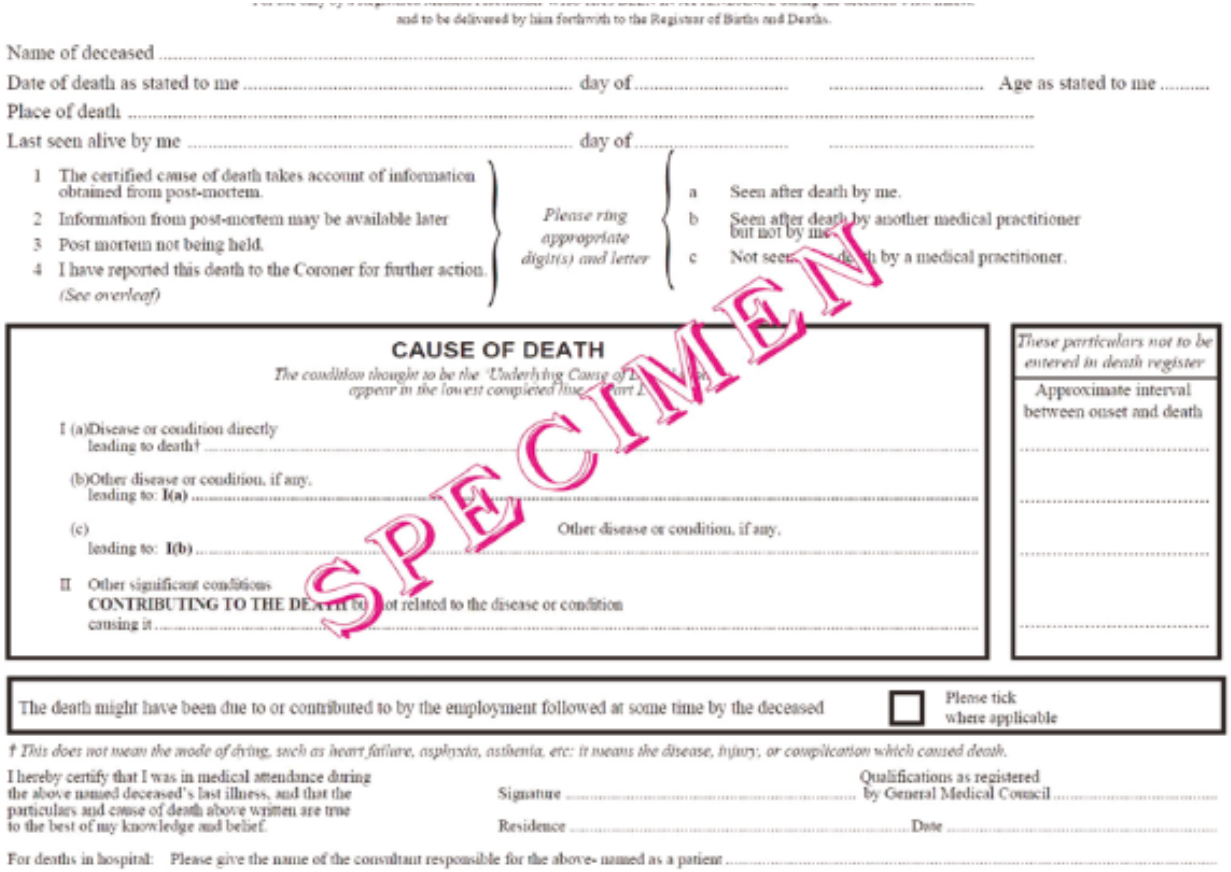
1.5: Detection rates target and achievement of cases prenatally diagnosed for the 11 Fetal Anomaly Screening Programme (FASP) congenital anomalies.[1]

Data from four English BINOCAR registers in 2012 (coverage: 28% of births in England): CAROBB, EMSYCAR, SWCAR and WANDA (Springett et al. 2014).

Anomaly[2]	Total cases	All cases prenatal diagnosis		FASP target detect-ion rates (%)	Achieve-ment of FASP target
		No. of cases	Percentage of total cases (95% CI)		
Anencephaly	98	95	96.9 (91.4-99.0)	98	Not met
Open spina bifida	118	108	91.5 (85.1-95.3)	90	Possibly
Cleft lip	142	106	74.6 (66.9-81.1)	75	Not met
Serious cardiac anomalies[3]	299	147	49.2 (43.5-54.8)	50	Not met
Diaphragmatic hernia	63	46	73.0 (61.0-82.4)	60	Exceeded
Gastroschisis	84	77	91.7 (83.8-95.9)	98	Not met
Exomphalos	78	72	92.3 (84.2-96.4)	80	Exceeded
Bilateral renal agenesis	28	25	89.3 (72.8-96.3)	84	Exceeded
Lethal skeletal dysplasia	18	17	94.4 (74.2-99.0)	60	Exceeded
Patau syndrome (Trisomy 13)	52	43	82.7 (70.3-90.6)	95	Not met
Edward syndrome (Trisomy 18)	137	105	76.6 (68.9-82.9)	95	Not met

[1]The overall detection rates for ultrasound screening are 83% for abnormalities incompatible with life, 50% for serious abnormalities where survival is possible, and 16% for those requiring immediate care after birth (NICE 2008; Bryant et al. 2007). [2]Conditions screened for as a minimum from 2011 in the NHS in England. [3]Hypoplastic left heart syndrome, tetralogy of Fallot, transposition of great arteries and atrioventricular septal defect.

1.6: UK Standard death certificate. (ONS 2020a)



and to be delivered by him forthwith to the Registrar of Births and Deaths.

Name of deceased .....

Date of death as stated to me ..... day of .... Age as stated to me .....

Place of death .....

Last seen alive by me ..... day of ....

1 The certified cause of death takes account of information obtained from post-mortem.
2 Information from post-mortem may be available later
3 Post mortem not being held.
4 I have reported this death to the Coroner for further action.
(See overleaf)

Please ring appropriate digit(s) and letter

a Seen after death by me.
b Seen after death by another medical practitioner but not by me.
c Not seen after death by a medical practitioner.

CAUSE OF DEATH

The condition thought to be the 'Underlying Cause of Death' should appear in the lowest completed line of Part I.

I (a) Disease or condition directly leading to death† .....

(b) Other disease or condition, if any, leading to: **I(a)** .....

(c) Other disease or condition, if any, leading to: **I(b)** .....

II Other significant conditions **CONTRIBUTING TO THE DEATH** but not related to the disease or condition causing it .....

These particulars not to be entered in death register

Approximate interval between onset and death

.....

.....

.....

.....

SPECIMEN

The death might have been due to or contributed to by the employment followed at some time by the deceased ☐ Please tick where applicable

† This does not mean the mode of dying, such as heart failure, asphyxia, asthenia, etc: it means the disease, injury, or complication which caused death.

I hereby certify that I was in medical attendance during the above named deceased's last illness, and that the particulars and cause of death above written are true to the best of my knowledge and belief.

Signature ..... Qualifications as registered by General Medical Council .....

Residence ..... Date .....

For deaths in hospital: Please give the name of the consultant responsible for the above- named as a patient .....

1.7: UK Neonatal death certificate. (ONS 2020a)

MED B 1 310481

Registrar to enter No. of Death Entry

BIRTHS AND DEATHS REGISTRATION ACT 1953

(Form prescribed by the Registration of Births and Deaths Regulations 1987)

MEDICAL CERTIFICATE OF CAUSE OF DEATH OF LIVE-BORN CHILD DYING WITHIN THE FIRST TWENTY-EIGHT DAYS OF LIFE

For use only by a Registered Medical Practitioner WHO HAS BEEN IN ATTENDANCE during the deceased's last illness, and to be delivered by him forthwith to the Registrar of Births and Deaths.

Name of child.....

Date of death.....day of.....Sex.....

Age at death.....days (completed period of 24 hours).....hours

Place of death.....

Place of birth.....

Last seen alive by me.....day of.....

1 The certified cause of death has been confirmed by post-mortem
2 Information from post-mortem may be available later.
3 Post-mortem not being held.
4 I have reported this death to the Coroner for further action. *[See overleaf]*

Please ring appropriate digit and letter.

a Seen after death by me.
b Seen after death by another medical practitioner but not by me.
c Not seen after death by a medical practitioner.

CAUSE OF DEATH

SPECIMEN

a. Main diseases or conditions in infant.....

b. Other diseases or conditions in infant.....

c. Main maternal diseases or conditions affecting infant.....

d. Other maternal diseases or conditions affecting infant.....

e. Other relevant causes.....

I hereby certify that I was in medical attendance during the above named deceased's last illness, and that the particulars and cause of death above written are true to the best of my knowledge and belief.

Signature.....

Address.....

Qualifications as registered by General Medical Council.....

Date.....

For deaths in hospital: Please give the name of the consultant responsible for the above-named as a patient.....

