Mortality amongst adults with congenital heart disease in Scotland: A population study

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Abstract

The number of adults living with congenital heart disease has increased greatly over recent years. This has broadly been attributed to advances in the surgical management of children and adolescents born with wide ranging abnormalities of cardiac anatomy. As a result, adult congenital cardiology has become a specialty in its own right and specialist care is centralised in tertiary referral centres.

Despite these improvements, patients rarely achieve a 'cure' and remain exposed to various clinical uncertainties and often premature mortality. Despite this, little is known regarding the current outlook for adults with congenital heart disease and the factors which influence outcomes. Furthermore, no substantive efforts have previously been made to describe ACHD mortality on a population basis in Scotland. These uncertainties and unanswered questions pose real problems to patients and clinicians alike. Providing guidance on seemingly simple matters such as participating in the workforce, the merits of a pension, or the risks involved with starting a family often defies consensus and is opinion based. Clearly in a modern age of evidence-based practice and shared decision making we must strive to do more.

Scotland has one of the most complete and comprehensive indexes of clinical records in the world. With the ability to link patient data over time and between different records, an individual patient's entire 'in hospital' history is logged and available in an anonymised format to facilitate academic study and service optimisation.

This thesis has sought to utilise the unique opportunity afforded by this Scottish Morbidity Database to define the present state, and recent trends of mortality amongst adults with congenital heart disease in a truly non-selective, population wide cohort. Context is provided via a comprehensive analysis of the current, international literature followed by analysis of the survival and causes of death encountered for ACHD patients between 1986 and 2017.

A total of 16,210 individuals were identified throughout the data period, of whom 4162 died. Anonymised data from the Scottish Morbidity Database was

examined to establish; age, sex, underlying congenital heart disease, deprivation status (as established by Scottish Index of Multiple Deprivation), and the presence of co-morbidity (diabetes, atrial fibrillation, ischaemic heart disease, cerebrovascular disease, hypertension and cancer).

Survival was seen to improve in more contemporary analyses. This improved survival was seen for both sexes, all degrees of socioeconomic deprivation and across the spectrum of ACHD complexity. Improved temporal survival persists upon adjustment for age, sex, co-morbidity and congenital lesion.

Survival of men with ACHD is relatively poorer than for women with ACHD and this is predominantly accounted for by non-cardiovascular death.

Individuals with ACHD were found to suffer disproportionate deprivation as compared to that of the general population. Women with ACHD experienced more deprivation than men with ACHD. Higher deprivation was associated with higher mortality and again, this persists in robustly adjusted analyses.

The reported causes of death for adults with congenital heart disease changed over time. At the begging of the data period the majority of deaths were by cardiovascular causes. In more recent analyses, non-cardiovascular death dominates. The rate of reduction in cardiovascular deaths outstrips that of the general population.

These analyses provide much needed insight into the survival prospects of the Scottish ACHD population and confirm the utility of the Scottish Morbidity Database as a resource. Improving survival coupled with a shift towards non-cardiovascular mortality highlights the importance of an holistic and integrated approach in the modern care of the ACHD patient. An important spotlight is shone on the socioeconomic disparity encountered by this cohort and provides a basis for further analyses to redress this as a matter of priority.

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Author's Declaration

I declare that, except where explicit reference has been made to the contribution of others, this thesis is the result of my own work and has not been submitted for the fulfilment of any other degree at the University of Glasgow or any other institution.

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Definitions/Abbreviations

95% CI – 95% confidence interval

ACHD – adult congenital heart disease

AF – atrial fibrillation

ASD – atrial septal defect

AVSD – atrioventricular septal defect

BAV – bicuspid aortic valve

BT shunt – Blalock-Taussig shunt

ccTGA – congenitally corrected transposition of the great arteries

CIS – continuous in patient stay

CHI – community health index

CHD – congenital heart disease

CoA – coarctation of the aorta

CPET – cardiopulmonary exercise test

CV - cardiovascular

CVD – cerebrovascular disease

d-TGA – dextro transposition of the great arteries

DILV – double inlet left ventricle

DORV – double outlet right ventricle

DQA – data quality assurance

eDRIS – Electronic Data Research and Information Services

GJNH – Golden Jubilee National Hospital

HLA – human leukocyte antigen

HR – hazard ratio

ICD – International Classification of Diseases

IHD – ischaemic heart disease

ISD – Information Services Division

IQR – interquartile range

l-TGA – levo transposition of the great arteries

MCCD – Medical Certificate of Cause of Death

MI – myocardial infarction

MR – mortality ratio

MRI – magnetic resonance imaging

NHS – National Health Services

NRS – National Records of Scotland

NSTEMI – non-ST segment elevation myocardial infarction

OPCS – Office of Population Censuses and Surveys Classification of Surgical Operations and Procedures

OR – odds ratio

PAPVD – partial anomalous pulmonary venous drainage

PBPP – Public Benefit and Privacy Panel

PDA – patent ductus arteriosus

PF – procurator fiscal

PVD – peripheral vascular disease

RV – right ventricle

SACCS – Scottish Adult Congenital Cardiac Services

SD – standard deviation

SIMD – Scottish Index of Multiple Deprivation

SMR – Scottish Morbidity Record

STEMI – ST segment elevation myocardial infarction

TAPVD – total anomalous pulmonary venous drainage

TCPC – total cavo-pulmonary connection

TGA – transposition of the great arteries

TOF – tetralogy of Fallot

VSD – ventricular septal defect

WHO – World Health Organisation

1 Introduction

1.1 Preamble

Congenital heart lesions are the most common birth defect (1) with a reported incidence among live births of 7 - 11 per 1000. When inclusive of the bicuspid aortic valve (BAV) and the often less clinically significant small, muscular ventricular septal defect (VSD) and silent patent ductus arteriosus (PDA), incidence rates as high as 75 per 1000 live births have been supported by robust epidemiology data (2). Better imaging, screening protocols and technical advances have improved preterm and postnatal diagnosis (3–5). Meta-analysis data suggests a rising incidence at birth over time, most recently estimated from 4.55 per 1000 live births in 1970 to 9.41 per 1000 in 2017 (5).The role of better imaging and screening protocols is suggested by an association of higher incidence amongst more advanced economies and health care systems (4,5). However, improved antenatal screening has been linked to a higher frequency of pregnancy termination when major congenital heart defects are detected (5), although it is likely that significant geographical variation exists. Relatively higher rates of preterm abortion have been reported amongst Scandinavian nations and lower rates among Asian countries and former Soviet states (6,7). It is likely that technological capabilities for screening, national laws and cultural practices impact this particular factor (5).

Overall it is probable that the true birth ***incidence*** of congenital heart disease (CHD) is relatively stable. What is certain is that the ***prevalence*** of congenital heart disease has increased greatly over recent years and decades (8,9) and this is a result of improved survival.

Historically, surgical treatment for congenital heart disease began in 1939 when the first patent ductus arteriosus (PDA) was surgically ligated at Boston Children's Hospital by Robert Gross (10). In 1945 Helen Taussig and Alfred Blalock famously published the first reported systemic arterial (subclavian artery) to pulmonary arterial shunt (11). The Blalock-Taussig (BT) shunt was performed on a young girl named Eileen Saxon who was known to have Tetralogy of Fallot (TOF). These operations were however exclusively external to the heart. Prior to the necessary technological advances required to perform cardiopulmonary bypass, a few 'life saving' intracardiac operations were attempted via hypothermia and caval inflow occlusion. This allowed the

operator a few minutes to carry out basic procedures and its utility was thus limited. Cardiac trauma was one application but relief from congenital disease was also attempted, with success in some cases. Both pulmonary valvotomy for congenital stenosis and closure of atrial septal defects under inflow stasis have been reported (12,13).

John Gibbon reported the first successful atrial septal defect (ASD) closure under cardiopulmonary bypass with his revolutionary 'heart-lung machine' in 1953 (14). In doing so the possibilities of intracardiac surgery were vastly expanded, and of course this legacy is not exclusive to congenital heart disease. Early mortality with cardiopulmonary bypass was however prohibitively high and with multiple engineering solutions offering varying hopes of success, other more 'physiological' techniques were trialled. Once such technique known as 'controlled cross circulation' offered comparatively favourable outcomes in this early phase. This technique involved using a live 'donor', usually the mother or father of the patient as the oxygenator. In this technique the femoral vein and artery of the donor were cannulated, and arterial blood extracted via an extracorporeal pump to supply the centrally cannulated patient's arterial circulation. Venous blood was then returned via the pump to the donor's femoral vein. This was of course a controversial technique, not least because it put an otherwise healthy individual at risk from potential complications as a donor. It did however provide potential hope from otherwise untreatable conditions. In a case series of 45 defects repaired under cross circulation at the University of Minnesota, a positive long-term outcome (greater than 30 years survival) was achieved in 49%. All donors survived with only one significant complication (15). In the early 1950s this was revolutionary and significantly better than the outcomes offered by rudimentary bypass machines.

With time and investment, technological advances in artificial oxygenation and the ability to anticoagulate the patient with heparin and reverse this with protamine saw mechanical cardiopulmonary bypass become safe and effective. Intracardiac surgery for simple congenital heart lesions was relatively common place by the 1970s. The technical surgical approach to the repair of many of the simpler lesions (ASD, PDA and VSD) has changed little since those early years of experimental intracardiac surgery.

The surgical management of more complex and cyanotic lesions has equally experienced significant advances. Francois Fontan reported the first successful ‘right heart bypass’ for tricuspid atresia in 1971 (16). Although much modified over the years, the physiological principles of the Fontan operation remain the mainstay for the treatment of cyanotic congenital heart disease where biventricular repair is not possible. A more recent advancement of similar magnitude is the arterial switch procedure for transposition of the great arteries (TGA). First performed by Jatene in 1975, initial outcomes were poor (17). Significant advances in the technique of anastomosing the coronary arteries and the adaptation and simplification by Lecompte (18) ensured that this would become the standard of care for the management of TGA. As with all procedural advances, implementation of this new practice varied from health system to health system and according to personnel and surgical capabilities but in general the arterial switch was fully established by the late 1980s – early 1990s in developed countries. This relatively recent advance is of particular note as the surgical predecessor to the arterial switch, the atrial switch (Mustard or Senning procedure) is still frequently encountered in surviving patients of the prior era. As a result, two patient cohorts born with the same condition and of a similar age experience vastly different physiology, complications and survival prospects (19,20).

Alongside the progress in open surgical practices, major advances in other fields of cardiology have improved outcomes for patients. A transcatheter approach has become the preferred method of intervention for many congenital heart defects. The first transcatheter closure of an ASD was achieved by King and Mills in 1975 (21). Numerous updated and improved technologies have been pioneered since the ‘King and Mills umbrella’, and over the last two decades minimally invasive ASD closure has become common place and the first line method when technically feasible. A similar evolution of transcatheter interventions has been witnessed in the treatment of VSDs, PDAs and certain types of aortic coarctation (22,23).

In the year 2000 Bonhoeffer successfully implanted the first transcatheter valve into the pulmonary position (24). Although a recent advent, percutaneous pulmonary valve implantation has become a safe and effective first line therapy

for re-do pulmonary valve replacement across the world. Transcatheter pulmonary valve implantation into the native right ventricular outflow tract is now becoming increasingly routine in some centres and marks another advance in ACHD intervention (25).

Following the successful implantation of a biological valve in the pulmonary position, Cribier successfully used a similar technology in the aortic position as a 'last resort' treatment for acquired aortic stenosis (26). Subsequently, transcatheter valve replacements have also been described in the tricuspid (27) and mitral (28) positions.

Cardiac transplantation remains as a therapeutic option in certain scenarios. After the first human-human cardiac transplant was performed by Dr Christiaan Barnard in 1967 (29) the operation rapidly gained popularity. However, the early mortality rate was significant and by 1970 it had fallen out of favour. Organ rejection was recognised as the cause for the majority of early failures and the eventual improvements in survival are more closely mirrored by the pioneering developments in the fields of immunology and immunosuppression than surgical practice per se (30,31).

In CHD, de novo or reconstructed anatomy and physiology is often complex and sometimes unique. As a result, cardiac transplantation in this population is more complex still. In addition to the obvious issues of implanting a heart where complex anatomical variations exist, patients with CHD have often had multiple previous procedures; compromising thoracic access as well as vascular options for cardiopulmonary bypass. Additionally, the presence of pre-formed human leukocyte antigen (HLA) antibodies from prior blood transfusions or the use of surgical homografts significantly complicates tissue typing. As a result of the increased complexity of cardiac transplantation in CHD, operative mortality is higher than for other patient groups. If this initial period is survived however, contemporary long-term outcomes in experienced centres are favourable (32).

In 1984 the first successful paediatric transplant was carried out on a 4-year-old with a single ventricle as a primary operation. The more usual scenario in modern practice is to obtain primary repair or palliation in the first instance with a small cohort exploring the option of transplantation later in life due to

late complications of the repaired phenotype or failing haemodynamics in the natural history of the disease.

Due to the myriad and often lifelong haemodynamic abnormalities observed in certain CHD (be it de novo or surgically altered), it is frequently not just the cardiovascular system which is affected. As a result, it is more frequent to pursue multi-organ transplantation in this patient population than others. Pulmonary hypertension may mandate the need for heart-lung transplant in the case of long standing or severe shunt lesions. Likewise, iatrogenic pulmonary hypertension may develop due to surgically created systemic arterial to pulmonary arterial shunts. Conditions where chronic systemic venous hypertension predominates, such as with Fontan physiology, may induce liver cirrhosis and in such cases the possibility of heart-liver transplant may be explored. Finally, it remains an unfortunate fact that for some patients with complex congenital heart disease or congenital heart disease with complicating features, transplantation is not a realistic option.

Described above is a synopsis of the rapid progression in the management of congenital heart disease. This can be summarized into three eras;

- The pre-surgical era (prior to 1940). No surviving patients with significant CHD can be expected under current follow-up.
- The extra-cardiac operative era (1940 – 1970). Few patients with significant CHD surviving to current follow-up. Often patients with milder phenotypes and later intracardiac operations.
- The intra-cardiac era (1970 – present). A greater than 90% survival to adulthood is predicted in modern cohorts (33).

It is clear that the major advances as outlined above have been instrumental in the improved initial survival of individuals, particularly those with more complex CHD. This has been demonstrated by Khairy *et al* (34) who reported a rising median age at death among those with severe CHD from 2 years to 23 years of age between 1987 and 2005. As a result, a new era of sustained improvement is now the collective goal of the CHD community. It is no longer the aim to simply provide a life-saving structural solution to a haemodynamic lesion. Lifelong care planning must consider complex issues such as; providing an attractive substrate for further intervention in time; the interaction of therapeutic options such as

cardiac devices with imaging modalities such as cardiac MRI and even the difficult choice taken not to intervene to preserve the future option of advanced therapies such as cardiac transplantation. All of these decisions must be taken into context with the concerns and health expectations of the patient. From previously being content with survival, the expectation of patients is now to lead a life far more comparable to the general population.

It is essential that we understand the impact of the shifting paradigms of the current era of congenital heart disease management and the effect that these are having on patient survival at a population level.

1.2 Cardiac development and lesion aetiology

Congenital heart disease comprises a vast array of structural abnormalities of the heart and great vessels which are present from birth. Despite the relatively simple function of the heart, which essentially serves as a series of pumps and valves, the embryological processes involved in normal cardiac development are complex with multiple time critical steps required for complete structural maturation. An in-depth review of the embryological processes is beyond the scope of this thesis, however a basic understanding of the developmental processes allows an understanding of the aetiology and physiology of commonly encountered defects.