1.8: ICD-9/10 codes to identify the underlying and contributory causes of death. (ONS 2011)

ICD-9 chapter group for coding based solely on death certificates	ICD-10 chapter group for coding based solely on death certificates
Congenital anomalies: 740-759.	Congenital anomalies: Q00-Q99.
Respiratory: 460-519.	Respiratory: J00-J99.
Endocrine/Metabolic/Genitourinary/ Pregnancy: 240-279, 520-676.	Endocrine/Metabolic/Genitourinary/ Pregnancy: E00-E90, K00-K93, N00-N99, O00-O99.
Symptoms/Cardiovascular: 390-459, 780-799.	Symptoms/Cardiovascular: I00-I99, R00-R99.
Infections: 001-139.	Infections: A00-B99.
Cancer/blood: 140-289.	Cancer/blood: C00-D89.
Mental health: 290-319.	Mental health: F00-F99.
Neurological/Perinatal/Sensory/Skin/ Musculoskeletal: 320-389, 680-709, 710-739, 760-779.	Neurological/Perinatal/Sensory/Skin/ Musculoskeletal: G00-G99, H00-H95, L00-L99, M00-M99, P00-P96.

1.9: Office for National Statistics (ONS) classification of neonatal deaths and associated ICD-10 codes, 2014 onwards: England and Wales. (ONS 2011)

Group	Description	ICD-10 codes
1	Congenital anomalies	Main or other infant conditions
		D550–D589, D610, D640, D66–D682, D691–D694, D70–D721, D740, D750, D760–D761, D800–D899, E700–E859, E880–E889, G120–G129, G318, G600–G609, G700–G719, G800–G809, G900–G909, I340–I379, I420–I425, I440–I459, K740–K746, Q000–Q079, Q200–Q239, Q242–Q249, Q251–Q269, Q271–Q289, Q310–Q313, Q315, Q318–Q319, Q320–Q349, Q382–Q459, Q600–Q609, Q610–Q611, Q613–Q619, Q620–Q639, Q641–Q649, Q673–Q676, Q743, Q750–Q759, Q761–Q799, Q800–Q819, Q850–Q939, Q960–Q999
		Main or other maternal conditions:
		Q048, Q249, Q777, Q999
2	Antepartum infections	Main or other infant conditions:
		A500–A509, P002, P027, P230–P239, P350–P359, P370–P379
		Main or other maternal conditions:
		O353 A500-A509, P002, P027, P230-P239, P350-P359
3	Immaturity related conditions	Main or other infant conditions
		P010–P011, P018, P070–P073, P220–P229, P250–P258, P270–P279, P280-P285, P288-P289, P520–P523, P578, P590, P77
		Main or other maternal conditions:
		P010-P011, P018, P070-P073, P220-P229, P250-P258, P270-P279, P280-P285, P288-P289, P520-P523, P77
4	Asphyxia, anoxia or trauma (intrapartum)	Main or other infant conditions:
		P000, P016–P017, P018, P020–P021, P022, P024–P026, P030–P039, P050–P059, P080–P082, P100–P159, P200–P219, P240–P241, P249, P292, P524,P525–P529, P90, P910–P919, Z352
		Main or other maternal conditions:
		P000, P016-P017, P018, P020, P021, P022, P024, P036, P038, P051, P059, Z352, Z369
5	External conditions	Main or other infant conditions:
		E40–E441, E46, J690, P242–P248, P800–P809, P830–P831, P833–P839, P920–P929, U509, V01–Y98
6	Infections	Main or other infant conditions:
		A000–A499, A510–B99, E321, G000–G09, H650–H669, H700–H709, I300–I309, I330–I339, J00–J069, J09, J100–J189, J200–J22, J36, J370–J371, J47, J850–J869, K350–K359, K610–K614, K650–K659, N111, N12, N136, N300, N390, P360–P369, P38, P390–P399
7	Other specific conditions	Main or other infant conditions:
		C000–C97, D100–D489, D600–D609, D684, E000–E320, E322–E349, P005–P006, P023, P028–P029, P293, P500–P519, P530–P549, P550–P570, P579, P580–P589, P591–P599, P60–P611, P613–P619, P700–P749, P760–P769, P780–P789, P819, P832, P93, P961–P962
9	Sudden infant deaths	Main or other infant conditions:

1.9 (continued): ONS classification of neonatal deaths and associated ICD-10 codes, 2014 onwards: England and Wales. (ONS 2011)

		R95-R99
0	Other conditions	All other codes

Source: Office for National Statistics

3.1: Search strategies and terms details for the systematic reviews (Chapters 3 and 4).

PubMed Searches (Date limit: 1.1.1990 to 31.8.2020)
Mesh terms
Search (((neural tube defect* OR congenital brain anomal* OR congenital brain malformation* OR congenital brain abnormal* OR congenital spinal anomal* OR congenital spinal malformation* OR congenital spinal abnormal* OR congenital central nervous system anomal* OR congenital central nervous system malformation* OR congenital central nervous system abnormal* OR spina bifida* OR myelomeningocele* OR meningomyelocele* OR meningocele* OR encephalocele*[MeSH Terms])) AND (newborn* OR birth* OR neonat* OR infan*[MeSH Terms])) AND (mortality OR death* OR survival*[MeSH Terms]) Filters: Publication date from 1990/01/01; Humans

Ovid/ Embase (Date limit: 1.1.1990 to 31.8.2020)	
Stage	Multi-field Search: All fields, advanced
2	limit 3 to (human and yr="1990 -Current")
1	((neural tube defect* or congenital brain anomal* or congenital brain malformation* or congenital brain abnormal* or congenital spinal anomal* or congenital spinal malformation* or congenital spinal abnormal* or congenital central nervous system anomal* or congenital central nervous system malformation* or congenital central nervous system abnormal* or spina bifida* or myelomeningocele* or meningomyelocele* or meningocele* or encephalocele*) and (newborn* or birth* or neonat* or infan*) and (mortality or death* or survival*)).af.

Web of Science Core collection (Limit Time span: 1990-2020)	
Stage	Basic search: Topic
1	(neural tube defect* OR congenital brain anomal* OR congenital brain malformation* OR congenital brain abnormal* OR congenital spinal anomal* OR congenital spinal malformation* OR congenital spinal abnormal* OR congenital central nervous system anomal* OR congenital central nervous system malformation* OR congenital central nervous system abnormal* OR spina bifida* OR myelomeningocele* OR meningomyelocele* OR meningocele* OR encephalocele*) *AND* **TOPIC:** (newborn* OR birth* OR neonat* OR infan*) *AND* **TOPIC:** (mortality OR death* OR survival*)

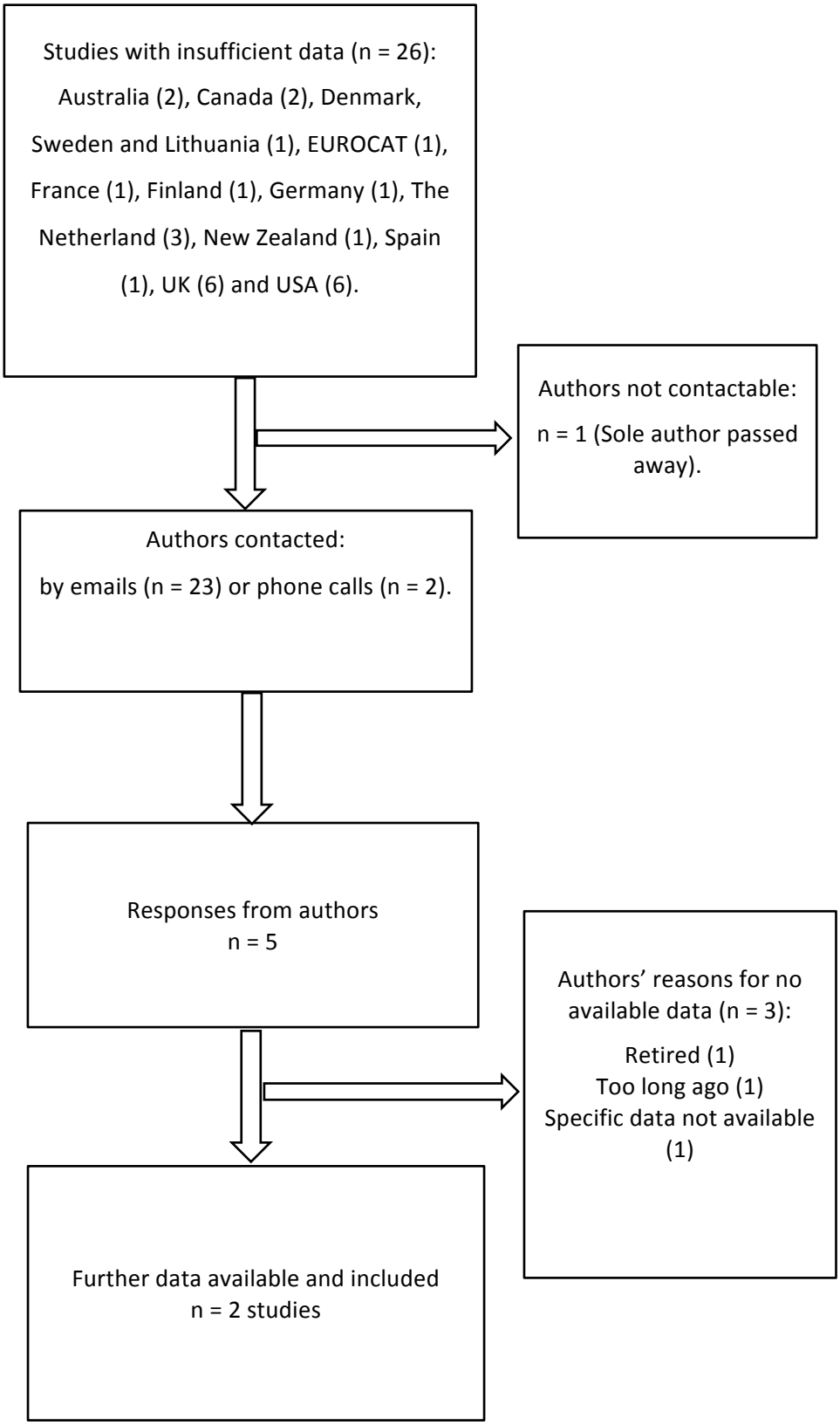
CINAHL (Published date: January 1990 to August 2020)	
Stage	Search mode: Boolean/ Phrase. All text
1	TX (neural tube defect* OR congenital brain anomal* OR congenital brain malformation* OR congenital brain abnormal* OR congenital spinal anomal* OR congenital spinal malformation* OR congenital spinal abnormal* OR congenital central nervous system anomal* OR congenital central nervous system malformation* OR congenital central nervous system abnormal* OR spina bifida* OR myelomeningocele* OR meningomyelocele* OR meningocele* OR encephalocele*) AND TX (newborn* OR birth* OR neonat* OR infan*) AND TX (mortality OR death* OR survival*)

3.1 (continued): Search strategies and terms details for the systematic reviews (Chapters 3 and 4).

Scopus (Limit published 1990 to present)	
Stage	Article title, abstract, keywords
1	TITLE-ABS-KEY ((neural tube defect OR spina bifida OR encephalocele OR myelomeningocele OR meningomyelocele OR meningocele OR encephalocele) AND (infant OR newborn OR neonatal) AND (mortality OR survival OR death)) AND PUBYEAR > 1989

Cochrane Library (Limit published 1990 to 2020)	
Stage	MeSH terms and search manager
1	MeSH descriptor: [Neural Tube Defects] explode all trees
2	MeSH descriptor: [Infant Mortality] explode all trees
3	#1 and #2

3.2: Summary of response from authors.



3.3: Meta-analyses of Observational Studies in Epidemiology (MOOSE) Checklist. (Stroup et al. 2000)

Infant mortality associated with spina bifida: A systematic review and meta-analysis.

Item No	Recommendation	Reported (Yes/No)
Reporting of background should include		
1	Problem definition	Y
2	Hypothesis statement	Y
3	Description of study outcome(s)	Y
4	Type of exposure or intervention used	Y
5	Type of study designs used	Y
6	Study population	Y
Reporting of search strategy should include		
7	Qualifications of searchers (eg, librarians and investigators)	Y
8	Search strategy, including time period included in the synthesis and key words	Y
9	Effort to include all available studies, including contact with authors	Y
10	Databases and registries searched	Y
11	Search software used, name and version, including special features used (eg, explosion)	Y
12	Use of hand searching (eg, reference lists of obtained articles)	Y
13	List of citations located and those excluded, including justification	Y
14	Method of addressing articles published in languages other than English	Y
15	Method of handling abstracts and unpublished studies	Y
16	Description of any contact with authors	Y
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	Y
18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	Y
19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	Y
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	Y
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	Y
22	Assessment of heterogeneity	Y
23	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	Y
24	Provision of appropriate tables and graphics	Y

3.3 (continued): Meta-analyses of Observational Studies in Epidemiology (MOOSE) Checklist. (Stroup et al. 2000)

Infant mortality associated with spina bifida: A systematic review and meta-analysis.

Reporting of results should include		
25	Graphic summarizing individual study estimates and overall estimate	Y
26	Table giving descriptive information for each study included	Y
27	Results of sensitivity testing (eg, subgroup analysis)	Y
28	Indication of statistical uncertainty of findings	Y

Reporting of discussion should include		
29	Quantitative assessment of bias (eg, publication bias)	Y
30	Justification for exclusion (eg, exclusion of non-English language citations)	Y
31	Assessment of quality of included studies	Y
Reporting of conclusions should include		
32	Consideration of alternative explanations for observed results	Y
33	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	Y
34	Guidelines for future research	Y
35	Disclosure of funding source	Y

4.1: Meta-analyses of Observational Studies in Epidemiology (MOOSE) Checklist. (Stroup et al. 2000)

Infant mortality associated with encephalocele: A systematic review

Item No	Recommendation	Reported (Yes/No)
Reporting of background should include		
1	Problem definition	Y
2	Hypothesis statement	Y
3	Description of study outcome(s)	Y
4	Type of exposure or intervention used	Y
5	Type of study designs used	Y
6	Study population	Y
Reporting of search strategy should include		
7	Qualifications of searchers (eg, librarians and investigators)	Y
8	Search strategy, including time period included in the synthesis and key words	Y
9	Effort to include all available studies, including contact with authors	Y
10	Databases and registries searched	Y
11	Search software used, name and version, including special features used (eg, explosion)	Y
12	Use of hand searching (eg, reference lists of obtained articles)	Y
13	List of citations located and those excluded, including justification	Y
14	Method of addressing articles published in languages other than English	Y
15	Method of handling abstracts and unpublished studies	Y
16	Description of any contact with authors	Y
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	Y
18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	Y
19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	Y
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	Y
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	Y
22	Assessment of heterogeneity	Y
23	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	Y
24	Provision of appropriate tables and graphics	Y

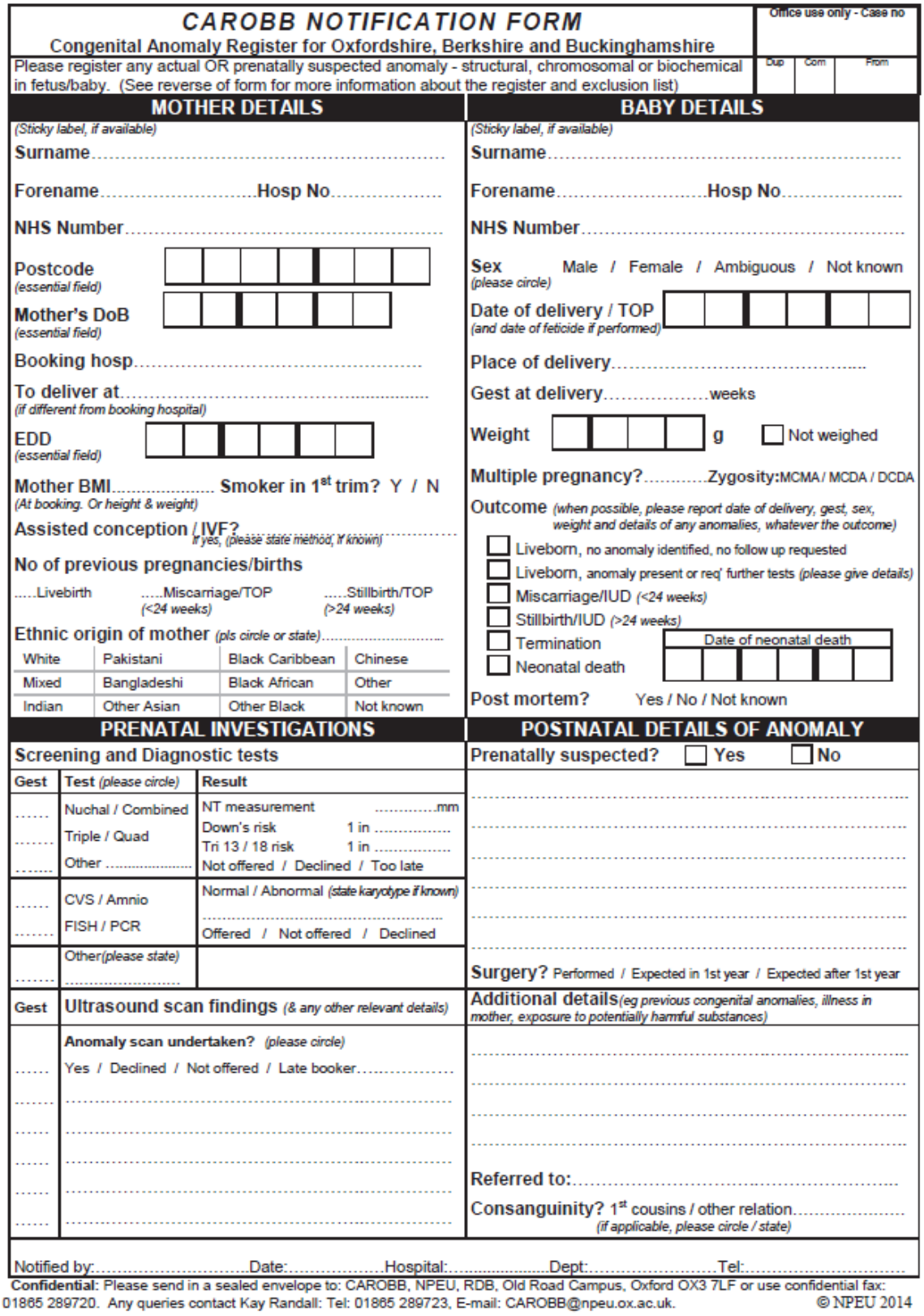
4.1 (continued): Meta-analyses of Observational Studies in Epidemiology (MOOSE) Checklist. (Stroup et al. 2000)