The cardiac structures begin to form at around 18-19 days post fertilisation and originate from the mesoderm, one of the three germ layers which will ultimately comprise all organ tissue (35). Initially two strands known as cardiogenic cords are produced. These develop a lumen at around day 20, becoming endocardial tubes. These then migrate and fuse to form a single heart tube. This in turn develops 5 distinct regions which will later define mature cardiac structures; the truncus arteriosus (later becoming the aorta and pulmonary trunk), the bulbus cordis (later to become the right ventricle), the primitive ventricle (which matures into the left ventricle), the primitive atrium (which will become the anterior atrial mass), and the sinus venosus (which will form the posterior right atrium, cavae and coronary sinus). At this stage all blood enters via the sinus venosus and is propelled via the primitive atrium, the primitive ventricle, the bulbus cordis and into the truncus arteriosus in sequence.

At around day 28 the primitive heart folds and ‘loops’ to form an ‘S’ shape, aligning chambers to approximate the mature heart. A complex process of chamber fusion and subsequent septation of the atrial and conotruncal masses ensues. Further maturation with valve development and integration of a blood supply via the coronary vessels comprises the mature foetal heart (36).

Developmental errors can give rise to defects at any one or several phases of cardiac development. Some of these are easy to comprehend even if the underlying processes are complex. For instance, failure in the septation of the atrial mass will result in an ASD. The processes involved and resulting spectrum of ASDs are myriad, however all result from a failure to septate the embryological shared atrial mass and will result in a pathological shunting of blood from the relatively high pressure left atrium to the relatively low pressure right atrium in the fully matured heart. Similarly, a failure to septate the conotruncal mass, or the bulbis cordis from the primitive ventricular mass will result in a common arterial trunk or VSD respectively.

As the primitive tube-like heart loops to oppose the embryological ventricular structures, errors of ventricular laterality may occur. In conventional development, a rightward, or dextro loop (D loop) gives rise to the usual arrangement where the morphological right ventricle lies to the anatomical right of the morphological left ventricle. Leftward or levo looping (L loop) confers the opposite arrangement where the morphological right ventricle lies to the anatomical left of the morphological left ventricle. As a single defect this will give rise to the condition, congenitally corrected transposition of the great arteries (ccTGA). The physiological implication is a morphological right ventricle and associated tricuspid valve in the systemic position.

Maturation of the inflow and outflow of the embryological structures occur broadly in unison. Myriad disorders can occur during these processes and in some respects may be considered on a spectrum. Ventricular inlet and outlet structures form as a tube and are thus in continuity. It is only with a complex process of leftward migration and differentiation that the conotruncal structures are appropriately septated and aligned with their appropriate ventricular chambers. A ‘complete’ failure to do so will result in a double outlet right ventricle (as it is the bulbis cordis which provides continuity with the truncus

arteriosus). Other errors in the process or spectrum of malformation of ventricular outflow comprises diseases such as TOF (where there is overriding of the aorta to the right ventricle), transposition of the great arteries (or ventriculo-arterial discordance) and aortic coarctation. Similar abnormalities of ventricular inflow development may result in complete double inlet left ventricle (as the primitive atrial tissue is in continuity with the primitive left ventricular mass) at the extreme end of the spectrum, with varying degrees of atrioventricular canal with atrioventricular valve override also possible.

Often more than one, or even multiple congenital lesions can co-exist, defying simple or eponymous nomenclature. In such circumstances an understanding of cardiac development, chamber continuity, laterality and connections is essential to allow a structured segmental approach to classification.

1.3 Classification and coding of congenital heart disease

An adult with congenital heart disease is any individual over 16 years of age who was born with any form of congenital heart disease i.e. a structural abnormality of the heart or great vessels which is present from birth. There is variation as to the age at which an individual is classified as an adult within the literature. The cut-off is usually between 15 and 18 years (37,38).

The spectrum of congenital heart disease is vast and requires some degree of classification and grouping to be manageable, of clinical relevance and allow categorisation for clinical and epidemiological study. There are many ways by which CHD can be divided-up, each with benefits and limitation. Additionally, the intended utility of classification systems extends beyond clinical usefulness. Informing the National Records of Scotland and providing a basis for remuneration of services at a trust level is also a function of certain coding systems.

1.3.1 ICD 10

Standardising the classification of pathologies has challenged physicians and statisticians for centuries. Perhaps the earliest, comprehensive attempt at classification can be credited to the French physician Francois Boissier de

Larcoix who published his *Nosologia methodica* in 1768, utilising methodology developed in the field of botany which he applied to medical pathology (39). A century later another French physician, Jacques Bertillon announced the introduction of the *Bertillon Classification of Cause of Death* at the congress of the International Statistical Institute in Chicago (40). This early edition can claim direct lineage to what is now the International Statistical Classification of Diseases and Related Health Problems (ICD). Bertillon classified the cause of death to reflect the organ system or anatomical locus of the pathology, and this remains the cornerstone of contemporary iterations.

Undergoing periodic review, it wasn't until the 6th revision (ICD 6) in 1949 that the system began to reflect morbidity as well as mortality, assuming the ICD moniker. It was also at this point that the World Health Organisation (WHO) assumed responsibility for the publication and upkeep of the classification system, and as such its applicability should be standardised within the health authority of the United Nations System.

The current format (ICD 10) was endorsed by the World Health Assembly in 1990 and was first adopted by WHO member states in 1994, with the UK being among the first to make the change. ICD 10 represented a significant expansion of the previous iteration to over 14,000 unique codes. Individual codes represent diseases, signs and symptoms, injuries and causes of death and are grouped by an alpha-numerical system into similar pathologies and by anatomical locus. Bacterial infections for instance will be prefixed with 'A' followed by up to 3 numerical characters to define the organism and affected tissue. The codes used to define congenital heart lesions are summarised in Table 1-1.

ICD coding is the most common means by which health care systems record activity within institutions. In the USA and Canada this is primarily mediated through health insurance databases and serves the primary purpose of financial remuneration. In Scotland, ICD data is translated at a trust level before being stored and managed at a national level by the Information Services Division of the NHS. This will be discussed in more detail in section 4.

There are some clear strengths to the ICD coding system and as such, advantages to its use as a classification tool. The foremost of these is the international

applicability of this system. As a WHO endorsed methodology, ICD coding is almost universally recognised. Furthermore, the binary nature of the coding system makes categorical analysis of epidemiological data particularly straight forward. This has been exploited by previous large scale CHD studies (34,41).

There are several drawbacks to the ICD coding system, some generic and some specific to CHD. Coding is not typically performed by clinicians and is performed retrospectively by case note review. Therefore, there is a degree of subjectivity regarding the translation from clinical notes to ICD codes. This may also be influenced by the training and experience of the clerical staff which may vary within a health care system and will certainly vary from country to country. Specific to CHD, the clinical problem affecting an individual does not always equate to their 'diagnosis'. In adult CHD in particular, it is the surgically created anatomy which often defines the clinical picture, and this cannot be accounted for by ICD coding alone. The most obvious example would be for patients with Fontan physiology. The Fontan physiology is surgically created and as such is not included in ICD coding which will reflect the birth diagnosis (e.g. tricuspid atresia or hypoplastic left heart syndrome) instead. Fortunately, in the UK a separate coding system is used to record surgical and interventional procedures and is coded alongside ICD diagnoses at point of care. This is known as the Office of Population Censuses and Surveys Classification of Surgical Operations and Procedures (OPCS).

The (ICD) provides an extensive breakdown of congenital cardiac lesions. It attempts to group them according to the structures affected and assign them a code. For example; lesions of the atrioventricular septum are grouped under the code Q21 with the addition of a third numerical character to increase the specificity of the lesion in question.

Table 1-1- ICD 10 codes for congenital heart disease

Code	Description
Q20.0	Common arterial trunk
Q20.1	Double outlet right ventricle
Q20.2	Double outlet left ventricle
Q20.3	Discordant ventriculoarterial connections
Q20.4	Double inlet ventricle
Q20.5	Discordant atrioventricular connections
Q20.6	Isomerism of atrial appendages
Q20.8	Other congenital malformations of cardiac chambers and connections
Q20.9	Congenital malformation of cardiac chambers and connections, unspecified
Q21.0	Ventricular septal defect
Q21.1	Atrial septal defect
Q21.2	Atrioventricular septal defect
Q21.3	Tetralogy of Fallot
Q21.4	Aortopulmonary septal defect
Q21.8	Other congenital malformations of cardiac septa
Q21.9	Congenital malformations of cardiac septum, unspecified
Q22.0	Pulmonary valve atresia
Q22.1	Congenital pulmonary valve stenosis
Q22.2	Congenita pulmonary valve insufficiency
Q22.3	Other congenital malformations of pulmonary valve
Q22.4	Congenital tricuspid stenosis
Q22.5	Ebstein's anomaly
Q22.6	Hypoplastic right heart syndrome
Q22.8	Other congenital malformations of tricuspid valve
Q22.9	Congenital malformations of tricuspid valve, unspecified
Q23.0	Congenital stenosis of aortic valve
Q23.1	Congenital insufficiency of aortic valve
Q23.2	Congenital mitral stenosis
Q23.4	Hypoplastic left heart syndrome
Q23.8	Other congenital malformations of aortic and mitral valves
Q23.9	Congenital malformations of aortic and mitral valves, unspecified
Q24.0	Dextrocardia
Q24.1	Laevocardia
Q24.2	Cor triatriatum
Q24.3	Pulmonary infundibular stenosis
Q24.4	Congenital subaortic stenosis
Q24.5	Malformation of coronary vessels
Q24.8	Other specified congenital malformations of heart
Q24.9	Congenital malformation of heart, unspecified
Q25.0	Patent ductus arteriosus
Q25.1	Coarctation of aorta
Q25.2	Atresia of aorta
Q25.3	Stenosis of aorta
Q25.4	Other congenital malformations of aorta
Q25.5	Atresia of pulmonary artery
Q25.6	Stenosis of pulmonary artery
Q25.7	Other congenital malformations of pulmonary artery
Q25.8	Other congenital malformations of great arteries
Q25.9	Congenital malformation of great arteries unspecified
Q26.0	Congenital stenosis of vena cava
Q26.2	Total anomalous pulmonary venous connection
Q26.3	Partial anomalous pulmonary venous connection
Q26.4	Anomalous pulmonary venous connection unspecified

The clinical coding of diagnoses is fallible in some respects. It is clear from reviewing the available ICD 10 codes that applying specificity to a code is of paramount importance. For example, a patient who has a congenital

abnormality of their tricuspid valve might be assigned the ICD 10 code Q22.4, Q22.5, Q22.8 or Q22.9 however without more detailed clinical information this important distinction cannot be made.

Since clinical coding is performed by non-clinical staff via case note review, a lack of detail in medical record keeping or a failure to appreciate the clinical coding process will inevitably translate into a lack of accuracy in coding output. Also, many of the congenital lesions listed are rarely encountered on an individual basis and so clinical coding staff may lack the esoteric knowledge to adequately apply the specificity required. To refer back to the example of congenital tricuspid valve disease, suppose this is further specified to be tricuspid atresia; a congenital lesion at the most severe end of the spectrum. This should be coded as Q22.4, representing 'congenital tricuspid valve stenosis'. It is easy to see how this could be missed due to the use of the specialist terminology 'atresia' which is not explicitly included in the code description. It is reasonable to see how this may end up being coded as Q22.8, representing 'other congenital malformation of tricuspid valve' which does not adequately represent the complexity of the condition and as a stand-alone indicator would seriously limit any interpretation of mortality data.

ICD coding is further complicated as versions change over time. The current iteration replaced ICD 9 in 1995. This previous version used a different, purely numerical method of coding and subtle differences in the available codes can make direct conversion between the two systems challenging. For example; in ICD 10 the aortopulmonary septal defect (aortopulmonary window) is given the code Q21.4. In ICD 9 however this lesion is included under the code 745.0 for common truncus, a lesion which has its own, separate code in ICD 10. WHO member states are currently reviewing and planning implementation for the latest revision, ICD 11. This promises increased complexity with expanded coding potential and increased functionality with the ability to link to other WHO endorsed classification systems. This will first be available for adoption in the UK in 2022.

ICD coding does not take into consideration operative procedures. As the majority of congenital heart diseases, particularly those of moderate and great complexity, remain reliant on early surgical intervention, this is a significant

limitation. In clinical practice a patient's 'diagnoses' are equally, or sometimes more dependent on the repaired anatomy as compared to the lesion that was present at birth. A patient born with tricuspid atresia who later has a Fontan operation is predominantly thought of as a Fontan patient thereafter. Although the original diagnosis of tricuspid atresia remains of some clinical relevance it is the Fontan discriminator which bears far more clinical significance. As this is a procedure not a diagnosis, ICD coding does not account for it. In such circumstances the OPCS coding system is used. This is currently in its fourth iteration (OPCS-4), although frequent amendments within each version are carried out. The OPCS system is coded in a similar way to ICD and is subject to similar vulnerabilities.

1.3.2 Bethesda classification

Due to the vast array of congenital cardiac lesions, efforts have been made to rationalise the list and separate it into cohorts depending on complexity.

The most commonly used system is that devised at the 2001 Bethesda conference (42) which groups all congenital lesions into those of simple, moderate and great complexity (Table 1-2). This system was not designed for use to remunerate health care providers in the same way as ICD coding. Neither was it meant to infer disease 'severity' or prognosis. Instead it was intended to stratify patients as to the frequency and level of specialty required for their ongoing care. That being said, it has become commonplace for this, or a variation on this system to be used in the CHD literature when studying outcomes, including mortality (43,44).

Table 1-2: Summary of lesion complexity according to 'Bethesda' classification

Complexity	Lesion
Simple	ASD (secundum septum)
	Isolated congenital aortic valve disease
	Isolated congenital pulmonary stenosis
Moderate	Anomalous pulmonary venous drainage
	Atrioventricular septal defect
	Tetralogy of Fallot
	Ebstein's anomaly
	Valvular lesions (unless isolated pulmonary stenosis or aortic valve disease)
	Aortic coarctation
	Sub and supravalvular aortic stenosis
Severe	Transposition of the great ateries (irrespective of repair)
	Congenitally corrected transposition of the great arteries
	Fontan
	Eisenmenger syndrome
	Truncus arteriosus
	Univentricular heart
	Hypoplatic left heart syndrome
	Tricuspid atresia
	Pulmonary atresia
	Aortopulmonary window

Unlike ICD coding, this system can take into consideration the surgically altered anatomy of the individual, refining its correlation to clinical practice. An additional benefit is that it allows grouping of often rare conditions into one of three comparably large cohorts. This permits a degree of generalisability for conditions which would otherwise be too uncommon to study. This also has implications to protect anonymisation which may otherwise be jeopardised by small patient cohorts.

The primary drawback to the use of this classification system is the considerable heterogeneity which remains within each cohort of complexity. For instance, transposition of the great arteries corrected by the arterial switch operation is considered of great complexity along with univentricular hearts and Fontan physiology. Although individuals with TGA arterial switch can encounter complex problems in adulthood, a significant cohort have a relatively uncomplicated adulthood and are considered to have low morbidity and good survival prospects, not dissimilar to the general population (19,20,45). The American Heart Association (AHA), American College of Cardiology joint 2018 ACHD guideline has sought to address this issue by significantly expanding this classification system

to incorporate the patient's physiological status (46). This 'ACHD anatomic and physiological' (ACHD-AP) classification incorporates metrics such as functional capacity, New York Heart Association (NYHA) class, degree of hypoxaemia and the presence of end organ dysfunction. As such, this classification system holds much promise in clinical practice and for the study of recruited cohorts but holds no utility in the presented studies hence forth.