Infant mortality associated with encephalocele: A systematic review

Reporting of results should include		
25	Graphic summarizing individual study estimates and overall estimate	Y
26	Table giving descriptive information for each study included	Y
27	Results of sensitivity testing (eg, subgroup analysis)	Y
28	Indication of statistical uncertainty of findings	Y

Reporting of discussion should include		
29	Quantitative assessment of bias (eg, publication bias)	Y
30	Justification for exclusion (eg, exclusion of non-English language citations)	Y
31	Assessment of quality of included studies	Y
Reporting of conclusions should include		
32	Consideration of alternative explanations for observed results	Y
33	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	Y
34	Guidelines for future research	Y
35	Disclosure of funding source	Y

5.1: Congenital Anomalies Notification Form (Congenital Anomaly Register for Oxfordshire, Berkshire and Buckinghamshire, CAROBB). (CARIS 2020a)



CAROBB NOTIFICATION FORM

Congenital Anomaly Register for Oxfordshire, Berkshire and Buckinghamshire

Office use only - Case no | Dup | Com | From

Please register any actual OR prenatally suspected anomaly - structural, chromosomal or biochemical in fetus/baby. (See reverse of form for more information about the register and exclusion list)

MOTHER DETAILS

(Sticky label, if available)

Surname.....

Forename.....Hosp No.....

NHS Number.....

Postcode (essential field)

Mother's DoB (essential field)

Booking hosp.....

To deliver at..... (if different from booking hospital)

EDD (essential field)

Mother BMI..... Smoker in 1st trim? Y / N (At booking. Or height & weight)

Assisted conception / IVF? If yes, (please state method, if known)

No of previous pregnancies/births

.....Livebirth .....Miscarriage/TOP (<24 weeks) .....Stillbirth/TOP (>24 weeks)

Ethnic origin of mother (pls circle or state).....

White	Pakistani	Black Caribbean	Chinese
Mixed	Bangladeshi	Black African	Other
Indian	Other Asian	Other Black	Not known

BABY DETAILS

(Sticky label, if available)

Surname.....

Forename.....Hosp No.....

NHS Number.....

Sex Male / Female / Ambiguous / Not known (please circle)

Date of delivery / TOP (and date of feticide if performed)

Place of delivery.....

Gest at delivery.....weeks

Weight g ☐ Not weighed

Multiple pregnancy?.....Zygosity: MCMA / MCDA / DCDA

Outcome (when possible, please report date of delivery, gest, sex, weight and details of any anomalies, whatever the outcome)

☐ Liveborn, no anomaly identified, no follow up requested
☐ Liveborn, anomaly present or req' further tests (please give details)
☐ Miscarriage/IUD (<24 weeks)
☐ Stillbirth/IUD (>24 weeks)
☐ Termination
☐ Neonatal death

Date of neonatal death

Post mortem? Yes / No / Not known

PRENATAL INVESTIGATIONS

Screening and Diagnostic tests

Gest	Test (please circle)	Result
.....	Nuchal / Combined	NT measurement .....mm
.....	Triple / Quad	Down's risk 1 in .....
.....	Other	Tri 13 / 18 risk 1 in .....
		Not offered / Declined / Too late
.....	CVS / Amnio	Normal / Abnormal (state karyotype if known)
.....	FISH / PCR	.....
		Offered / Not offered / Declined
.....	Other (please state)	

POSTNATAL DETAILS OF ANOMALY

Prenatally suspected? ☐ Yes ☐ No

.....

.....

.....

.....

.....

.....

Surgery? Performed / Expected in 1st year / Expected after 1st year

Gest	Ultrasound scan findings (& any other relevant details)
	Anomaly scan undertaken? (please circle)
.....	Yes / Declined / Not offered / Late booker.....
.....	.....
.....	.....
.....	.....
.....	.....
.....	.....

Additional details (eg previous congenital anomalies, illness in mother, exposure to potentially harmful substances)

.....

.....

.....

.....

Referred to:.....

Consanguinity? 1st cousins / other relation..... (if applicable, please circle / state)

Notified by:.....Date:.....Hospital:.....Dept:.....Tel:.....

Confidential: Please send in a sealed envelope to: CAROBB, NPEU, RDB, Old Road Campus, Oxford OX3 7LF or use confidential fax: 01865 289720. Any queries contact Kay Randall: Tel: 01865 289723, E-mail: CAROBB@npeu.ox.ac.uk. © NPEU 2014

5.1 (continued): Congenital Anomalies Notification Form (CAROBB). (CARIS 2020a)

Congenital Anomaly Register for Oxfordshire, Berkshire and Buckinghamshire (CAROBB)

Please complete the form overleaf as fully as possible, registering any anomalies found at whatever stage you become aware of them in the pregnancy/postnatal period.

Uses of the register:

- Audit for prenatal diagnosis
- Evaluation and monitoring of new invasive and non invasive prenatal tests
- Evaluation of new screening programmes
- Provision of data for health care policies and planning
- Provision of data for the investigation of cluster of abnormalities
- Investigation of putative teratogens
- Research on aetiology and natural history of particular malformations
- Improving ascertainment for surveillance by the British Isles Network of Congenital Anomaly Registers (BINOCAR).

Congenital anomalies exclusion list
It is not necessary to report any of the following conditions to us POSTNATALLY, unless there was a prenatal suspicion of an anomaly.

- Spina bifida occulta uncomplicated
- Phymosis
- Stenosis or stricture of lacrimal duct
- Minor skin anomalies less than $4cm^2$: skin tag, naevus, angioma, haemangioma, glomus tumor, lymphangioma, birth mark
- Minor anomaly of auricle
- Clicking hip
- Minor anomaly of face or nose
- Minor anomaly of nipple, accessory or ectopic nipple
- Postural clubfoot
- Minor anomalies of the foot: hallux valgus/varus, "orteil en marteau", metatarus valgus/adductus
- Postural talipes calcaneovalgus or pes calcaneovalgus
- Congenital umbilical hernia, inguinal or para umbilical
- Functional or unspecified cardiac murmur
- Absence or hypoplasia of umbilical artery
- Congenital hydrocele or hydrocele of testis

If in doubt, report to us, we will feed back any inappropriate reporting

Confidentiality and data protection

All information held on the register is strictly confidential. Data are stored in a secure environment at the National Perinatal Epidemiology Unit, University of Oxford (data protection registration number: Z575783X). Any research undertaken is subject to ethical approval. The register holds Confidentiality Advisory Group (CAG) approval and NHS IG Toolkit approval (submission number: 8J017)

Confidential: Please fax or send in a sealed envelope to:

Confidential fax: 01865 289720

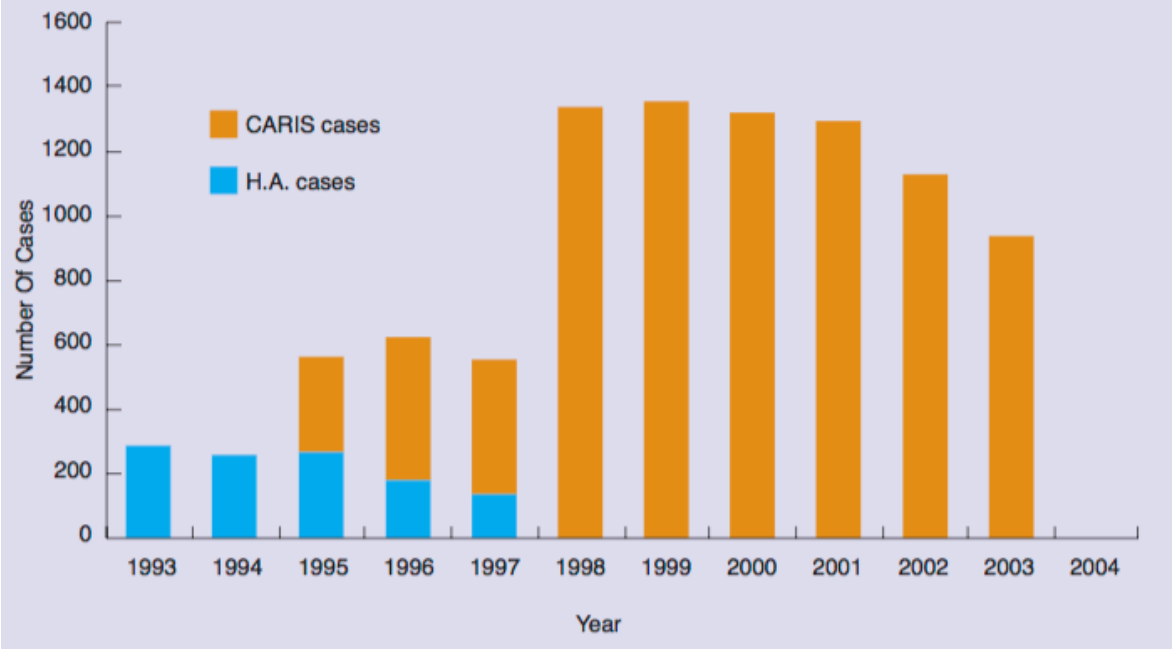
CAROBB Co-ordinator
National Perinatal Epidemiology Unit
University of Oxford,
Old Road Campus
Headington
Oxford OX3 7LF
Website: www.npeu.ox.ac.uk/carobb/

Please do not hesitate to contact us with any queries, or requests for more forms.

Tel: 01865 289723
E-mail: carobb@npeu.ox.ac.uk
kay.randall@nhs.net

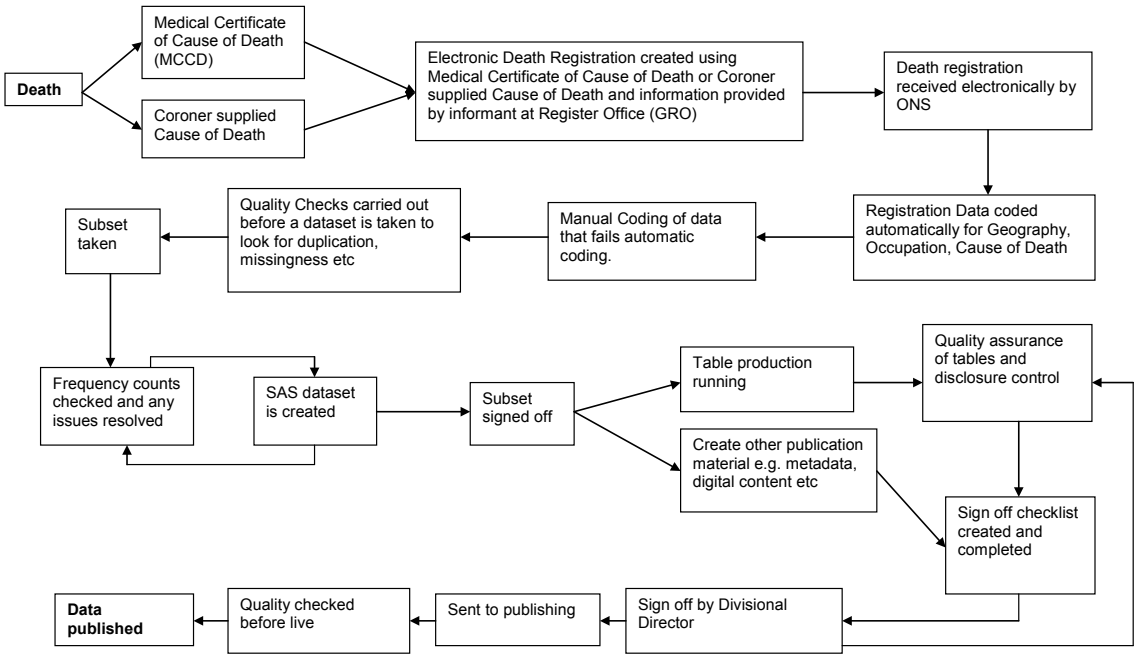
PLEASE DO NOT SEND ANY NOTIFICATIONS BY E-MAIL, UNLESS USING NHS.NET

5.2: Cases of congenital anomaly reported to ONS using the Health Authority paper-based system and CARIS. (CARIS 2020a)



5.3: Mortality case ascertainment, validation and data quality. (ONS 2020b)

Annex K Flow chart of deaths process



March 2016

Office for National Statistics

5.4: DPhil timetable and progress.

DPhil timetable

Milestones	Completed	2016			2017			2018			2019			2020		
Registration (PRS)	✔		M	H	T	M	H	T	M	H	T	M	H	T	M	
Rapid literature search and review	✔		M	H	T	M	H	T	M	H	T	M	H	T	M	
English Data application: Registries data and HES linkage via NHS Digital (unlikely to be accessible for this project)*	N/A		M	H	T	M	H	T	M	H	T	M	H	T	M	
Welsh Data application: CARIS, PEDW dand ONS datasets via SAIL	✔		M	H	T	M	H	T	M	H	T	M	H	T	M	
Receipt of CARIS, PEDW dand ONS datasets	✔		M	H	T	M	H	T	M	H	T	M	H	T	M	
Chapter 1: Introduction and Background	✔		M	H	T	M	H	T	M	H	T	M	H	T	M	
Chapter 2: Aims and Objectives	✔		M	H	T	M	H	T	M	H	T	M	H	T	M	
Chapter 3: Data sources and updates	✔		M	H	T	M	H	T	M	H	T	M	H	T	M	
Methodology (Protocol) for systematic reviews and meta-analyses (Chapters 4 & 5)	✔		M	H	T	M	H	T	M	H	T	M	H	T	M	
Chapter 4: Systematic literature review and meta-analysis: Infant mortlaity associated with spina bifida	✔		M	H	T	M	H	T	M	H	T	M	H	T	M	
Chapter 5: Systematic literature review and meta-analysis: Infant mortlaity associated with encephalocele	✔		M	H	T	M	H	T	M	H	T	M	H	T	M	
Methodology (Protocol and revisions) for main data analyses (Chapters 6 & 8)	✔		M	H	T	M	H	T	M	H	T	M	H	T	M	
Chapter 6: An investigation into the nature and clinical features of congenital anomalies leading to infant mortality	✔		M	H	T	M	H	T	M	H	T	M	H	T	M	
Chapter 7: Literature reivew: Hospitalisation of infants born with congenital anomalies	✔		M	H	T	M	H	T	M	H	T	M	H	T	M	
Chapter 8: An investigation into the pattern, reasons for and outcomes of hospitalisation of infants with anomalies	✔		M	H	T	M	H	T	M	H	T	M	H	T	M	
Chapter 9: Discussion and Conclusions	✔		M	H	T	M	H	T	M	H	T	M	H	T	M	
Transfer of status	✔		M	H	T	M	H	T	M	H	T	M	H	T	M	
Confirmation of status	✔		M	H	T	M	H	T	M	H	T	M	H	T	M	
Write up	✔		M	H	T	M	H	T	M	H	T	M	H	T	M	
First full draft of thesis for supervisors to comment	✔		M	H	T	M	H	T	M	H	T	M	H	T	M	
Finalise thesis and submit	✔		M	H	T	M	H	T	M	H	T	M	H	T	M	
Training courses (per TNA)	up to date		M	H	T	M	H	T	M	H	T	M	H	T	M	
Conferences and Presentations	up to date		M	H	T	T	T	T	M	H	T	M	H	T	M	

** This application has been made by J. Morris on behalf of BINOCAR*
PRS = Probationer Research Student; HES = Hospital Episode Statistics; NTD = Neural Tube Defects;
SAIL = The Secure Anonymised Information Linkage Databank; PEDW = Patient Episode Database for Wales;
CARIS = Congenital Anomaly Register and Information Service