1.3.3 Lesion physiology

At its most basic, the essence to understanding congenital heart disease stems from the understanding of cardiac anatomy, chamber connections and the physiology of blood flow. As I have alluded to within this chapter, surgical intervention for congenital heart disease remains common and of crucial importance. The proposed or even 'correct' intervention is not necessarily determined by the underlying cardiac lesion but the unrepaired and the intended post-surgical physiology of blood flow and chamber continuity. As such the same or similar operations may be used for more than one and often many native diagnoses. In such circumstances it is the physiological grouping of lesions which is most clinically useful. This method of classifying lesions has been used to teach congenital heart disease to prospective practitioners for decades and is a cornerstone of textbook methodology (47,48).

Recent years have seen attempts to formalise and standardise the physiological grouping of CHD in the literature. One such system of classification proposed by Thiene *et al*. (49) is summarized in Table 1-3.

Table 1-3: Classification of congenital heart disease by common physiology

CHD with increased pulmonary blood flow (septal defects with left to right shunt)
Isolated atrial septal defect
Isolated ventricular septal defect
Partial anomalous pulmonary venous drainage
Atrioventricular septal defect
CHD with decreased pulmonary blood flow (septal defects with pulmonary obstruction and right to left shunt)
Pulmonary valve stenosis with ASD
Tetralogy of Fallot
Tricuspid atresia
CHD with obstruction to blood progression and no shunt
Coarctation of the aorta
Aortic and subaortic stenosis
Pulmonary stenosis
CHD incompatible with postnatal circulations (arterial duct dependance)
Pulmonary atresia
Transposition of the great arteries
Total anomalous pulmonary venous drainage
CHD silent until adulthood
Bicuspid aortic valve
Non cyanotic anomalous coronary arteries
Congenitally corrected transposition of the great arteries

Using the examples outlined in Table 1-3 it is easy to understand the benefits of utilising a physiological classification system, the foremost of which being the practical implications for management options. For CHD with increased pulmonary blood flow a common goal of therapy will be to protect the pulmonary vasculature from irreversible damage and subsequent right heart failure. CHD with reduced pulmonary blood flow shares the common strategy of augmenting pulmonary blood flow when required and mitigating cyanosis. Obstructive lesions require assessment of severity and intervention to relieve the obstruction where appropriate. CHD incompatible with postnatal physiology requires persistence of the arterial duct, procedures to encourage non-septation and/or early reparative intervention. And CHD silent until adulthood requires effective identification, referral procedures and decision making for intervention timing. The main drawback to this methodology is that its utility is spent in the post-operative phase, limiting usefulness particularly for more severe lesions. Notable examples of surgically altered physiology for more complex lesions include operations for complete transposition of the great arteries where

physiological normality of blood flow is achieved either by ‘switching’ the inflow of blood to the atria (atrial switch procedure) or by ‘switching’ the outflow of the ventricles (arterial switch procedure). The former procedure involves baffling the atrial blood into the contralateral ventricular mass to achieve physiological flow. This has the drawback of maintaining the morphological right ventricle in the systemic position and carries a significant long term burden of heart failure, systemic tricuspid valve regurgitation atrial arrythmias. The arterial switch procedure has the marked benefit of restoring the left ventricle into the systemic position. The procedure does however involve re-anastamosis of the coronary arteries to the aorta which can have short and long term sequalae. Perhaps the most notable surgically modified physiology which limits this system as a tool in adults is following the Fontan operation or a modification thereof. This operation (or more commonly, series of operations) has utility for several native congenital heart lesions. In-particular, instances where there is marked mixing of oxygenated and deoxygenated blood at atrial and/or ventricular level, and repair to physiological normality is not possible, ‘Fontan physiology’ may be preferred. This is achieved by a series of two or three operations with the ultimate goal of bypassing the systemic venous return away from the heart entirely with direct anastomosis to the pulmonary arteries. This results in the heart acting as a single functional atrial and ventricular mass which deals solely with the systemic circulation. This has the benefit of mitigating cyanosis and protecting the pulmonary circulation from what may otherwise be systemic pressures. This does however result in a delicately balanced physiological state with no subpulmonary ventricle, and myriad cardiovascular and non-cardiovascular complications can occur in the short and medium term and ultimately will occur in the long term.

Additional to the complications posed by the surgical alteration of physiology, the natural history of certain lesions may mean that physiology changes over time. A notable example of this is amongst the lesions in Table 1-3 with increased pulmonary blood flow due to left to right shunting. In this circumstance, where the pulmonary vascular bed is exposed to increased flow over the long term, pulmonary pressures may rise dramatically. Over time, in some instances this may result in an equalisation and then reversal of the gradient of pulmonary to systemic pressure, reversing the shunt and rendering

the patient cyanotic and significantly increasing the potential for morbidity and mortality.

To the best of my knowledge, and likely due to the significant limitations stated above, this method of categorising lesions by common physiology has not been used in the study of outcomes in ACHD.

1.4 Prognosis in ACHD

1.4.1 Morbidity in ACHD

Improvements in paediatric care and early intervention has led to an increasing prevalence of CHD in the adult sector (42). Additionally, adults with CHD are living longer that previously (50,51). Morbidity in ACHD has therefore increased in two main ways; there are now adults with critical CHD who previously did not survive to adulthood; and, adults with CHD are living longer and acquiring more comorbidity (52). The result has been a dramatic increase in the number of hospital admissions amongst ACHD patients. From the mid 1990s until 2005, ACHD related admissions in the US doubled (53). Admissions have since been shown to increase until at least 2010 and be accounted for by ACHD of all degrees of complexity (52).

The prevalence of comorbidity in adults with ACHD has also increased dramatically in recent years. One large US population study reported that from 2003 – 2012, the percentage of ACHD patients with diabetes increased from 13.1% – 21.7%, systemic hypertension from 37.3% - 54.4% and chronic kidney disease from 2.8% - 12.1% (52). A similar increase in rates of smoking and obesity were also found. Despite the growing body of population data regarding increased morbidity in the ACHD population, many questions remain unanswered. In particular, no study has examined how multimorbidity has affected cause of death over time.

Section 4.2.2 will outline how we intend to utilise this wealth of ACHD data from hospital admissions using the Scottish Morbidity Database to address mortality and cause of death in the Scottish ACHD population.

1.4.2 Survival

Advances in the care of individuals with CHD have led to a shift away from infant and towards adult mortality (54). Despite surgical advances, few, if any, congenital heart lesions can be considered to be 'cured' by intervention.

A study by Diller *et al* (43) reported age and sex standardised mortality ratios for congenital lesions between 1991 and 2014 and found that survival amongst individuals with lesions of simple complexity (ASD, VSD and PDA) was similar to that of the general population. In all other lesions, a significantly higher mortality was observed. Individuals with a Fontan circulation or Eisenmenger syndrome had the highest age and sex standardised mortality ratios of 23.40 (95% CI 15.97 -34.29) and 12.79 (95% CI 9.67-16.91) respectively. Survival amongst individuals with CHD of moderate complexity (as defined by the Bethesda classification (Table 1-2)) was worse than for simple lesions, however the absolute difference in point estimates was relatively small (standardised mortality rations 1.3, 95% CI 1.1-1.5 and 2.2, 95% CI 1.8-2.3 respectively). Prognosis amongst those with lesions of great complexity on the other hand was far poorer with a combined standardised mortality ratio of 10.9 (95% CI 9.3-12.8).

1.4.2.1 Survival and year of birth

There is clear consensus in the literature that survival with congenital heart disease has improved over time (33,51,55,56). Although the absolute survival varies from cohort to cohort and is dependent on several factors such as the definition of CHD; whether this includes silent patent arterial ducts and small membranous VSDs for instance; and whether active screening recruitment was undertaken or if cohorts were observational; universally, temporal trends show improved survival.

A large Belgian study of over 7000 individuals with CHD compared rates of survival to adulthood according to birth era. For individuals born in 1970-1974, 81% survived to age 18, compared with 88.6% for those born in 1990-1992 (33). Similar trends have been demonstrated in more contemporary cohorts. *Marelli et al*. (3) confirmed that the adult prevalence of CHD continued to rise steeply

between 2000 – 2010, increasing by 20%. A corresponding increase in age at death corroborates these findings. Figure 1.1 demonstrates the changing distribution of age at death in a Canadian CHD population (51). This data clearly illustrates the shift from frequent infantile mortality in the late 1980s to adult mortality by 2005, which is more comparable to that of the general population.

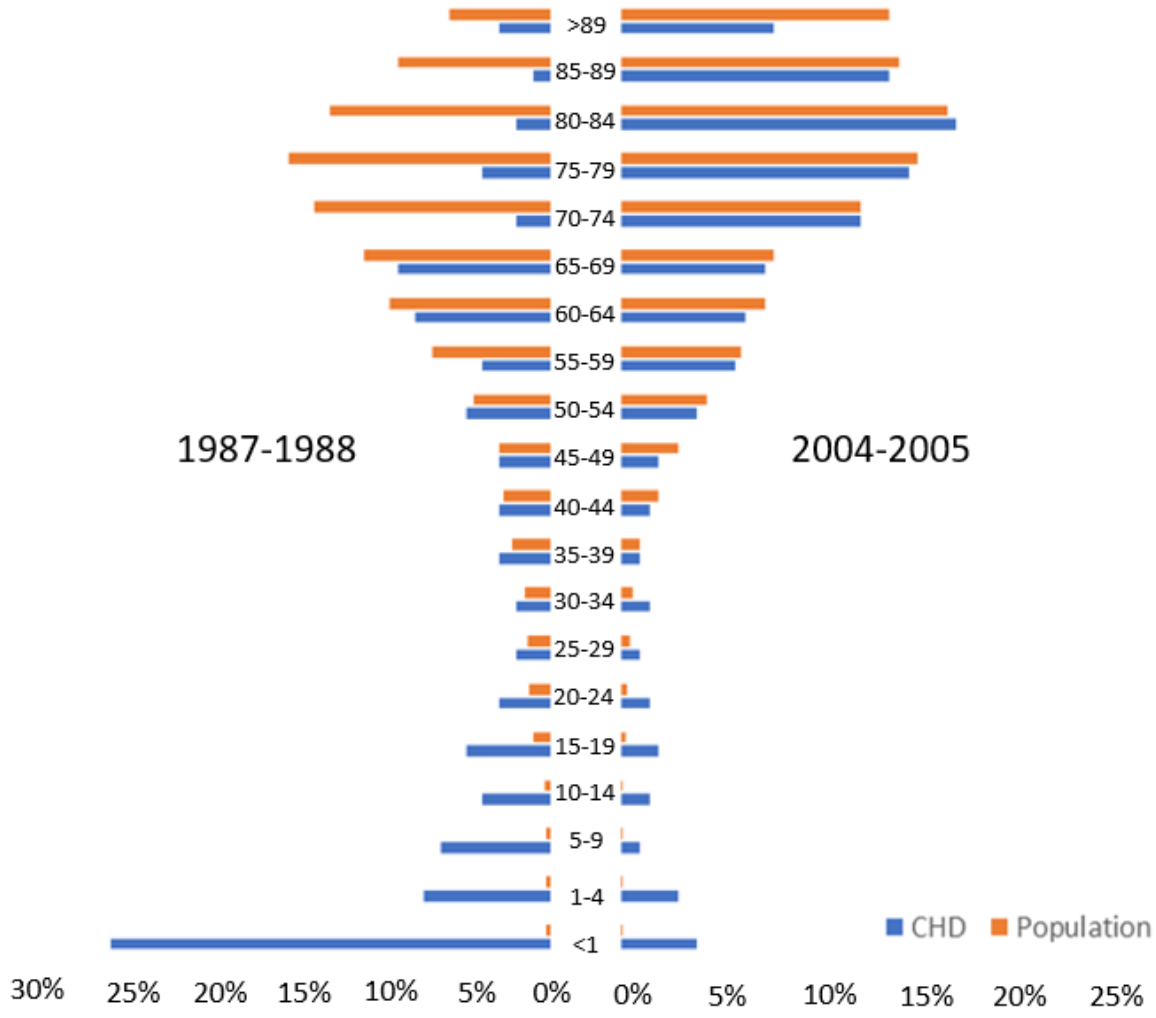


Figure 1-1: Age at death compared to the general population.
Age at death during two time periods for individuals with congenital heart disease and the general population of Quebec, Canada. Reproduced using data from Khairy *et al.* (51)

1.4.2.2 Sex differences in Survival with ACHD

Sex differences in the distribution, presentation, management and outcome of cardiovascular disease in general are well recognised (57–60). The important attention provided to the excess mortality observed for women with cardiovascular disease over recent years is likely to have played an important

part in closing the gap in outcomes (61). Unfortunately, no such consensus exists for CHD. This issue will be discussed further in section 6.1 but results to date have been contradictory. Of the three large studies to compare all-cause mortality according to sex; one found men to be at higher risk (62), one found women to be at higher risk (41), and one found no significant difference (63). In terms of specific clinical outcomes there is some consensus of higher rates of pulmonary hypertension among women, and higher rates of aortic syndromes and infective endocarditis amongst men (41,63).

As well as being conflicting in outcomes, attempts to delineate the influence of sex on mortality in CHD have been limited by an inability to adjust for patient characteristics such as pre-existing comorbidity and socioeconomic factors.

1.4.2.3 Socioeconomic factors associated with survival in ACHD

There are few published data concerning socioeconomic deprivation in CHD. A small number of studies have evaluated the effect of socioeconomic status on birth incidence of CHD with a recent systematic review with meta-analysis suggesting no correlation (64).

A recent US observational study has suggested a correlation between lower socioeconomic status and a higher risk of the composite outcome of unexpected hospital admissions and mortality amongst children with the most severe forms of congenital heart disease (hypoplastic left heart and single ventricle physiologies) (65). In this case, maternal higher education and private health insurance were the metrics used to determine socioeconomic status. The authors correlated this to Hispanic race and suggested an interaction between socioeconomic status and race/ethnicity in the US and as a potential explanation for the previously noted higher mortality in non-white children with CHD (66).

To the best of the author's knowledge, no published data is available concerning socioeconomic status and survival amongst adults with CHD. One potential barrier to the study of socioeconomic status and outcomes in ACHD is the lack of a universally accepted measure. Furthermore, postulated interactions between ethnicity and socioeconomic status should not be taken at face value and are not necessarily transferable from one health care system to another. As a result, the

afore referenced interaction between Hispanic ethnicity, socioeconomic status and certain health outcomes in the US is of very little relevance to the congenital heart disease population of Scotland.

1.4.3 ACHD prognosis in clinical practice

Understanding the survival and circumstances of death amongst adults with CHD is desirable on two fronts: firstly, to inform service development and strategy for service provision on a national and regional level; and secondly, to inform patients on an individual basis, promoting informed decision making regarding both clinical and non-clinical factors. Regarding the former, Scotland utilises the gold standard 'hub and spoke' model for ACHD care where the majority of care for the majority of patients takes place in regional referral centres with occasional care in the single, national centre located at the Golden Jubilee Hospital in Clydebank. It is therefore essential that the right patients get the right care in the right place. Currently, no population data is available regarding the mortality of Scottish adults with congenital heart disease and therefore decision making with regards to all aspects of care; from frequency and locale of review, to timing and method of intervention, is based on clinical judgement and extrapolation from often significantly heterogenous data pools. Furthermore, in June 2018 the Population Health Directorate for Health and Social Care Scotland published a list of six priorities which represent an agreement between the Scottish government and local councils regarding how best to focus efforts, and by extension resources, to best improve the health of the Scottish population (67). Priority five asserts that we should have a 'sustainable economy with equality of outcomes for all'. Paramount to this statement must be an ability to measure and respond to outcomes, such as mortality, across Scotland as a whole, and more specifically amongst different demographic and socioeconomic groups. To the best of my knowledge there has been no successful efforts to evaluate the equity of outcomes for adults with congenital heart disease in Scotland and no bespoke tool exists to this end.