M= Michaelmas **H= Hilary** **T = Trinity**

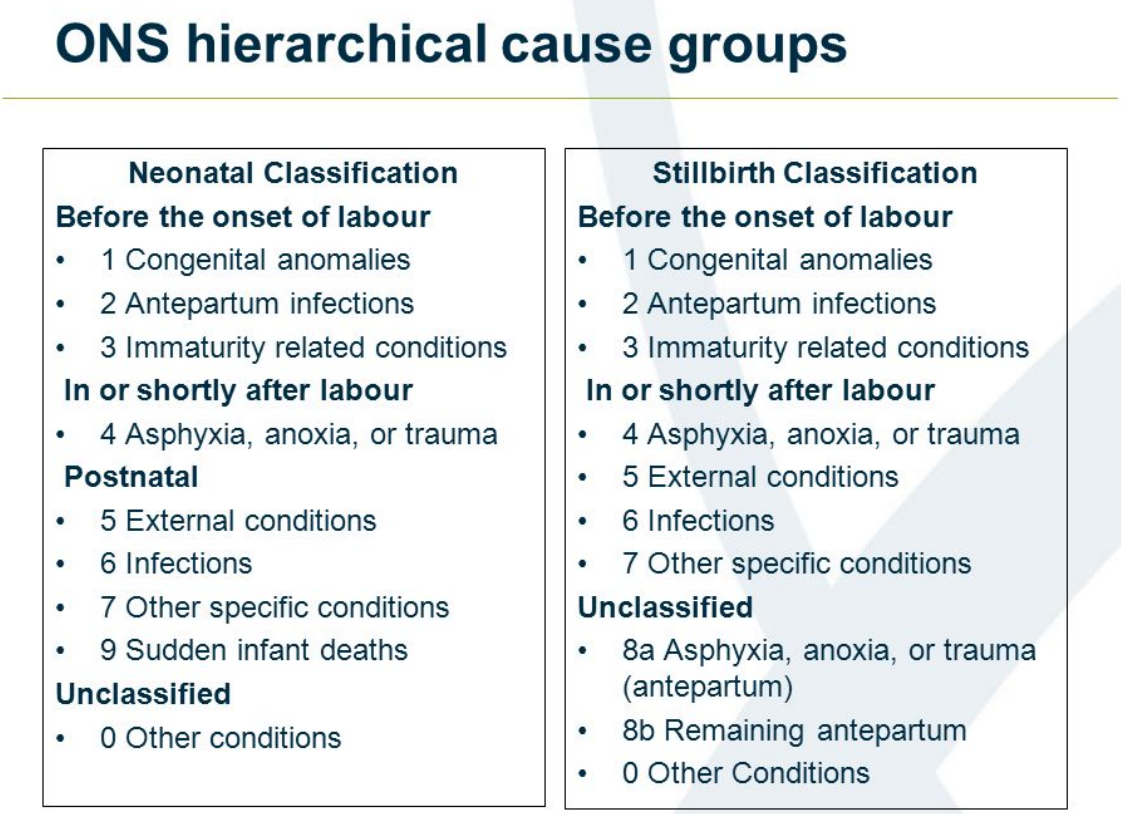
5.4 (continued): DPhil timetable and progress.

DPhil Training Schedule Year 1-4 (2017/18/19/20)			
Research Practice and Skills			
Course	***When?***	***Enrolled?***	***Attended?***
Introduction to systematic review and meta-analysis (Johns Hopkins University online course)	10.12.2016 (course over 6w)	√	√
7 Secrets of highly successful research students (MSD)	8.12.2016	√	√
Literature searching methodologies and strategies with outreach librarian	Half-termly sessions	√	Year 1 and 2
Databases searching strategy (Online)	01.2017	√	√
Introduction to Endnote (Bodleian Libraries)	15.11.2016	√	√
Endnote online tutorial	Michaelmas 2016	√	√
Managing Large Document: Good Practice with formal documents (IT department)	6.12.2016	√	√
Managing Large Document: Building long documents (IT department)	Hilary/ Trinity 2017	√	√
Data extraction analysis (online material)	Hilary 2017	√	Cochrane handbook √
GTC Research Workshop: How to Plan & Execute a Research Project	31.3.2017	√	√
Excel Essentials (charts)	Trinity 2017	√	√
Research skills toolkit for MedSci Division	Hilary 2018	√	√
Introduction to HES (NDPH, Oxford)	13.12.2018	√	√
Introduction to HES (UCL)	13-14 June, 2019	√	√
Research Planning and Time Management Skills			
Course	***When?***	***Enrolled?***	***Attended?***
How to plan your PhD (Podcast)	18.11.2016	√	√
The Balanced Researchers (Podcast)	Michaelmas 2016	√	√
Transfer of status assessment workshop	Hilary/Trinity 2017	√	√
DPhil Confirmation workshop (departmental)	14.1.2019	√	√
DPhil viva seminar (departmental)	20.5.2019	√	√
DPhil viva seminar (MedSci)	Trinity 2020	√	√
Ethical and legal understanding			
Course	***When?***	***Enrolled?***	***Attended?***
Research Integrity (MSD)	24.11.2016	√	√ (MT)
Good academic practice: Avoiding Plagiarism (Online)	Hilary/ Trinity 2017	√	√
Information Security Awareness	7.4.2017	√	√
Communication and networking skills			
Course	***When?***	***Enrolled?***	***Attended?***
Writing skills for PRS students	23.1.2017	√	√
Thesis and report writing	22.2.2017	√	√
Scientific writing (MPLS)	2.3.2017	√	√
Online learning materials on academic and scientific writing	Michaelmas/ Hilary 2017	√	√
Career Development			
Course	***When?***	***Enrolled?***	***Attended?***
Presentation skills	Trinity, 2017	√	√
GTC Management in Medicine workshop	2017-2020	√	√
Large group and lecturing	Michaelmas 2020	√	√
Teaching assistant for MSc Global Health Science and Epidemiology Statistical modules	Michaelmas 2020 – Hilary 2021	√	√

5.4 (continued): DPhil timetable and progress

Conferences			
NDPH symposium, Oxford (oral presentation of data analysis of the DPhil study main aim 1: mortality analysis)	01.2020	√	√ (Presenter)
International Clearinghouse for Birth Defects Surveillance and Research 46th Annual meeting, Bratislava, Slovakia (oral presentation of findings of the DPhil study main aim 1: mortality study)	8.9-12.9.2019	√	√ (Presenter)
EUROCAT registry leaders meeting and scientific symposium, Italy (poster presentation of the systematic review of DPhil study main 1: spine bifida)	12.6-15.6.2018	√	√ (Presenter)
Clarendon Scholar's symposium, Oxford (oral presentation of the systematic review of DPhil study main 1: neural tube defects)	5.6.2018	√	√ (Presenter)
Pete symposium	29.6.2018	√	√
BAPS International Congress, London (oral presentation of MSc NEC project)	08.2017	√	√ (Presenter)
Richard Doll Society Conference, GTC	11.2017	√	√
NDPH symposium, Oxford (poster presentation of the systematic review of DPhil study main 1: spina bifida)	01.2017	√	√ (Presenter)
Global Perinatal Mental Health Conference, GTC	01.2017	√	√

6.1: Office for National Statistics (ONS) hierarchical cause group. (ONS 2020a)



6.2: ICD-9/10 Chapter Headings. (WHO 2004)

Variable	ICD chapter	ICD-10	ICD-9
Infections	I. Certain infectious and parasitic diseases	A00-B99	001-139
Neoplasms	*II. Neoplasms*	*C00-D49*	*140-239*
Blood	III. Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	D50-D89	280-289
Endocrine	IV. Endocrine, nutritional and metabolic diseases	E00-E89	240-279
Mental	*V. Mental and behavioral disorders*	*F01-F99*	*290-319*
Nervous	*VI. Diseases of the nervous system*	*G00-G99*	*320-389*
Eye	VII. Diseases of the eye and adnexa	H00-H59	360-379
Ear	VIII. Diseases of the ear and mastoid process	H60-H95	380-389
Circulatory	*IX. Diseases of the circulatory system*	*I00-I99*	*390-459*
Respiratory	*X. Diseases of the respiratory system*	*J00-J99*	*460-519*
Digestive	*XI. Diseases of the digestive system*	*K00-K94*	*520-579*
Skin	XII. Diseases of the skin and subcutaneous tissue	L00-L99	680-709
Musculoskeletal	*XIII. Diseases of the musculoskeletal system and connective tissue*	*M00-M99*	*710-739*
Genitourinary	*XIV. Diseases of the genitourinary system*	*N00-N99*	*580-629*
Pregnancy	XV. Pregnancy, childbirth and puerperium	O00-O99	630-676
Perinatal	XVI. Certain conditions originating in the perinatal period	P00-P96	760-779
Congenital	XVII. Congenital malformations, deformations and chromosomal abnormalities	Q00-Q99	740-759
Symptoms and signs	*XVIII. Symptoms, signs and abnormal clinical and laboratory findings, not classified elsewhere*	*R00-R99*	*780-799*
Injury	*XIX. Injury, poisoning and certain other consequences of external causes*	*S00-T88*	*800-999*
External	XX. External causes of morbidity	V00-Y99	E01-E99
Factors	XXI. Factors influencing health status and contact with health services	Z00-Z99	V01-V82

6.3: To examine whether there were any associations between missing data for maternal ethnicity and other covariates in the analysis[1].