Understanding survival and mortality in ACHD is arguably just as important for the front-line clinician on a day to day basis. From a clinical perspective it is easy to imagine that understanding which patients are most 'at risk' might be useful as it helps to prioritise patient care. What are perhaps less obvious are the myriad real-life practical questions and problems faced by adult survivors with CHD. It is not uncommon to face questions such as "if I have a child am I likely to see them graduate?" or "should I pay into my work pension scheme?". And in fact, questions of this ilk should be encouraged. However, as things

currently stand, the response is often based on insufficient and/or outdated data based on a population remote and quite distinct from that of Scotland. Of course, robust epidemiological data alone does not provide the whole picture regarding mortality in ACHD. Even within a single diagnosis e.g. ASD or TOF, significant heterogeneity exists. There are multiple variables, both inherent to the natural history of the lesion and the interventional strategy which must be taken into consideration when informing the patient. Taking the relatively straightforward example of ASD, factors which may be expected to influence outcome include;

- The position of the defect within the atrial septum (secundum, coronary sinus, superior or inferior sinus venosus)
- Associated lesions e.g. anomalous pulmonary venous drainage, persistent left superior vena cava or an 'unroofed' coronary sinus
- Age at detection
- Biventricular function
- History of atrial arrhythmia
- Pulmonary vascular resistance at the time of detection
- Surgical or percutaneous method of closure
- Complete versus incomplete closure
- The need for additional procedures e.g. tricuspid valve intervention or surgical ablation (Maze procedure)

As things currently stand, assessment of how these variables influence prognosis is largely down to experience and clinical judgement. Although some evidence exists regarding outcomes of surgical compared with percutaneous ASD closure (68), this is limited to short term measures and survival outcome data are lacking. It is a similar picture across the spectrum of CHD lesions. Clearly this situation must be improved if we are to robustly advise our patients on important matters as previously stated.

2 Literature Review

2.1 Introduction

Despite the advances in the early surgical management of congenital heart lesions as outlined in the above chapter, long term survival remains largely uncertain. Although representing the most common group of in-born structural pathologies, congenital heart disease in the adult cardiology clinic and in patient cardiology wards is still uncommon. This relative sparsity of patients makes answering important questions regarding survival and mortality even more difficult. Furthermore, the rapidly evolving landscape of structural intervention for this group of patients and continued improvements in survival to adulthood makes studying mortality in this population analogous to a moving target.

Much of the literature regarding long-term follow up in congenital heart disease are concerning outcomes of interventions as case series or surgical cohorts. Establishing prognosis for ‘all comers’ at a population level is significantly more challenging. In this chapter I aim to review the literature with a view to characterising the survival of adults with congenital heart disease; where possible describing causes of death and temporal trends for all CHD and according to lesions.

2.2 Methods

2.2.1 Search strategy

I systematically searched the Embase and Ovid MEDLINE databases from inception to April 2018 to identify articles pertaining to mortality among adult survivors of CHD as a whole or for any one of ten pre-defined lesions; **ASD, VSD, PDA, aortic coarctation, Ebstein's anomaly, atrioventricular septal defect (AVSD), systemic right ventricle, TGA with arterial switch** and **Fontan circulations.** Eligibility for inclusion was established against these criteria:

1. Must refer to 'all-comer' survival. If survival was only provided according to exposure to a certain procedure or intervention these were excluded.
2. Must contain survival data during adulthood. Where paediatric data is included, adult survival must be reported independently or be extricable from paediatric survival data
3. Published in English language
4. As a minimum, long term outcome must be reported in one of three ways
    1. Mean or median age at death
    2. Survival according to person years of follow-up – or be calculable by the provided information
    3. Percentage survival at predefined age points

A title and abstract word search was carried out across the Ovid MEDLINE and Embase databases. Three search queries, representing the domains of **patient population, study design,** and **outcome** were utilised and search terms include;

Patient population:

> "congenital heart", "atrial septal defect*", patent duct*", "PDA", "ventricular septal defect", "VSD","coarctation", "supra-valvular stenosis", "atrioventricular septal", "AVSD", "coronary sinus defect", "tetralogy of Fallot", "Fallot's tetralogy", "TGA", "transposition of the great arteries", "DTGA", "d-TGA", "LTGA", "l-TGA", "ccTGA", "congenitally corrected", "Fontan", "total cavo-pulmonary", "TCPC", and "adult"

Study design

"population", "epidemiology", "registry", "population-based", "cross section*", "cross-section", or "cohort"

Outcome

"long term", "long-term", "late", "circumstance*", "temporal", "extent", and "prognosis", "outcome", "survival", "death" or "mortality"

I screened all titles and abstracts for relevance and those deemed appropriate were accepted for full article review.

2.2.2 Data duplication

Much of the data contained within the returned searches is derived from local, national and multinational databases and registries. As such the potential for duplication of patient information across two or more articles is significant. At times this was obvious; for example multiple studies derived from the Dutch national CONCOR registry, with significantly overlapping data periods were reviewed. When competing data sets were encountered the more contemporary paper was selected. When the data period was the same, or sufficiently similar as to bear no clinical significance, the article with the greater combined patient follow-up was selected.

In several instances it was more difficult to assess for overlapping patient cohorts, for example where multinational registries have small numbers of patients from a large number of countries/centres which are represented in overlapping articles. Instances such as this were assessed on a case-by-case basis. Where both studies were included, results were assessed by means of sensitivity analysis to limit potential bias. At times, overlapping studies from the same centre or registry were encountered where one contained 'all ACHD' and another contained data concerning a single lesion (e.g. ASD only). In such cases the 'all ACHD' article would be favoured. However, when the 'ASD only' paper contained a large patient cohort (greater than the ASD cohort in the 'all ACHD' study), this data may also be included and the ASD data form the "all ACHD" article disregarded in the analysis. This was in an attempt to maximise the review cohort.

2.2.3 Defining groupings

2.2.3.1 Congenital lesions

When defining lesions within a study, little variability was encountered. By and large there is not much controversy regarding lesion definition however there are a few examples where clarifying heterogeneity within a diagnostic group is likely of significance to outcome. The 'Fontan' cohort is one such example. Clinically the Fontan patient most commonly refers to all who undergo complete 'right heart bypass' surgical palliation. In procedural terms however, the Fontan operation is more accurately a specific method of right ventricular bypass using the right atrium as a conduit (otherwise referred to as the atriopulmonary Fontan) and several other forms or right heart bypass exist. Only cohorts inclusive of all methods of complete right heart bypass were considered. Similarly, the ASD group includes all except ostium primum forms of atrial septal defect. It is therefore inclusive of secundum type as well as sinus venosus and coronary sinus defects. A notable exception is where ICD coding was used for identification of ASDs. In such cases these are inextricable from PFOs due to the same ICD code being used for both. Ostium primum defects are physiologically better thought of as partial atrioventricular septal defects. The obligatory involvement of atrioventricular valve morphology and other deep cardiac structures renders them suitably distinct from other forms of ASD as to reasonably assume distinct mortality outcomes. Finally, a lesion group of systemic right ventricles was formed. This consists of two groups of patients; those with congenitally corrected transposition of the great arteries and those with complete transposition of the great arteries who have undergone an 'atrial switch' procedure (Mustard or Senning palliation). More complex lesions involving a systemic right ventricle such as hypoplastic left heart syndrome following surgical palliation or unoperated double outlet right ventricle were not included in this group as the governing physiology and impact on mortality are not comparable. This method of defining the systemic right ventricle has precedence within the literature (43,69).

2.2.3.2 Cardiovascular and non-cardiovascular death

Causes of death were grouped as either being cardiovascular or non-cardiovascular in nature. I regarded cardiovascular death to be death due to;

heart failure, ischaemic heart disease, sudden cardiac or arrhythmic death, pulmonary thromboembolism, stroke, death attributed to cardiovascular intervention, or peripheral vascular disease including aneurysmal haemorrhage. Non-cardiovascular death included all remaining causes as long as a cause was clearly defined. Where the cause of death was unclear it was removed from the denominator. As such calculations regarding cause of death may not always be equal to 100 percent of the deaths within the total study cohort. Deaths due to infective endocarditis were considered to be non-cardiovascular in nature.

Cause of death is also reported according to lesion complexity. This approximates the Bethesda groupings as described in section 1.3.2.

2.2.4 Statistics

Descriptive statistics are quoted as either mean +/- standard deviation (SD) or median and interquartile range (IQR) depending on the availability from the source article. Where both were available the mean +/- SD was favoured. This was in order to allow combining of data. For example, when age at death is given for sinus venosus ASD and secundum ASD separately using the mean, they were multiplied out by the number of deaths in each group and a total 'ASD group' mean age at death with SD were calculated.

Mortality rate is quoted in terms of number of deaths per 1000 years of cumulative follow up. Where this was not provided in the source material it was calculated using the mean number of years followed up per person, the cohort size, and the total number of deaths encountered. Where the average follow up period per person was given as a median only, the mean was calculated using the method described by Hozo et all (70) where the median approximates the sample mean when the sample size is large but can otherwise be calculated by the method shown below (Equation 1).

$$\bar{x} \approx \frac{a + 2m + b}{4} \quad a = minimum\ value, b = maximum\ value, m = median$$

Equation 1, estimating the sample mean from the median and range (70)

2.3 Results

2.3.1 Search results and article eligibility

Initial search by the manner described above yielded 509 articles. Following exclusion of duplicates, 323 articles were screened for eligibility by abstract and title according to the predetermined inclusion criteria and to exclude any non-English language and non-human subject publications. Ultimately, 56 full texts were reviewed in detail, 34 of which were excluded: 11 referred to the wrong patient population, frequently paediatric populations or subsets of patients who have undergone certain interventions or fulfil certain biochemical criteria; 9 reported the wrong outcomes, either no survival data was given or composite outcomes only were provided with no breakdown of mortality; 8 articles were deemed to have a high probability of significant patient population overlap; 6 articles were editorials or review articles. Figure 2-1 summarises article screening and inclusion.

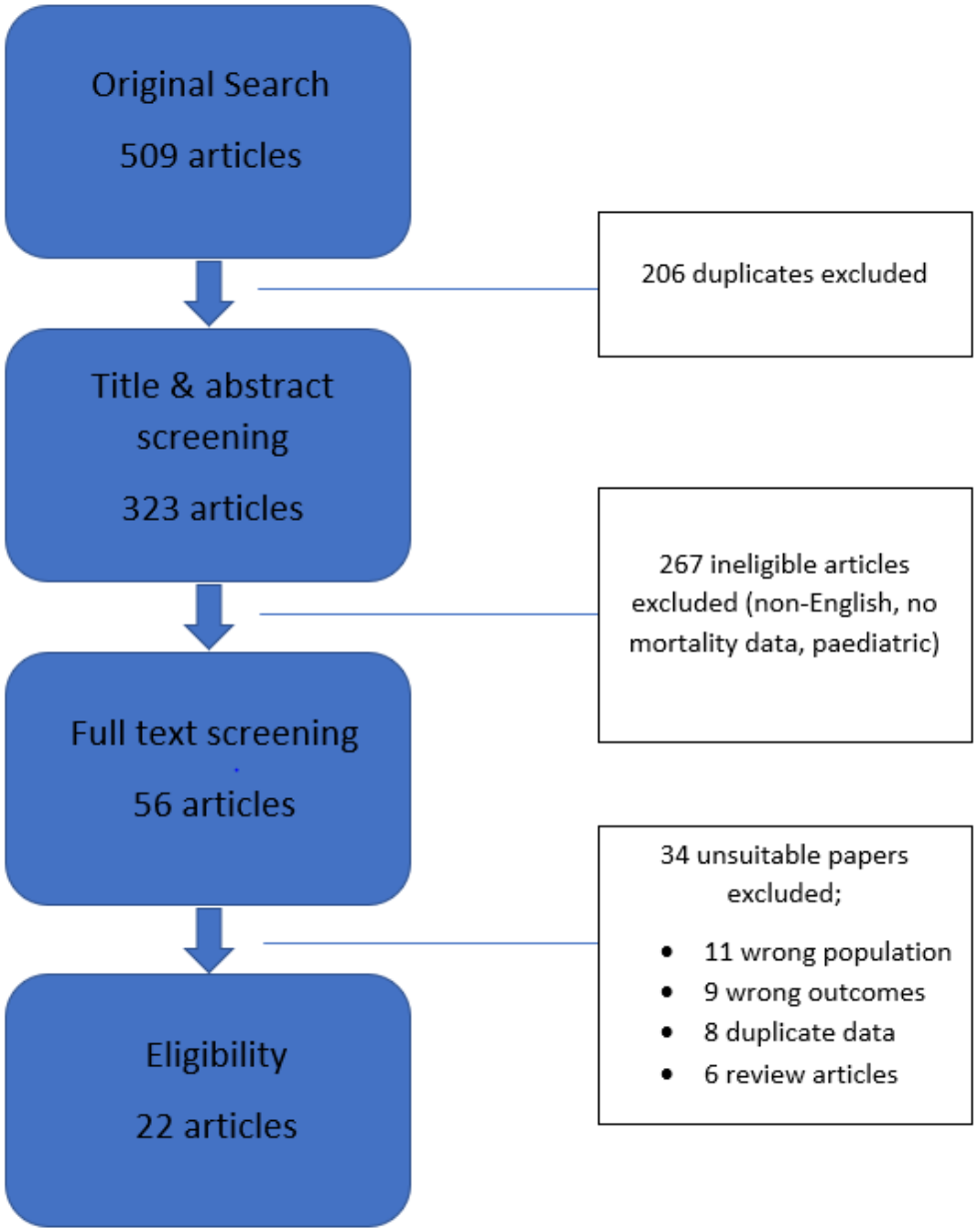


Figure 2-1: PRISMA diagram of article eligibility

2.3.2 Survival

A total of 22 articles provided data regarding survival. 7 articles included data for all CHD subsets (43,44,71–75); 6 articles for ASD (43,73,75–78); 4 for Fontan patients (43,79–81); 6 for TOF (41,43,82–85); 5 for systemic RV (43,69,73,75,86); 5 for CoA (43,73,75,87); 5 for VSD (37,43,73,75,88); 3 for PDA (37,43,73); 3 for Ebstein's anomaly; 3 for AVSD (43,73,89); and 1 for TGA arterial switch (43).

All but two articles originated from Europe or North America: 14 Europe; 6 North America; 2 Australasia. A variety of data sources were encountered across the studies. Most frequently (n=12) cases were identified from single centre databases or clinic list review. Regional or nationally developed databases were utilised on 4 occasions, national registries on 3 occasions and a multinational registry on one occasion. Only one study utilised a centrally controlled coding system to identify individuals with ACHD, and this was on a regional basis (72). No data retrieval method was therefore able to identify unselected ACHD patients, independent of enrolment in a registry or database, on a national level. Data regarding cause of death was derived either from direct inspection of medical notes and certificates in 12 cases, or from national death registries in 10 cases.

The study characteristics and populations are summarised below (Table 2-1).

Table 2-1 - Summary of included articles

Study	Patients, N	Year(s) of Study	Location	Study Design	Source of Cases	Source of Death Information	CHD subtypes
Diller et al, 2015 (43)	6969	1991 - 2013	London, England	Single centre, retrospective cohort	Royal Brompton Hospital database	Medical records, death certification	All CHD, ASD, PDA, VSD, AVSD, TOF, Ebstein's, systemic RV, Fontan, CoA, Arterial switch
Engelfriet et al, 2008 (71)	4110	1998 - 2004	Europe (79 centres, 56 countries)	Multinational, retrospective cohort	Locally derived, casenote	Locally derived	All CHD
Khairy et al, 2010 (34)	74,686	1983 - 2005	Quebec, Canada	Population based, regional, retrospective cohort	Quebec Health Insurance Board	Quebec Health Insurance Board	All CHD
Oliver et al, 2017 (73)	1625	1989 - 2014	Madrid, Spain	Single centre, retrospective cohort	La Paz University Hospital ACHD database	Spanish National Death Index	All CHD, ASD, PDA, VSD, AVSD, TOF, Ebstein's, systemic RV, CoA
Popelova et al, 2015 (74)	646	2003 - 2013	Prague, Czech Republic	Single centre, prospective cohort	Hospital Na Homolce	Czech National Mortality Register	All CHD
Trojnarska et al, 2009 (44)	1304	1995 - 2004	Poznan, Poland	Single centre, retrospective cohort	ACHD Clinic, University of Medical Sciences, Poznan	Medical records, death certification	All CHD
Zomer et al, 2010 (75)	8595	2001 - 2010	Amsterdam, Netherlands	National registry	CONCOR database	Medical records, death certification	All CHD, ASD, VSD, AVSD, TOF, Ebstein's, systemic RV, CoA
Kotowycz et al, 2013 (76)	718	1988 - 2005	Quebec, Canada	Population based, regional, retrospective cohort	Quebec CHD database	Quebec Health Insurance Board	ASD
Kuijpers et al, 2015 (77)	2207	2001 - 2014	Amsterdam, Netherlands	National registry	CONCOR database	Medical records	ASD
Nyboe et al, 2017 (78)	2277	1977 - 2013	Aahrus, Denmark	Population based, national, retrospective cohort	Danish national registries	Danish Register of Causes of Death	ASD
Burchill et al, 2015 (79)	106	2004 - 2012	Toronto, Canada	Single centre, prospective cohort	Toronto Congenital Cardiac Centre	Medical records	Fontan
Dennis et al, 2017 (80)	683	2008 - 2017	Sydney, Australia	Multinational, retrospective cohort	ANZFR	National Death Reristry	Fontan
Elder et al, 2015 (81)	123	1999 - 2013	Atlanta, USA	Single centre, retrospective cohort	Emory Adult Congenital Database	Medical records	Fontan
Bokma et al, 2017 (82)	794	2001 - 2016	Amsterdam, Netherlands	National registry	CONCOR database	Medical records	TOF
Buys et al, 2012 (83)	92	2000 - 2003	Leuven, Belgium	Single centre, prospective cohort	Gasthuisberg University Hospital	Medical records	TOF
Harrison et al, 2001 (84)	242	1990 - 1995	Toronto, Canada	Single centre, retrospective cohort	University of Toronto Congenital Cardiac database	Medical records	TOF
Mouws et al, 2017 (85)	225	2000 - 2015	Rotterdam, Netherlands	Single centre, retrospective cohort	DANAR database	Medical records	TOF
Chaix et al, 2017 (86)	140	1989 - 2017	Montreal, Canada	Single centre, retrospective cohort	CONGREGATE database	Medical records	Systemic RV
Dobson et al, 2012 (69)	129	2011 - 2012	Glasgow, Scotland	Single centre, retrospective cohort	Golden Jubilee National Hospital Database, and medical records	Medical records	Systemic RV
Choudhary et al, 2015 (87)	151	1993 - 2013	Sydney, Australia	Single centre, retrospective cohort	Prince Alfred Hospital, Sydney database	National Death Index	CoA
Gabriels et al, 2017 (88)	266	2005 - 2013	Leuven, Belgium	National registry	Belgian Registry on ACHD	Medical records	VSD
Videbaek et al, 2016 (37)	871	2013	Aahrus, Denmark	Population based, national, retrospective cohort	Medical records	Danish Register of Causes of Death	VSD, PDA

2.3.2.1 All CHD subtypes

Survival data as well as demographics and study period for all CHD and for each CHD lesion are summarised in Table 2-2.

Of the 7 articles for which survival data across all CHD subtypes was reported, 6 were European cohorts and one was Canadian. The era of study ranged from 1983 (51) to 2014 (73). The median year of study for each article ranged from 1990 (51) to 2013 (37) with one article presenting survival across two distinct data periods, from 1987 – 1993 and 1999 – 2005 (51).

The number of individuals included within the studies ranged from 646 (74) to 71686 (51) with a combined total across all studies of 95886 persons. The proportion of female patients ranged from 49.9% (43) to 55.1% (44) with a combined proportion of 52.7% across all studies (44,261 of 83,916 persons; not reported in two articles (71,75)).

Age at time of study ranged from 22.5 (IQR 18-39) (73) to 35.0 (SD 12) years (74). The total number of years of follow up ranged from 3,876 (74) to 982,363 (51) with a total combined person follow up across all articles of 1,143,117 person years. Mortality rates ranged from 5.87 (71) to 9.03 (74) deaths per 1000 person years. The combined mortality rate across all studies was 8.59 per 1000 person years. Age at death ranged from 40 years (74) to 59 years (73) across the total study cohorts and from 40 years (74) to 75 years (34) across the studied data periods.

Table 2-2 - Demographics and survival according to lesion studied
(NR=not reported, NC=not able to calculate).

Subtype	Article	Year (mid point)	N	Female %	Age	Dead (%)	Mortality rate (per 1000 person years)	Age at death
All CHD	Khairy et al	1990	NR	NR	NR	NR	NC	60 (3-76)
	Khairy et al	2000	NR	NR	NR	NR	NC	75 (60-83)
	Trojnarska et al	2000	1304	55.1	29.4 +/-10.6	29 (2.2)	6.3	NC
	Engelfriet et al	2001	3375	NR	28 +/- 3.0	101 (3.0)	5.9	NC
	Diller et al	2002	6969	49.9	29.9 +/- 15.4	524 (7.7)	7.4	47 34-65
	Oliver et al	2002	3311	51	22.5 (18-39)	336 (10.1)	8.9	59 (36-75)
	Zomer et al	2006	8595	NR	NR	231 (2.7)	8.7	48 +/-11.8
	Popelova et al	2008	646	53.4	35 +/-12	35 (5.4)	9	40 +/-14
ASD	Nyobe et al	1995	2277	61	45.4 +/-0.4	315 (13.8)	7.6	NC
	Kotowycz et al	1997	718	70.5	45.8	27 (3.8)	NC	56 +/-13.7
	Oliver et al	2002	472	65.9	39.4 (23-55)	57 (12.0)	12.1	NC
	Diller et al	2003	1092	61.3	39.8 +/-18.3	66 (6.2)	NC	72 (62-79)
	Kuijpers et al	2008	2207	67	44.8 +/-17	102 (4.6)	7.5	83
VSD	Oliver et al	2002	356	53	19.1 (17-23)	5 (1.4)	1.4	NC
	Diller et al	2002	713	50.6	26.1 +/-12.5	19 (5.9)	NC	48 (39-60)
	Zomer et al	2006	1358	NR	NR	17 (1.3)	NC	51
	Gabriels et al	2009	266	NR	NR	NR	NC	51 +/-9.5
	Videbaek et al	2013	598	55	45.9 (42-49)	41 (6.9)	1.5	NC
PDA	Oliver et al	2002	90	79	28.1 (19-44)	10 (11.0)	8.4	NC
	Diller et al	2002	117	77.8	32.8 +/-16.4	2 (1.7)	NC	74 (63-88)
	Videbaek et al	2013	281	68	48.1 (44-52)	19 (6.8)	1.4	NC
TOF	Harrison et al	1993	242	45.5	33.9	10 (4.1)	1.9	40.4
	Buys et al	2002	92	30	26.1 +/-7.7	2 (2.7)	3	NC
	Oliver et al	2002	327	46	20.3 (18-27)	18 (5.5)	5.3	NC
	Diller et al	2002	869	45.9	26.8 +/-13.1	54 (6.3)	NC	50 (35-66)
	Zomer et al	2006	868	NR	NR	28 (3.2)	NC	51
	Mouws et al	2008	225	43.1	41 +/-12	27 (12.0)	3.4	NC
	Bokma et al	2009	794	45	27 20-38	46 (5.8)	6.5	NC
Coarctation	Oliver et al	2002	353	42	20.2 (18-29)	21 (5.9)	6.3	NC
	Diller et al	2002	860	41.3	28.9 +/-14.3	39 (4.6)	NC	48 (37-65)
	Choudhary et al	2003	151	42	35 +/-15	7 (4.6)	1.8	59 (29-72)
	Zomer et al	2006	868	NR	NR	13 (1.5)	NC	59
Ebstein's	Oliver et al	2002	76	72	32.4 (20-47)	9 (12.0)	15	NC
	Diller et al	2002	153	54.3	34.5 +/-16.2	19 (12.6)	NC	52 (37-73)
	Zomer et al	2006	138	NR	NR	8 (5.8)	NC	47
AVSD	Oliver et al	2002	148	61	20.0 (17-29)	8 (5.4)	6.9	NC
	Diller et al	2002	255	57.6	29.1 +/-14.8	15 (5.9)	NC	52 (48-63)
	Zomer et al	2006	129	NR	NR	8 (6.2)	NC	37
Systemic RV	Oliver et al	2002	42	40	29.4 (20-48)	12 (29.0)	57.1	NC
	Diller et al	2002	279	46	27.6 +/-12.4	34 (12.5)	NC	37 (28-42)
	Chaix et al	2003	140	37.1	25.1 +/-6.7	7 (5.0)	5.1	32
	Zomer et al	2006	112	NR	NR	8 (7.1)	NC	47
Fontan	Dennis et al	1996	683	NR	26 +/-8	62 (9.1)	10.6	NC
	Diller et al	2002	180	53.3	21.4 +/-7.4	34 (19.2)	NC	28 (23-36)
	Elder et al	2006	123	43.9	28.5 +/-7.7	13 (10.6)	4.7	32
	Burchill et al	2008	106	51	30 +/-10	7 (6.7)	6	NC

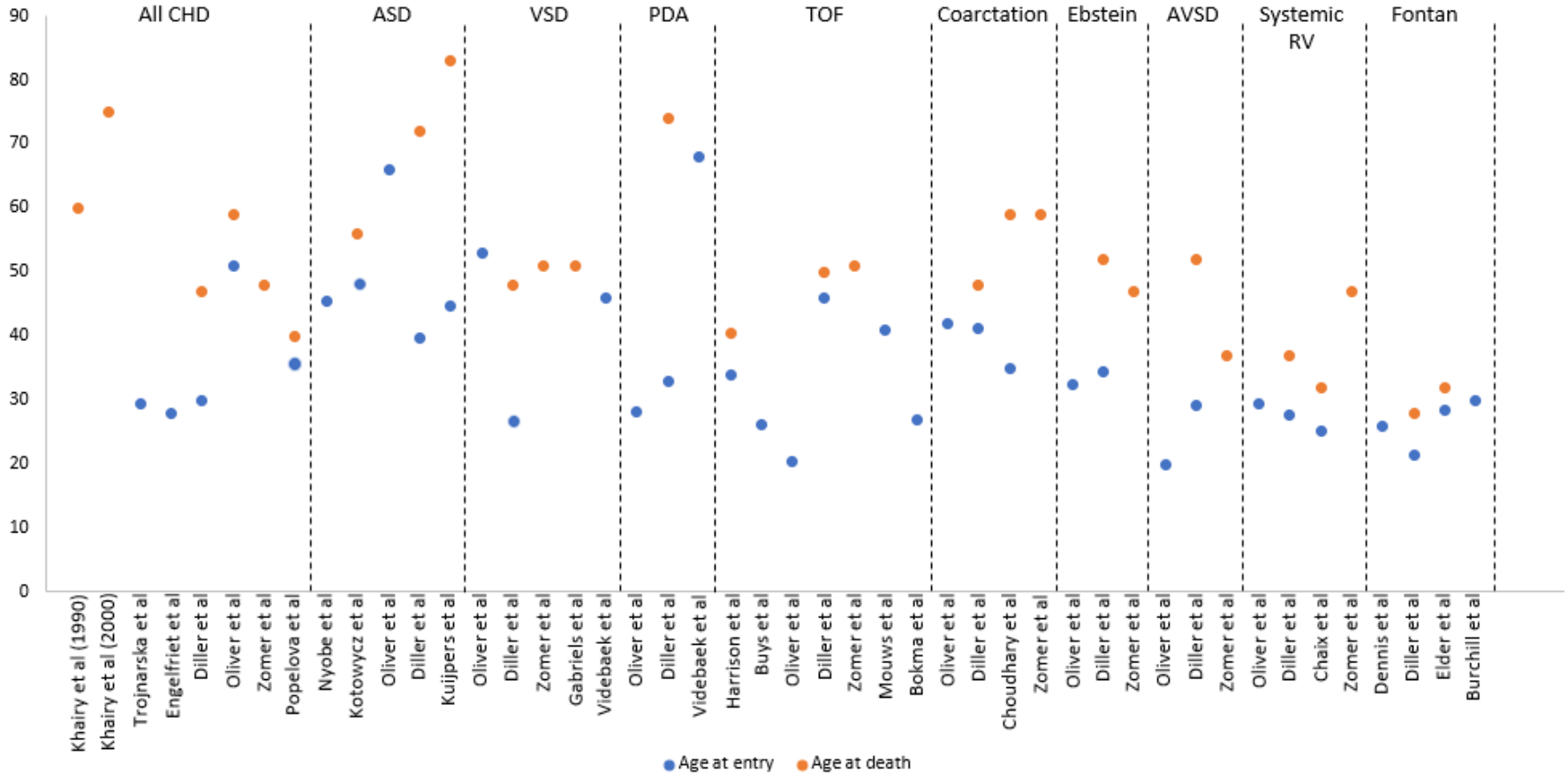


Figure 2-2: Age at entry and age at death for each article included and according to lesion

2.3.2.2 ASD

Of the 6 articles for which survival data regarding ASD was included, three were subsets from larger cohorts involving multiple CHD subtypes (43,73,75) and three were dedicated to ASD alone (76–78). The number of patients in each study ranged from 472 (73)to 2,277 (78) with a total of 8,236 across all studies. The proportion of women ranged from 61.0% (78) to 70.5% (76) and was cumulatively 64.3% (4351 of 6766; data not reported for one article (75)). Age at study ranged from 39.4 (73) to 45.8 years (76).

Cumulative patient follow up could be calculated for 3 articles and ranged from 4,723 (73) to 41,214 years (78). Amongst these articles mortality rate ranged from 7.5 (77) to 12.1 (73) deaths per 1000 person years and yielded a combined mortality rate of 7.9 per 1000 person years (474 deaths in 59,521 years of follow up).

Age at death ranged from 55.6 (SD 13.7) years (76) to 83.4 (SD not given or calculable) years (77). Age at death according to study period is shown in Figure 2-3.

2.3.2.3 VSD

Of the 5 articles contributing survival data for VSD; 4 were subsets from larger studies (37,43,73,75) and one was a dedicated VSD cohort (88). The number of VSD patients in each study ranged from 266 (88) to 1,358 (37) with a total combined cohort of 3,291 patients. The proportion of women ranged from 50.6% (43) to 55.0% (37) with a combined proportion across the three studies for which it could be extrapolated of 52.7% (879 of 1,667).