Missing data for maternal ethnicity	Adjusted odds ratio (95% CI)
Townsend quintile[2]	0.92 (0.90-0.94)
Maternal age at birth[2]	0.95 (0.93-0.98)
Parity[2]	1.79 (1.71-1.87)
Gestational age at birth[2]	1.20 (1.09-1.32)
Birthweight[2]	1.04 (0.95-1.14)
CARIS registration year[2]	1.18 (1.17-1.18)
[1]The sizes and directions of any significant associations were not relevant for the inclusion of the observed variables in the multiple imputation model. [2]Categories of Townsend quintile, maternal age, gestational age and birthweight were fitted in linear trends.	

6.4: To examine whether there were any associations between missing data for maternal smoking and other covariates in the analysis[1].

Missing data for maternal smoking	Adjusted odds ratio (95% CI)
Townsend quintile[2]	0.93 (0.91-0.95)
Maternal age at birth[2]	0.95 (0.92-0.97)
Parity[2]	1.96 (1.87-2.05)
Gestational age at birth[2]	1.13 (1.03-1.24)
Birthweight[2]	1.09 (0.99-1.20)
CARIS registration year[2]	1.17 (1.17-1.18)
[1]The sizes and directions of any significant associations were not relevant for the inclusion of the observed variables in the multiple imputation model. [2]Categories of Townsend quintile, maternal age, gestational age and birthweight were fitted in linear trends.	

6.5: To examine whether there were any associations between missing data for anomalies in previous pregnancies and other covariates in the analysis[1].

Missing data for anomalies in previous pregnancies	Adjusted odds ratio (95% CI)
Townsend quintile[2]	0.91 (0.90-0.93)
Maternal age at birth[2]	0.94 (0.91-0.96)
Parity[2]	2.30 (2.19-2.40)
Gestational age at birth[2]	1.16 (1.05-1.28)
Birthweight[2]	1.11 (1.01-1.23)
CARIS registration year[2]	1.18 (1.17-1.18)
[1]The sizes and directions of any significant associations were not relevant for the inclusion of the observed variables in the multiple imputation model. [2]Categories of Townsend quintile, maternal age, gestational age and birthweight were fitted in linear trends.	

6.6: To examine whether there were any associations between missing data for surgery and other covariates in the analysis[1].

Missing data for surgery	Adjusted odds ratio (95% CI)
Townsend quintile[2]	0.99 (0.97-1.01)
Maternal age at birth[2]	1.00 (0.97-1.02)
Parity[2]	0.97 (0.93-1.01)
Gestational age at birth[2]	1.01 (0.93-1.11)
Birthweight[2]	0.99 (0.91-1.08)
CARIS registration year[2]	0.88 (0.88-0.89)
[1]The sizes and directions of any significant associations were not relevant for the inclusion of the observed variables in the multiple imputation model. [2]Categories of Townsend quintile, maternal age, gestational age and birthweight were fitted in linear trends.	

6.7: Multiple imputation conditional models and their outputs.

MI conditional models:

Maternal Ethnicity: logit i.MaternalEthnicityCat HistoryPrevPregCat i.SurgeryCat i.MaternalSmokerCat ParityCat LengthGestCat BirthweightCat QuintileCat MaternalAgeatDeliveryCat CARISYear

MaternalSmoker: logit i.MaternalSmokerCat HistoryPrevPregCat i.SurgeryCat i.MaternalEthnicityCat ParityCat LengthGestCat BirthweightCat QuintileCat MaternalAgeatDeliveryCat CARISYear

History of anomalies in previous pregnancy: logit HistoryPrevPregCat i.SurgeryCat i.MaternalSmokerCat i.MaternalEthnicityCat ParityCat LengthGestCat BirthweightCat QuintileCat MaternalAgeatDeliveryCat CARISYear

Infant surgery status: logit SurgeryCat HistoryPrevPregCat i.MaternalSmokerCat i.MaternalEthnicityCat ParityCat LengthGestCat BirthweightCat QuintileCat MaternalAgeatDeliveryCat CARISYear

Isolated and multiple anomalies

Variable	Observation per m (add (35))			
	Complete	Incomplete	Imputed (%)	Total
Maternal Ethnicity	17,513	12,911	11,349 (87.9)	30,424
Maternal Smoking	17,624	12,800	11,220 (87.6)	30,424
History of anomalies in previous pregnancy	19,251	11,173	9,631 (86.2)	30,424
Infant surgical status	18,919	11,505	10,866 (94.4)	30424
Isolated anomalies				
Maternal Ethnicity	10,277	9,655	8,492 (88.0)	19,932
Maternal Smoking	10,296	9,636	8,457 (87.8)	19,932
History of anomalies in previous pregnancy	11,356	8,576	7,424 (86.6)	19,932
Infant surgical status	12,128	7,804	7,355 (94.2)	19,932
Multiple anomalies				
Maternal Ethnicity	7,183	3,191	2,813 (88.2)	10,374
Maternal Smoking	7,277	3,097	2,717 (87.7)	10,374
History of anomalies in previous pregnancy	7,841	2,533	2,164 (85.4)	10,374
Infant surgical status	6,727	3,647	3,469 (95.1)	10,374
Cardiovascular anomalies				
Maternal Ethnicity	1,845	1,304	1,173 (90.0)	3,149
Maternal Smoking	1,863	1,286	1,151 (89.6)	3,149
History of anomalies in previous pregnancy	2,054	1,095	964 (88.0)	3,149
Infant surgical status	1,351	1,798	1,717 (95.5)	3,149

6.8: Sensitivity analyses (in the final model) for isolated or multiple anomalies: 1. With probable cases excluded; 2. Complete case analysis; and 3. Multiple imputation: add(35).

	Confirmed and probable cases (n = 30,424)		Confirmed cases only (n = 24,133)	Complete case analysis (n = 30,424)	Multiple imputation (n = 28,775)
Risk factors	**Crude OR[1] (95% CI)**	**aOR[1] (95% CI) in final model**	**aOR[1] (95% CI) in final model**	**aOR[1] (95% CI) in final model**	**aOR[1] (95% CI) in final model**
Maternal ethnic origin					
White	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Other	2.18 (1.73-2.75)	2.25 (1.77-2.86)	2.13 (1.61-2.80)	2.49 (1.87-3.31)	1.92 (1.51-2.42)
Not known/ missing	0.46 (0.39-0.53)	0.66 (0.54-0.81)	0.62 (0.48-0.79)	-	
Parity					
Nulliparous	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
≥ 1	1.24 (1.09-1.41)	1.24 (1.08-1.41)	1.21 (1.04-1.41)	1.25 (1.03-1.51)	1.25 (1.10-1.43)
Not known/ missing	0.49 (0.37-0.65)	0.92 (0.67-1.27)	0.87 (0.56-1.34)	-	0.57 (0.42-0.77)
Maternal smoking					
Smoker	1.24 (1.07-1.44)	1.20 (1.02-1.40)	1.15 (0.96-1.37)	1.22 (1.00-1.49)	1.21 (1.03-1.41)
Non/ Ex smoker	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Not known / missing	0.47 (0.40-0.55)	0.73 (0.60-0.90)	0.66 (0.52-0.85)		
Infant sex					
Male	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Female	1.29 (1.14-1.46)	1.28 (1.13-1.46)	1.24 (1.07-1.44)	1.32 (1.10-1.59)	1.29 (1.14-1.47)
Gestational age, week					
< 37^{+0} (preterm)	4.53 (4.00-5.14)	4.38 (3.86-4.98)	4.25 (3.66-4.94)	4.08 (3.39-4.91)	4.50 (3.96-5.12)
≥ 37^{+0} (term)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Surgery					
Performed in the first year of life	0.86 (0.73-1.01)	0.80 (0.68-0.95)	0.84 (0.69-1.03)	0.75 (0.61-0.91)	0.90 (0.77-1.05)
Not performed in the first year of life[2]	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Not known/ missing	0.83 (0.72-0.95)	0.76 (0.66-0.88)	0.75 (0.63-0.89)	-	

[1]Corrected to 2 decimal places. [2]Including a minority of conditions which were too severe for surgery.

6.9: Sensitivity analyses (in the final model) for isolated anomalies: 1. With probable cases excluded; 2. Complete case analysis; and 3. Multiple imputation: add(35).