Cumulative person follow up could be calculated for two studies yielding a combined 30,946 years (37,73). Mortality rate ranged from 1.39 (73) to 1.50 (37) per 1000 person years giving a combined mortality rate of 1.49 per 1000 person years.

Age at death could be calculated for 3 articles and ranged from 48 (IQR 39-60) (43) to 51.3 (SD 9.5) (88) years. Age at death according to era of study is shown in Figure 2-3

2.3.2.4 PDA

Data regarding survival in PDA was available from three articles, all of which were subsets of larger cohorts (37,43,73). The number of PDA patients in each study ranged from 90 (73) to 281 (37) with a combined total of 488. The proportion of women ranged from 68.0% (37) to 79.0% (73) and a combined 73.0% (356 of 488) across the three studies.

Combined follow up could by calculated for two studies (37,73) yielding a total combined follow up of 14,686 years. Mortality rate ranged from 1.41 (37) to 8.35 (73) deaths per 1000 person years.

Age at death was only provided by one study (43) and was 74.0 years (IQR 63-88).

2.3.2.5 Aortic coarctation

Survival data concerning aortic coarctation was included from 4 studies; 3 were subsets of larger studies (43,73,75), where one was a dedicated coarctation cohort (87).

The total number of coarctation patients across the four studies was 2,232 (range; 151 (87) to 868 (75)). The proportion of female patients ranged from 41.3% (43) to 42.0% (73) giving a combined 41.5% (566 of 1364).

Cumulative person follow up could be calculated for two studies (73,87) yielding a total of 7,244 person years. A combined 28 deaths were observed in these two studies, yielding a combined mortality rate of 3.9 deaths per 1000 person years (range; 1.78 (87) to 6.3 per 1000 person years (73)).

Age at death could be extrapolated for three studies and ranged from 48.0 (IQR 37-65) (43) to 59.0 (IQR 29-72) (87).

2.3.2.6 Ebstein's anomaly

Three articles provided survival data on Ebstein's anomaly, all of which were subsets of larger cohorts (43,73,75). A combined 367 patients with Ebstein's anomaly across the three studies were included (range; 76 (73) to 153 (43)). The proportion of women ranged from 54.3% (43) to 72.0% (73) comprising 60.3% (138 of 229) overall.

Cumulative follow up and mortality rate could only be calculated for one study (73) and yielded 9 deaths in 600 person years, equivalent to 15.0 deaths per 1000 person years.

Age at death ranged from 46.8 (SD not given or calculable) (75) to 52.0 (IQR 37-73) (43) years.

2.3.2.7 AVSD

Three articles provided survival data on AVSD, all of which were subsets of larger cohorts (43,73,75). A combined 532 patients across the three studies were included (range; 129 (75) to 255 (43)). The proportion of female patients ranged from 57.6% (43) to 61% (73) giving a combined proportion of 58.8% (237 of 403).

A mortality rate of 6.93 deaths per 1000 person years could be calculated from one study (73). Age at death ranged from 37.3 (SD not given or calculable) (75) to 52 (IQR 48-63) (43) years.

2.3.2.8 Tetralogy of Fallot

Of the six studies contributing survival data concerning TOF, 2 were subsets of larger cohorts (43,73) and four included TOF patients only (82–85). A total of 2,549 patients were included across all six studies (range; 92 (83) to 869 (43)). The proportion of female patients ranged from 30.4% (83) to 46.0% (73). A combined proportion of 44.8% (1141 of 2549) were women.

Cumulative patient follow up could be calculated for 5 of the 6 articles and yielded a total cumulative follow up of 24,393 years (range; 677 (83) to 7875

(85) years). The cumulative mortality rate across these studies was 4.2 per 1000 person years (range 1.87 (84) to 6.46 (82) per 1000 person years).

Age at death was provide by two studies and ranged from 40.4 (unable to calculate SD) (84) to 50.0 (IQR 53-66) years.

2.3.2.9 Arterial Switch

One study included survival data regarding patients with TGA post arterial switch operation (43). A total of 171 patients were included (30.5% female). Only 3 deaths were reported.

2.3.2.10 Systemic right ventricle

Of the 5 studies contributing survival data regarding systemic right ventricles, 3 were subsets of larger cohorts (43,73,75) and 2 were of systemic RV patients only (69,86). A total of 702 individuals across the 5 studies were included (range; 42 (73) to 279 (43)). The proportion of women ranged from 34.9% (69) to 46.0% (43) with a combined 41.2% (243 of 590) across the four studies for which sex was reported.

A total combined follow up of 3,066 person years was observed across the three studies for which it could be calculated (69,73,86). The mortality rate across these studies was 18.3 deaths per 1000 person years (range; 5.1 (86) to 57.1 (73)). Age at death ranged from 31.7 (unable to calculate SD) (86) to 46.8 (SD not given or calculable) years (75).

2.3.2.11 Fontan

A total of four articles contributed survival data concerning Fontan patients; one was a subset of a larger study (43), and three included Fontan patients only (79-81). A total of 1,092 patients were included across the four studies (range; 106 (79) to 683 (80)) yielding a total combined patient follow up of 9,636 years (unable to calculate for one study (43)). The proportion of female patients ranged from 43.9% (81) to 53.3% (43) with a combined 49.9% (204 of 409) across the three studies for which sex was reported.

Mortality rate ranged from 5.96 (79) to 10.6 (80) deaths per 1000 person years. The combined mortality rated across the three included studies was 8.51 per 1000 person years.

Age at death was given or could be calculated from two studies and ranged from 28.0 (IQR 23-36) (43) to 31.8 (SD not calculable) years (81).

2.3.2.12 Age at death according to study period

Other than for PDA, 2 or more articles referring to each CHD lesion reported age at death.

Figure 2-3 shows age at death according to the mid-point of each study for which it could be calculated.

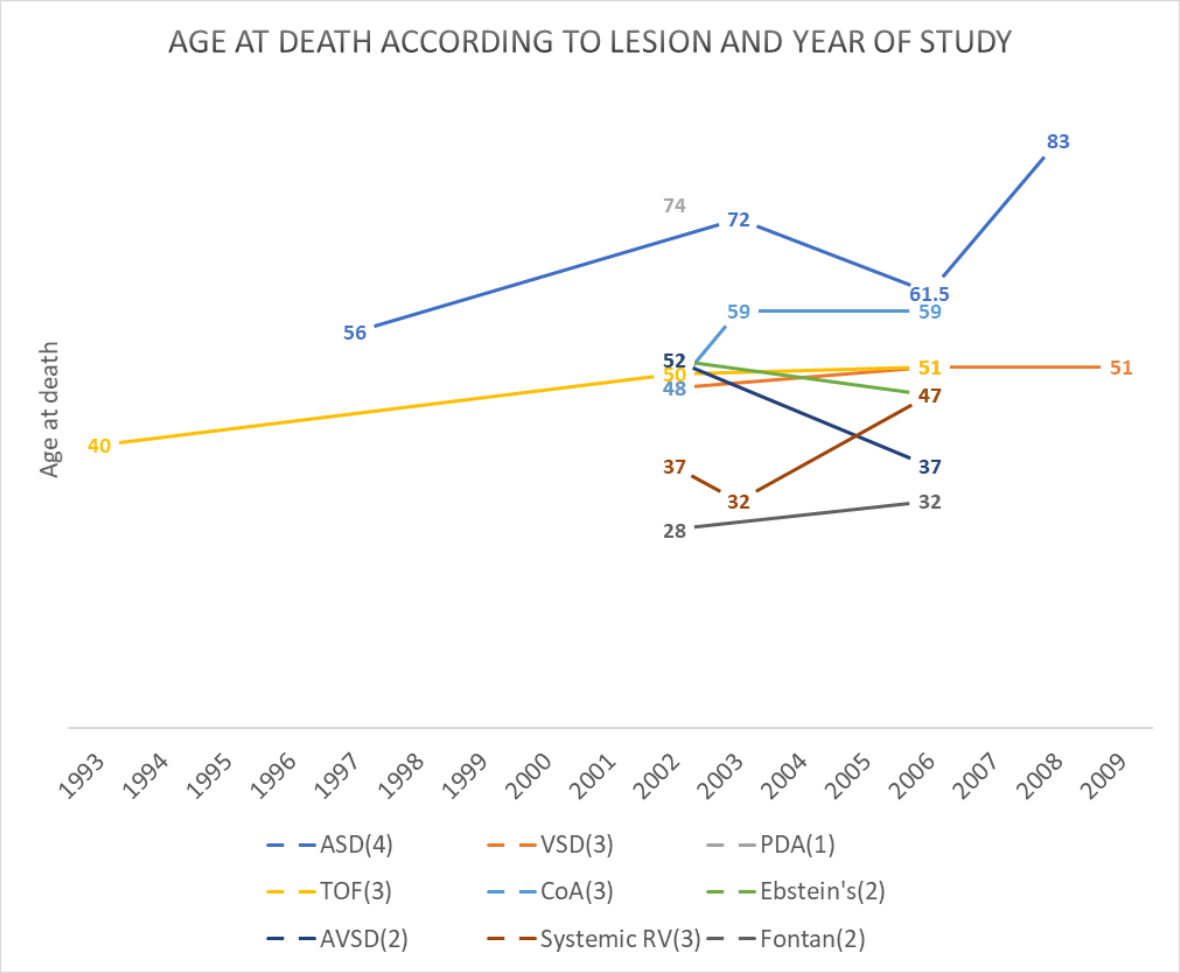


Figure 2-3 - Age at death for each lesion according to the midpoint of each study. Number of studies for each lesion given in brackets (*).
Age at death from earliest to most recent point of study increased for all lesions other than AVSD and Ebstein's anomaly.

2.3.3 Cause of death

Cause of death was reported in 13 articles in total (43,71,73–78,80,82,85–87). Table 2-3 summarizes the studies, absolute, and proportional breakdown of CV and non-CV death according to the lesion reported.

Table 2-3 - Cardiovascular and non-cardiovascular death for all CHD and by lesion.
* no definition of CV / non-CV given in the source data

Subtype	Article	Year (mid point)	CV deaths	Non-CV deaths	CV%	Non-CV%
All CHD	Engelfriet et al*	2001	81	20	80.2	19.8
	Oliver et al	2002	194	137	94.3	5.7
	Diller et al	2002	331	191	63.5	36.5
	Zomer et al	2006	177	54	76.6	23.4
	Popelova et al	2008	33	2	94.3	5.7
ASD	Nyboe et al	1995	147	155	48.7	51.3
	Kotowycz et al	1997	10	13	43.5	56.5
	Diller et al	2002	30	36	45	55
	Kuijpers et al	2008	50	35	58.8	41.2
VSD	Diller et al	2002	9	9	50	50
	Zomer et al	2006	13	4	76.5	23.5
PDA	Diller et al	2002	1	1	50	50
TOF	Diller et al	2002	36	18	66.7	33.3
	Mouws et al	2008	16	8	66.7	33.3
	Bokma et al	2009	34	8	81	19
CoA	Diller et al	2002	26	13	66.7	33.3
	Choudhary et al	2003	6	1	85.7	14.3
	Zomer et al	2006	9	4	69.2	30.8
Ebstein's	Diller et al	2002	12	7	63.2	36.8
	Zomer et al	2006	7	1	87.5	12.5
AVSD	Diller et al	2002	13	2	86.7	13.3
	Zomer et al	2006	4	4	50	50
Systemic RV	Diller et al	2002	32	2	94.1	5.9
	Chaix et al	2003	6	1	85.7	14.3
	Zomer et al	2006	8	0	100	0
Fontan	Dennis et al	1996	33	11	75	25
	Diller et al	2002	29	5	85.3	14.7
	Zomer et al	2006	11	2	84.6	15.4

The combined proportion of cardiovascular deaths for the 5 articles which reported on all CHD was 66.9% (816 of 1,220 deaths). When all studies were combined to include single lesion only studies the proportion of CV deaths was 63.7% (1,118 of 1,754 deaths).

For individual lesions, the proportion of cardiovascular deaths ranged from 49.8% (237 of 476 deaths) for ASD to 93.9% (46 of 49 deaths) for systemic RV.

For lesions of simple complexity (ASD, VSD and PDA) the proportion of cardiovascular deaths was 50.7% (260 of 513 deaths). For lesions of moderate and great complexity the proportion of cardiovascular deaths was 76.4% (282 of 369 deaths).

2.4 Discussion

This literature review utilised a systematic search of the OVID and Medline databases. The ideal patient cohort was to be a cross-sectional representation of the ACHD population. For that reason, only articles reporting survival for non-selected patient cohorts were included. This effectively ruled out surgical cohorts unless a non-selected comparator or total cohort was also reported, this represents the bulk of the published literature within ACHD and is the primary reason that the total number of studies included was low at 22. Ideally an analysis using population-based studies only would be optimal, as regional cohorts are invariably of specialist centres and bias is towards more complex or severe lesions and phenotypes. Due to the lack of unselected population-based studies identified in the literature, this degree of selectivity would have prohibited meaningful review or analysis.

Overlap of patient populations between articles was also common. In particular, the CONCOR Dutch national registry reported multiple studies with overlapping data periods. It is unclear to what extent data overlap exists in less obvious cases. The specialist nature of much of the management of ACHD means that patients may receive some interventions away from their follow up centre and could therefore be included in more than one study. For example; patients with systemic RV who are under follow up in Scotland but attend a centre in England for an intervention such as a catheter ablation for arrhythmia may well be included in more than one cohort. Overall, I felt that the influence of these undoubtedly small numbers of patients who are duplicated across data sets was less important than the exclusion of entire data sets on their behalf, particularly given the overall paucity of data.

All of the included studies were derived from cohorts in developed countries with predominantly Caucasian populations. This review is not therefore representative of a worldwide ACHD population cohort. In particular, no data from Asian or African cohorts was suitable for inclusion. One Japanese study did report a reduced trend in mortality rate from the late-1970s to the mid-1990s but unfortunately this was only available as graphical trends for predetermined age strata and absolute figures for the total ACHD cohort could not be extracted (90). A TOF cohort from Taiwan reported a 30 year post repair survival of 89.3%

however age at death and survival independent from surgery could not be calculated (91).

When considering all CHD lesions combined, a large total patient cohort and combined patient follow up was achieved (95,886 patients and 1,143,117 years respectively). However, it is worth noting that 74.8% of all patients and 85.9% of the cumulative patient follow up was achieved by a single, large study (51).

Overall, there was a slight predominance of women across the studies at 52.7% but this was highly variable depending on lesion, ranging from 73.0% for PDA to 30.5% for TGA arterial switch (results reported from one article only). The pure shunt lesions (ASD, PDA, VSD and AVSD) as well as Ebstein's anomaly were more common in women. Conotruncal lesions (TOF, TGA arterial switch and systemic RV) and aortic coarctation conversely were more common in men. The Fontan population was a near exact split with 49.9% being women.

Survival and mortality were presented by various methods across the literature. Survival to predefined age points was reported by four studies (69,80,81,87) however the predefined age cut-offs varied between studies making comparison difficult. Surprisingly, a mid-point estimate of age at death was only available for 12 of the 22 included studies. Although a crude measure of survival, mean age at death is extremely informative, particularly when considering cross-sectional cohorts and trends over time. Two studies present standardised mortality ratios as corrected for age and sex matched population cohorts (43,73). This method has the clinically orientated appeal of implying a lesion specific mortality burden for an individual patient in comparison to their unaffected peers.

Measuring survival in terms of mortality rate in ACHD is significantly flawed as the point of entry to the data will alter the mortality rate equally as much as survival. It is therefore not possible to definitively compare survival between data sets based solely on crude mortality rates. Having said that, mortality rates do at least provide context to the number and frequency of deaths observed and help to describe the patient population. Given the variable age at inclusion to the data sets and different recruitment methods across studies, mortality rates as reported for all CHD lesions were surprisingly relatively uniform. The highest

reported mortality rate (9 deaths per 1000 person years) for all CHD was reported in a single centre Czech cohort (74) which was the smallest (646 patients) and oldest patient cohort in this group with a baseline age of 35.0 years. The observed mortality rates for the individual lesion groups were variable and did not simply correlate with lesion complexity. The highest combined mortality rate was for the systemic RV group (18.3 per 1000 person years). This is higher than that observed for the Fontan group (8.5 per 1000 person years) which was actually more comparable to the ASD group (7.9 per 1000 person years) in this respect. This may be partly explained by lesions such as ASD and the ccTGA subset of systemic RV patients often presenting to follow up later in life; either at onset of symptoms, or as an incidental finding. They would therefore have shorter follow up periods prior to death when compared with patients who require Fontan palliation and invariably present in the neonatal period and are followed thereafter, amounting greater follow up but potentially dying younger. This is supported by the age at death data. Figure 2-3 illustrates this and more predictably the Fontan group die at a younger age than any other at any given data period. The remaining lesions also follow a clinically logical pattern with ASD and PDA living to the oldest age, with AVSD and Ebstein's next to Fontan demonstrating the youngest age at death. Observed age at death increased as the median year of study progressed for all but two lesions (AVSD and Ebstein's) for which the results are based on sparse data (a total of 27 and 22 deaths respectively) and so should be interpreted with caution. Comparison of age at death according to period of study was not attempted for articles reporting all CHD as the study populations were suitably heterogenous to render this meaningless. In particular the proportional breakdown of each lesion within the cohort would need to be comparable for any conclusions to be drawn. The only reasonable comparison of all CHD age at death according to data period is provided from two study periods within the same article by Khairy *et al* (92), and suggests an increase from 60 to 75 years between 1990 and 2000 (Table 2-2).

Throughout the included studies there was little attempt to delineate mortality data according to patient characteristics and demographics. Sex differences in mortality and circumstances of death were surprisingly sparsely reported. Although sex was often included in univariate and multivariate models, absolute figures for age at death, mortality rate etc were almost never provided.

Therefore, the frequently encountered increased hazard ratio associated with male sex is of little practical use as this is also the case in the general population and cannot be further interpreted. One study did report age at death according to sex amongst ASD patients, finding a significantly higher age at death for women (75.8 IQR 65.7-81.5) vrs 69.5 IQR 59.8-77.3) (77). Oliver *et al* (73) looked at sex differences in more detail and although mortality rates and age at death were not presented, hazard ratios adjusted by a population cohort show the usual female survival benefit to be lost in ACHD (41). This study also suggests a slight female preponderance towards CV death (61%) when compared to men (56%). This uncommon example of sex stratified mortality data is taken from a single centre cohort.

One Dutch registry reported by Zomer *et al* (89) reported geographical and seasonal variations in mortality (with some increased mortality in rural postcodes and little difference with seasonality). No study however reported socioeconomic influences on mortality or circumstances of death. Overall the reported influence of patient characteristics on mortality was piecemeal and lack of standard reporting methodology prevented any real compilation or comparison of findings.

Establishing cause of death as cardiovascular or non-cardiovascular was reliant on reporting within the source material. All but one article contributing to the cause of death results either defined CV death or reported specific causes of death, allowing extrapolation as either CV or non-CV. Cause of death was broadly established by one of two methods throughout the studies;

- Objectively – regional or national databases were interrogated, and predefined cause of death data extracted, usually as coded by the ICD system
- Subjectively – by case-note interrogation or in one case by contacting next of kin. Author adjudication of cause of death then prevails

The objective method, such as that used by Nyboe *et al* (78) has the benefits of limiting observer bias, and when the ICD system is used, standardising diagnoses by a universally accepted definition. The subjective method such as was used by Diller *et al* (43) has the benefit of ensuring internal validity, where the objective method is validated only according to the local or national requirements which

may be highly variable in their efficacy. It is likely that regional variations in the practice of diagnosing causes of death exist. For instance; in the UK, stating an organ failure as the primary cause of death is discouraged unless a clear underlying cause for said organ failure is stipulated. Despite this Diller *et al* (43) reported heart failure as the leading cause of death in their patient cohort. a result which would likely be significantly different had the objective method utilising ICD coding been used.

An overall predominance of CV death was seen across all studies, but this varied according to the CHD lesion and according to lesion complexity. ASD was the only lesion to show a slight predominance towards non-CV death at 50.2%. At the other end of the complexity spectrum the Fontan and systemic RV groups had a strong predilection for CV death at 80.2% and 93.9% respectively.

No study compared causes of death according to study period. Establishing temporal trends in causes of death by combining data from the included studies was not possible for several reasons, most of which have already been alluded to: study heterogeneity with regards to the breakdown of lesions; discrepancies in the way cause of death was established and the necessary biases imposed by each; and the regional variations which govern acceptable practice in diagnosing cause of death.

2.5 Conclusions

Population based studies of outcomes in unselected ACHD cohorts remain sparse amongst the literature. The available data is limited to European, North American and Australasian populations.

A lack of standardisation in reporting of survival and mortality data makes analysis difficult, but an estimate of age at death should be considered as a minimum measure. Age and sex standardised mortality rates are an informative means of reporting in ACHD.

Age at death appears to be increasing in more contemporary data periods however lesion specific data at given time points are of low volume and so this is not fully robust.

Cardiovascular death predominates over non-cardiovascular death. The proportion of CV death is greater for lesions of moderate and great complexity, as compared with simple complexity. Temporal changes in cause of death have not been established.

Mortality data stratified by patient characteristics such as sex and socioeconomic influencers are few and have never been explored on a population level.

3 Aims and Objectives

3.1 Aims

Following a review of the available literature, the following thesis aim was devised

- To describe the mortality and circumstances of death amongst adults with congenital heart disease throughout Scotland and explore how this has changed over time.

From this aim, the following objectives were derived

3.2 Objectives

- To establish the utility of the Scottish Morbidity Record in the study of congenital heart disease in Scotland.

- To describe the baseline characteristics including comorbidity of adults with CHD.

- To establish univariate and adjusted survival according to the underlying congenital lesion and how this has changed over time.

- To outline the causes of death for adults with congenital heart disease, how these have changed over time and how this compares with the general population.

- To establish the influence of patient characteristics (sex and socioeconomic deprivation) on cardiovascular and non-cardiovascular mortality amongst adults with congenital heart disease.

- To examine causes of death according to patient characteristics (sex and socioeconomic status) and if this has changed over time.

4 Methods

4.1 Preamble

This Chapter describes the common methodology encountered throughout my thesis. Where more specific techniques or divergencies from this methodology exist, they will be clarified within the respective results Chapter.

4.2 Introduction

4.2.1 Congenital Heart Disease in Scotland

As of August 2016 the population of Scotland was estimated at 5.4 million (93). NHS Scotland consists of 14 health boards (Table 4-1) which subtend geographical regions. Additionally, there are a number of Special Health Boards which are responsible for educational and health improvement mandates as well as certain acute and elective services. As of 2002 the National Waiting Times Centre, operating out of the Golden Jubilee National Hospital (GJNH) in Clydebank, west of Glasgow was established, providing both regional and national services.

Table 4-1 - Scottish health boards and the geographical area covered

Name	Geographical Area
NHS Ayrshire and Arran	East Ayrshire, North Ayrshire, South Ayrshire
NHS Borders	Scottish Borders
NHS Dumfries and Galloway	Dumfries and Galloway
NHS Western Isles	Outer Hebrides
NHS Fife	Fife
NHS Forth Valley	Clackmannanshire, Falkirk, Stirling
NHS Grampian	Aberdeenshire, City of Aberdeen, Moray
NHS Greater Glasgow and Clyde	City of Glasgow, East Dumbartonshire, West Dumbartonshire, East Renfrewshire, Inverclyde, North Lanarkshire (in part), South Lanarkshire (in part)
NHS Highland	Highland, Argyll and Bute
NHS Lanarkshire	North Lanarkshire (in part) South Lanarkshire (in part)
NHS Lothian	City of Edinburgh, East Lothian, Midlothian, West Lothian
NHS Orkney	Orkney Islands
NHS Shetland	Shetland Islands
NHS Tayside	Angus, City of Dundee, Perth and Kinross

In 2007 the Scottish Adult Congenital Cardiac Service (SACCS) was instated as a branch of the National Services Division (NSD) of NHS Scotland. It was centralised in the GJNH and became the national centre for ACHD. By 2010 it was fully established as the single advanced centre for adult congenital cardiology in Scotland. This remains the case today; employing what is commonly considered to be the gold standard structure of a ‘hub and spoke’ health care system for adults with congenital heart disease.

As the only tertiary centre for ACHD in Scotland, the GJNH alone houses the full complement of facilities and expertise for the advanced investigation and management of all facets of ACHD care. A single exception is cardiac transplant for ACHD patients which is currently referred to the Freeman Hospital in Newcastle with which SACCS collaborate on a case-by-case basis.

As such the GJNH acts as the 'hub' with local and regional ACHD services, provided within the geographical health board of each respective patient acting as the 'spoke'. The division of care between local and regional teams and the tertiary centre at the GJNH is broadly dependent upon the complexity of the underlying congenital lesion and ongoing needs of the patient.

Patients with lesions of least complexity such as small ASDs or PDAs will likely receive the majority of their review and investigation by local and regional services. Utilisation of the national centre will predominantly be for structural intervention; be it surgical or transcatheter, and any advanced investigations required in the decision-making process, such as cardiac magnetic resonance imaging (cMRI) and cardiopulmonary exercise testing (CPET).

Patients with lesions of moderate complexity will often have shared care between regional centres and the national service, with routine follow up and monitoring being co-ordinated locally but advanced non-invasive and invasive monitoring as well as all cardiac intervention being centralised at the GJNH.

Where individuals have ACHD lesions of great complexity, the majority of care will be undertaken in the national centre. These patients require relatively frequent advanced investigation with modalities such as cMRI, CPET, cardiac catheterisation and advanced echocardiography techniques. All cardiac intervention and even some non-cardiac intervention will be undertaken at the GJNH.

4.2.2 The Scottish Morbidity Database

The Information Services Division (ISD) acts on behalf of NHS National Services Scotland as collator and custodian of wide ranging health and administrative data. As part of the Scottish Informatics Programme, ISD delivers eDRIS

(Electronic Data, Research and Innovation Services) which acts as point of contact and data administrator for researchers to access anonymised population health records via the Scottish Morbidity Database. Health data in Scotland enters the Scottish Morbidity Database via one of the Scottish Morbidity Records (Table 4-2). The record used is generally determined by the type of care provided. Some SMRs have been discontinued since its inception in the 1970s but the current Scottish Morbidity Database contains four data sets as shown in Table 4-2.

Table 4-2 - The Scottish Morbidity Database

Dataset	Year of inception	Description
SMR01	1981	Episode data on hospital admissions
SMR04	1981	Episode data on psychiatric admissions
SMR06	1980	Cancer registrations
National Record of Scotland - Deaths	1980	Record of deaths

Each SMR episode allows a principle diagnosis, up to 5 secondary diagnoses and four operative procedures to be coded. Coding is done via the WHO ICD and OPCS systems.

Alongside the SMRs, the Scottish Morbidity Database contains the NRS Death Records. National Records of Scotland (formerly the General Register Office for Scotland) is responsible for recording the cause of death for all residents of Scotland. Cause of death information is recorded using ICD coding which is derived from information provided on the Medical Certificate of Cause of Death (MCCD). This allows a primary cause of death (event directly leading to death), 3 antecedent causes, and multiple contributary but non antecedent causes to be compiled and coded. SMR and death records can then be linked and studied. Data linkage predominantly relies on the Community Health Index (CHI) number but when this is not possible an algorithm-driven system allows for record matching based on probabilities using patient identifiable information such as surname, date of birth and postcode.

As part of information governance, ISD periodically carries out a national assessment of SMR01 records to uphold standards and consistency. This is carried

out by the Data Quality Assurance (DQA) team and was last published in 2015 (94). The accuracy of main diagnosis and main operation coding, as well as non-clinical data collection, is assessed across representative centres from all Scottish health boards, including the Golden Jubilee National Hospital. In 2015, accuracy to 3 digits for main diagnosis coding was 89% and main operation was 94%. This study was in line with previous national assessments. The GJNH, through which a disproportionately high proportion of ACHD episodes occur performed above the Scottish average achieving a diagnostic coding accuracy of 96% and procedural accuracy of 97%.

Previously published epidemiology data has relied on diagnostic and procedural coding information supplied via privatised health insurance providers (92). It has been suggested that financial incentives lead to more complete coding. Internal validation of ISD data would suggest favourable accuracy despite remuneration incentives being less clear cut. As the NHS provides a free at point of care service, our data set has the additional benefit of lacking the financial disincentive biases affecting access to care in privatised and semi-privatised healthcare systems.

4.2.3 Scottish Morbidity Record (SMR) 01

Also known as ‘the General / Acute and In patient Day Case data set’, SMR01 contains data generated following discharge from any acute in patient or day case episode throughout all relevant facilities in Scotland. Practically speaking an individual patient episode is not synonymous with what most clinicians would refer to as an ‘admission’ which in reality will likely contain multiple episodes and so multiple SMR01 records. To avoid confusion an admission is better thought of by the term ‘continuous in patient stay’ (CIS). For example; a patient admitted to an acute medical ward with pneumonia (episode 1) then transferred to a respiratory medicine ward (episode 2) before being discharged home will generate 2 separate episodes and so 2 SMR01 records. Each will likely contain distinct health data corresponding to diagnoses and procedures coded at point of discharge from each episode. Together they amount to a single CIS. Although separate records, these can be readily linked (via the CHI number) and identified as a single CIS. Linkage can also be accomplished longitudinally throughout all

previous or subsequent episodes and CISs for an individual as well as to records within the other data sets compiling the Scottish Morbidity Database (Table 4-2)

4.2.4 Utility of the Scottish Morbidity Record and data linkage

The systematic coding and record linkage of all in-patient records in Scotland provides a unique substrate for studying patterns in health care and outcomes at a population level. World-wide, few if any similar systems exist. Most large datasets are registry based or confined to health regions within a country.

SMR data has been used to study large scale populations in the field of diabetes (95), cardiology (96) and psychiatry (97) amongst others. Lewsey *et al*. (98) established a falling rate of recurrent stroke hospitalisation trends among 128,511 individuals using SMR01 records between 1986 and 2001. Short term mortality following incident heart failure admission has recently been described in the adult Scottish population (99). Over 115,000 SMR01 records were recovered and data linkage cross referenced to death records identified 16,406 (14.2%) deaths within 30 days.

One strength of this methodology is that it generates large study population numbers even when the discriminator in question is rare. For example SMR data has been used to define prognosis in patients with idiopathic pulmonary arterial hypertension (100) by reporting outcomes for 374 patients. This is more than threefold what is described in similar longitudinal studies utilising other methods of recruitment (101).

There are two predominant limitations to SMR data linkage in the study of clinical outcomes; firstly, it cannot be used for individualised clinical information such as test results, symptomatology or performance status. As such data derived from SMRs must be interpreted with this knowledge in mind. Secondly, persons cared for entirely in the out-patient sector will not produce an SMR01 record and may be ‘hidden’ from study populations. Consequently, the data obtained may not represent the entire population of interest and/or may be biased towards more severe phenotypes.

With the advantages and limitations of the utility of SMR in mind, in its current form SMR and data linkage should be best suited to studying patient populations well defined by diagnostic coding and well defined outcomes, such as death.