	Confirmed and probable cases (n = 20,008)		Confirmed cases only (n = 16,510)	Complete case analysis (n = 20,008)	Multiple imputation (n = 18,719)
Risk factors	**Crude OR[1] (95% CI)**	**aOR[1] (95% CI) in final model**	**aOR[1] (95% CI) in final model**	**aOR[1] (95% CI) in final model**	**aOR[1] (95% CI) in final model**
Maternal ethnic origin					
White	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Other	1.77 (1.11-2.82)	1.87 (1.16-3.02)	1.98 (1.21-3.24)	2.05 (1.27-3.33)	1.61 (1.04-2.50)
Not known/ missing	0.59 (0.47-0.75)	0.77 (0.55-1.09)	0.69 (0.47-1.01)	-	
Parity					
Nulliparous	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
≥ 1	1.48 (1.16-1.89)	1.48 (1.16-1.89)	1.43 (1.09-1.86)	1.23 (0.91-1.65)	1.49 (1.17-1.91)
Not known/ missing	0.99 (0.67-1.46)	1.55 (1.00-2.40)	1.40 (0.82-2.39)	-	
Maternal smoking					
Smoker	1.52 (1.15-2.01)	1.44 (1.07-1.92)	1.46 (1.07-1.97)	1.33 (0.98-1.80)	1.36 (1.02-1.79)
Non/ Ex smoker	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Not known / missing	0.66 (0.52-0.85)	0.89 (0.62-1.26)	0.93 (0.63-1.37)	-	
Infant sex					
Male	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Female	1.08 (0.86-1.35)	1.06 (0.85-1.33)	1.07 (0.83-1.37)	0.85 (0.63-1.14)	1.08 (0.86-1.35)
Gestational age, week					
< 37^{+0} (preterm)	4.72 (3.78-5.90)	4.53 (3.62-5.67)	4.13 (3.22-5.29)	4.00 (2.99-5.35)	4.60 (3.67-5.77)
≥ 37^{+0} (term)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)

[1]*Corrected to 2 decimal places.*

6.10: Sensitivity analyses (in the final model) for multiple anomalies: 1. With probable cases excluded; 2. Complete case analysis; and 3. Multiple imputation: add(35).

	Confirmed and probable cases (n = 10,374)		Confirmed cases only (n = 7,583)	Complete case analysis (n = 10,374)	Multiple imputation (n = 9,977)
Risk factors	**Crude OR[1] (95% CI)**	**aOR[1] (95% CI) in final model**	**aOR[1] (95% CI) in final model**	**aOR[1] (95% CI) in final model**	**aOR[1] (95% CI) in final model**
Maternal ethnic origin					
White	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Other	2.34 (1.78-3.08)	2.38 (1.79-3.16)	2.27 (1.61-3.20)	2.35 (1.68-3.29)	2.02 (1.53-2.68)
Not known/ missing	0.56 (0.46-0.68)	0.63 (0.51-0.78)	0.50 (0.38-0.67)	-	
Parity					
Nulliparous	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
≥ 1	1.18 (1.01-1.39)	1.19 (1.02-1.40)	1.16 (0.95-1.41)	1.20 (0.97-1.49)	1.21 (1.03-1.42)
Not known/ missing	0.37 (0.23-0.61)	0.54 (0.32-0.93)	0.33 (0.13-0.83)	-	0.43 (0.26-0.72)
Infant sex					
Male	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Female	1.33 (1.14-1.55)	1.37 (1.17-1.61)	1.30 (1.07-1.58)	1.41 (1.14-1.74)	1.37 (1.17-1.60)
Gestational age, week					
< 37^{+0} (preterm)	3.84 (3.29-4.49)	3.86 (3.30-4.53)	3.93 (3.24-4.77)	3.51 (2.83-4.35)	3.90 (3.33-4.57)
≥ 37^{+0} (term)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Surgery					
Performed in the first year after birth	0.68 (0.56-0.82)	0.71 (0.58-0.86)	0.77 (0.60-0.99)	0.63 (0.51-0.79)	0.77 (0.64-0.93)
Not performed in the first year after birth[2]	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Not known/ missing	0.76 (0.64-0.91)	0.77 (0.64-0.92)	0.75 (0.60-0.93)	-	

[1] *Corrected to 2 decimal places.*
[2] *Including a minority of conditions which were too severe for surgery.*

6.11: Sensitivity analyses (in the final model) for cardiovascular anomalies: 1. With probable cases excluded; 2. Complete case analysis; and 3. Multiple imputation: add(35).

	Confirmed and probable cases (n = 3,149)		Confirmed cases only (n = 2,838)	Complete case analysis (n = 3,149)	Multiple imputation (n = 3,009)
Risk factors	**Crude OR[1] (95% CI)**	**aOR[1] (95% CI) in final model**	**aOR[1] (95% CI) in final model**	**aOR[1] (95% CI) in final model**	**aOR[1] (95% CI) in final model**
Maternal ethnic origin					
White	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Other	1.00 (0.31-3.26)	1.08 (0.29-4.04)	1.12 (0.39-1.19)	0.85 (0.14-5.06)	0.96 (0.26-3.52)
Not known/ missing	0.71 (0.44-1.13)		0.68 (0.39-1.19)		
Infant sex					
Male	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Female	0.79 (0.51-1.22)	1.26 (0.78-2.06)	1.28 (0.76-2.14)	1.12 (0.50-2.51)	1.25 (0.77-2.04)
Gestational age, week					
$< 37^{+0}$ (preterm)	2.76 (1.75-4.35)	3.67 (2.19-6.15)	3.13 (1.79-5.48)	2.74 (1.06-7.04)	3.63 (2.16-6.11)
$\geq 37^{+0}$ (term)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
CHD severity					
Less severity	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Moderate severity	10.1 (4.9-21.1)	18.4 (8.10-41.7)	22.3 (9.20-54.0)	19.5 (4.79-79.4)	15.8 (6.89-36.41)
Most severity	90.7 (43.4-189)	229 (90.8-579)	331 (118.6-924)	713 (122.0-4161)	182 (72.53-460.76)
PDA and other CHDs unclassified	5.8 (2.9-11.6)	6.29 (3.14-12.6)	7.76 (3.67-16.41)	3.84 (1.15-12.87)	6.11 (3.05-12.23)
Surgery					
Performed in the first year after birth	2.93 (1.66-5.17)	0.34 (0.15-0.75)	0.29 (0.12-0.69)	0.16 (0.04-0.64)	0.54 (0.25-1.19)
Not performed in the first year after birth[2]	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Not known/ missing	0.75 (0.44-1.26)	0.60 (0.34-1.06)	0.70 (0.40-1.22)		

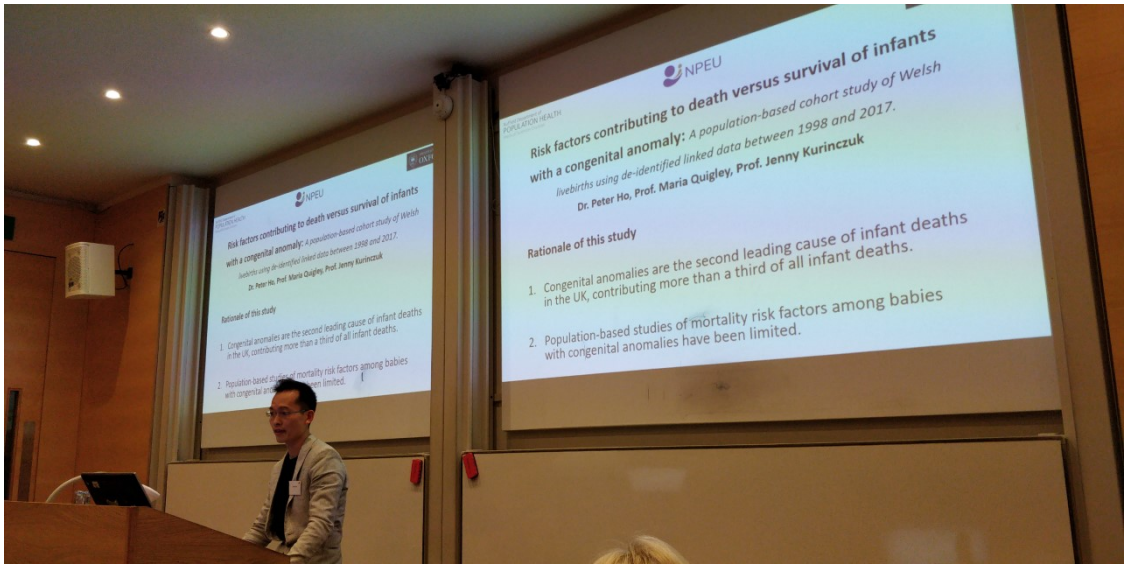
[1] *Corrected to 2 decimal places.*
[2] *Including a minority of conditions which were too severe for surgery.*

8.1: Centers for Disease Control and Prevention (CDC) classification of major congenital anomalies (Selected external major congenital anomalies). (CDC 2019a)

- Anencephaly
- Cleft lip
- Cleft palate
- Cleft palate with cleft lip
- Craniorachischisis
- Encephalocele
- Exomphalos /omphalocele
- Gastroschisis
- Hypospadias
- Iniencephaly
- Reduction defects of upper and lower limbs
- Spina bifida
- Talipes equinovarus/clubfoot

10.1: Conference presentations

ICBDSR Annual meeting (Slovakia, 2019)/ NDPH symposium (Oxford, 2020)



EUROCAT scientific symposium (Italy, 2018)