4.3 Data request and extraction

4.3.1 Privacy panel application

Prior to submitting a data extraction request to eDRIS, approval from the Public Benefit and Privacy Panel (PBPP) for Health and Social Care was necessarily sought. The information governance standards as presented within the Scottish Government guidance requires an application to the PBPP when data pertaining to individuals for use other than direct clinical concern is required. Additionally, access to any of the NHS Scotland databases requires approval. The SMR is an example of such a database.

PBPP approval was sought and subsequently granted for the attainment of nonidentifiable information from all Scottish health boards and pertaining to multiple NHS Scotland patient databases. The stated purpose of my data request was for research and service planning and improvement.

An application amendment was required to achieve approval based on satisfactory anonymisation of individual data. That date specific data (death date, admission date and discharge date) be amended to simply month and year was considered appropriate, particularly in the event where administrative health data related to an individual may be uncommon (such as with certain ICD codes encountered in our data proposal) and as such rendered identifiable when encountered in combination with an exact date. Date of birth was refused, instead providing the individual's age at each given episode for the same reasons of anonymisation.

A second application for amendment was later sought and approved to extend the data period for identification of death records from December 2015 until September 2017.

4.3.2 ICD inclusion

The identification of health records for inclusion into our dataset was guided by the recognition of diagnostic (ICD) or procedural (OPCS) codes specific to congenital heart disease. ICD coding has been described in section 1.3.1. Table

4-3 summarizes the ICD codes used to identify suitable health records for inclusion into the dataset.

For the purposes of clinical coding it would be considered appropriate that previously 'repaired' congenital defects are no longer coded as an active diagnosis. For example; should a 16-year-old patient presenting with chest pain and with a history of an ASD, surgically repaired at age two be admitted to hospital. They might be coded as R07.4 (chest pain, otherwise unspecified) in the primary diagnostic position and either Q21.1 (atrial septal defect) or Z87.74 (personal history of congenital or chromosomal malformation) depending on the semantics of the clinical documentation.

A CIS consists of one or more patient episodes. Additional episodes are added to a CIS record at the point of transfer to a new ward, consultant or in patient facility. Coding takes place at each transfer between episodes and at the point of discharge from the CIS. Coding in up to six diagnostic positions is allowed at each change of episode. We identified patients based on an inclusion ICD code as outlined in Table 4-3 as present in any diagnostic position. Once patient identification was achieved, record identification by record linkage (as described in the previous Chapter) allowed all corresponding CIS records within the data period to be pulled for analysis, irrespective of whether a CHD code was represented during these other episodes.

Table 4-3: ICD codes used to determine inclusion suitability

Inclusion diagnosis	ICD 9 code (up to 31st March 1996)	ICD 10 code (from 1st April 1996)
ACHD	745 - 747	Q20 - Q28
History of corrected ACHD	V13.65	Z87.74

4.3.3 OPCS inclusion

Prior studies concerning the epidemiology of CHD have relied solely on ICD coding for patient identification (72,102). Section 3.2.2 refers to an example where patient identification by ICD coding alone may be vulnerable. Many individuals who have a 'repaired' CHD lesion are at ongoing risk of future sequelae and the tendency to repeated or further interventions later in life

provides an opportunity to use procedural coding to improve the sensitivity of patient identification.

Table 4-4 summarizes the OPCS codes used for patient identification for inclusion into the data set. The process for coding procedures is similar to that described for diagnoses (section 3.2.2). Up to four procedures can be coded at each change of episode and again we identified those with an inclusion code in any one of those positions, pulling the entire CIS record and all linked CIS records for that individual within the total data period.

OPCS 4 has been updated six times since its inception in 1989. Most iterations have undergone relatively minor change but from OPCS 4.2 (1989-2006) to OPCS 4.3 (2006-2007) significant differences in the manner of procedural coding were instigated. For instance, reliable coding for transluminal procedures of the heart cannot be specifically coded by OPCS 4.2 and earlier.

Table 4-4: Description of OPCS codes used for patient identification.

Operation	OPCS3 code (up to 31st Dec 1988)	OPCS4 code (from 1st Jan 1989)
Tetralogy of Fallot	3101, 323.1	K04
Interatrial transposition of great arteries (TGA)	3153, 323	K05
Other TGAs (switch)	323, 3249, 3269, 3299	K06
Repair of total anomalous pulmonary venous drainage	3248, 3249, 315, 3222	K07
Repair of partial anomalous pulmonary venous drainage	NA	K20.2
Repair of double outlet ventricle	3177, 3178, 3179	K08, (K19.8 + Z94.2), (K19.8 + Z94.3)
Repair of complete atrioventricular septal defect	3152, 3153, 3154, 3157, 3159, 3158	K09, excluding K09.4
Surgical closure of secundum and sinus venosus atrial septal defects	3152, 3153, 3154, 3157, 3158, 3159	K10, K20, K09.4
Device ASD closure	NA	K13.3, K13.4, (K10.1+Y53.1), (K10.4+Y53.1)
Surgical closure of ventricular septal defects	3152, 3153, 3154, 3157, 3159	K11
Device closure VSD	NA	K13.1, K13.2, (K11.1+Y53.1), (K11.4+Y53.1)
Repair of septum	3152, 3153, 3154, 3157, 3158, 3159, 3061	K11-16
Repair of univentricular heart	3241, 323	K17
Truncus arteriosus	3222, 326	L01.1
Creation of conduit	3238, 3239	K18,K19
Surgical Patent Ductus closure	3221	L02
Device closure of patent duct	NA	L03
Fontan-type procedures	323, 3241	K19.2, K19.4, L09, K17.1, K17.2, K17.3, K17.7
HLH repair/Norwood type	NA	K17.4, K17.5, K23.8
Pulmonary valve procedure	3114, 3124, 3134, 3144	K28
Transcatheter Pulmonary Valve Replacement	NA	K35.7, (K35.8+Z32.4)
Truncal Valve Surgery	NA	K29.6, K29.7,
Closed shunts	323, 3268, 3231	L05, L06, L07, L08
Pulmonary artery banding	3222, 3201, 3298, 3299	L12.1, L12.2, L12.3
Transluminal pulmonary artery procedures	NA	L13
Surgical coarctation procedures	3251, 3252	L23.1, L23.2, L23.3, L26
Transluminal aortic stent	NA	L26.5
Intervention on major systemic to pulmonary collateral arteries	NA	L69, L70.8
Pulmonary Vein Surgery	NA	L80

4.3.4 Deprivation

Two postcode-derived methods for determining socioeconomic status in Scotland have been established. The Carstairs-Morris index (103), originally developed

using 1981 census data and compiled as a composite marker of four indicators (Table 4-5) has since been superseded by the SIMD as the primary tool for determining relative deprivation and social inequality throughout Scotland (104).

Table 4-5: Determinants of Carstairs-Morris Index

Variable	Description
Over crowding	Proportion of those in private households living at a density of more than one per room
Male unemployment	Proportion of male adults seeking work
Proportion in social class 4 or 5	Proportion of those living in private households where the highest level of employment is partially skilled or unskilled
Car ownership	Proportion of all persons in private housholds with no car

The SIMD was updated on four occasions from the start of the data period until the initial data request (2004, 2006, 2009 and 2012) with one subsequent update during the analysis period in 2016. Similar to the Carstairs-Morris index, SIMD is a composite statistic derived of indicators. A total of 38 indicators are grouped in to 7 ‘domains’ which combine to a single SIMD score (Table 4-6). SIMD scores are applied to small postcode areas known as data zones. Scores are ranked from 1 (most deprived) to 6,976 (least deprived). Given a Scottish population of 5.4 million, this corresponds to roughly 770 people per data zone. It should be stressed that this is a ranking score and so relative and not absolute deprivation is implied. Hence it cannot be supposed how much more deprived one area is compared to another.

Table 4-6: Domains and weighting contribution to the Scottish Index of Multiple Deprivation

Domain	Description	Weight
Employment	Propotion of those who are employment deprived and receive certain benefits and tax credits	12 (28%)
Income	Proportion of people who are income deprived and receive certain benefits	12 (28%)
Health	Comparative illness factor (combined count of Disabled Living Allowance, Attendance Allowance, Incapacity Benefit and Severe Disablement Allowance) Hospital stays related to drug or alcohol misuse Emergency stays in hospital Proportion of population prescribed medication for anxiety, depression and Proportion of low birthweight births Standardised mortality ratio	6 (14%)
Crime	Crimes of violoence, sexual offences, housebreaking, vandalism, drug offences and assault per 10,000 population	2 (5%)
Housing	Percentage living in overcrouded housing Percentage living in houses with no central heating	1 (2%)
Education	School pupil attendance Attainment of school leavers Working age people with no qualifications training Proportion of 17-21 year olds entering into higher education	6 (14%)
Access	Average drive time to a petrol station, GP surgery, post office, a school and a retail centre Public transport time to a GP surgery, a post office and a retail centre	4 (9%)

SIMD has been widely used in the study of many conditions and is generally considered to be reliable (105–109), winning the Royal Statistical Society's Excellence in Official Statistics Award in 2017 (110).

For the purpose of analysis within this document, and in a similar way to previous published biomedical literature (106,109), SIMD has been divided into quintiles; 5 groups of 1,395 data zones each, ranked from 1 (most deprived) to 5 (least deprived). The data zones are as applied according to the most recent incarnation (2012) of SIMD. In cases where outcomes according to deprivation were compared according to specific congenital lesions, comparison by SIMD quintile was felt inappropriate due to low numbers in each quintile group when uncommon conditions were concerned. This may jeopardise anonymity. In such cases SIMD was dichotomised into two groups of equal numbers of data zones corresponding to 'higher deprivation' and 'lower deprivation'.

4.3.5 Comorbidity

Diagnostic information was collated for 7 key comorbidities (diabetes, cancer, atrial fibrillation, systemic hypertension, cerebrovascular disease, acute myocardial infarction and other ischaemic heart disease). These co-morbidities

were chosen to reflect known influencers of cardiovascular mortality (diabetes, cancer, AF, ischaemic heart disease and hypertension) with malignancy included as the recognised major cause of non-cardiovascular mortality in the general population of Scotland (111). Although tobacco smoking and obesity are established risk factors for cardiovascular disease and mortality, these were not included as prior studies have established significant inaccuracies with their coding, particularly as a result of under-reporting and recording in the clinical notes (112–114). This may well reflect attitudes and clinician training where these variables may be thought of as a social characteristic as opposed to a co-morbidity per-se.

Individuals were recognised as having a comorbidity if the corresponding ICD 9 or ICD 10 code(s) was identified in any one of the six coding positions on either the index inclusion episode or in any episode within the 5 years prior to the index episode. The ICD codes used to identify comorbidities are shown in Table 4-7.

Table 4-7: Comorbidity and corresponding ICD identification code

Comorbidity	ICD 9 code	ICD 10 code
Diabetes	250	E10-E14
Cancer	140-208	C00-C99
Cerebrovascular disease	430-438	I60-I69, G45
Atrial fibrillation	427.3	I48
Hypertension	401	I10-I13
Acute myocardial infarction	410	I21, I22
Other ischaemic heart disease	411-414	I20, I23-I25

Comorbidity classification is broadly inclusive of disease subtypes. We did not discriminate between Type 1 and type 2 diabetes mellitus, not least as these are indistinguishable by ICD 9 coding (up to 31st March 1996). Equally, malnutrition and pancreatitis related diabetes are included. Gestational diabetes is the notable exception as this is coded via a different section of ICD. The codes pertaining to atrial fibrillation (I48 and 427.3) are inclusive of atrial flutter (both ‘typical’ and ‘atypical’) but do not include supraventricular tachycardias or focal atrial tachycardia.

Cancer coding is inclusive of all malignant neoplasms of solid organ, haematopoietic and lymphoid tissue. Benign neoplasms and carcinoma in situ are not included. Neuroendocrine tumours are not specifically included as these are

not differentiated by the ICD 10 coding system but may be included if they have been coded as a solid malignant tumour in an identified organ. A specific ICD 9 code is provided for neuroendocrine tumours but was not included due to its unavailability through ICD 10. It is possible that a small number of neuroendocrine/carcinoid patients may have been labelled with a cancer comorbidity after April 1st 1996 where they would have been omitted prior to this.

Cerebrovascular disease refers to ischaemic or atraumatic haemorrhagic strokes as well as transient ischaemic attacks. Spontaneous subdural haemorrhage is included. Strokes occurring during pregnancy and the puerperium were not included.

Acute myocardial infarction is inclusive of ST segment elevation (STEMI) and non-ST segment elevation (NSTEMI) myocardial infarction. These are not differentiated by ICD 9 and have therefore been considered in combination throughout this document. The subcategorization of myocardial infarction into types I – VI as stated in the Fourth universal definition (115) and accepted in common practice are not differentiated by ICD coding.

4.3.6 Mortality data

As discussed previously, data linkage allows data extraction to include information from the NRS database of births, marriages and deaths. Death certification is a legal process which starts with the issuing of the MCCD. This is usually completed by a member of the attending medical team when the death occurs in hospital or by the usual medical practitioner (general practitioner) when the death occurs in the community. If a death is sudden or unexplained the Procurator Fiscal (PF) will be involved in decision making and a postmortem examination may be required, at which point the responsibility for issuing the MCCD will fall to the PF. The MCCD is then presented by a representative (usually family of the deceased) to the local council registrar who then registers the death and issues a Certificate of Registration of Death. Under normal circumstances it is a legal requirement that the death should be registered within 8 days of the date of death. This may need to be extended if further examinations are planned. Since 2015 the Death Certification Review service has

been in place in Scotland. This is to uphold standards of MCCD accuracy. As a result, around one in eight MCCDs are randomly selected for review. A team of medical reviewers then either; approve the MCCD, amend the MCCD, or order a fully revised MCCD.

We used data linkage to the ICD/OPCS identified population (sections 4.3.2 and 4.3.3) to ascertain all individuals who had died up until the point of a data extraction amendment (30th September 2017). For all such individuals, additional data obtained included; month and year of death, age at death, whether or not a post mortem examination was performed, the time from in patient episode until the date of death in days, and the causes of death (coded as per ICD 9 and 10).

Additionally, the NRS database of births, marriages and deaths was separately searched to identify any individual who had not been identified to have had a CIS episode but had died and had an ICD code corresponding to congenital heart disease (Table 4-3) listed as the primary or any secondary cause of death.

4.4 Lesion classification

The considerable heterogeneity of congenital heart disease has been discussed. Even within most congenital diagnoses, considerable variability exists. There is additionally some discourse between the range and separation of congenital heart disease as it exists in clinical practice and as it is segregated by clinical coding. This document is intended to inform and reflect clinical practice and as such lesions have been separated to reflect this. Previous unselected, epidemiology studies which utilise ICD coding rather that hospital databases have been limited in classifying diagnoses as procedural information has been lacking (116,117). Only by combining ICD coding and procedural information (OPCS coding) can individuals be identified as Fontan patients or having TGA with arterial or atrial switch.

Overall, the lesion groups used within this document are similar to those reflected in prior literature (9,33,41,63,118–121). In total 13 major groups were segregated (ASD, PDA, VSD, aortic lesions, Ebstein's anomaly, AVSD, TOF, TGA with arterial switch, systemic RV, Fontan, complex lesions, valvular lesions, and other lesions).

4.4.1 ASD

The ICD and OPCS codes used to identify ASDs are summarised in Table 4-8. The ICD 9 code 745.5 and ICD 10 code Q21.1 refer to all defects of the interatrial septum other than ostium primum defects and are inclusive of; secundum defects, coronary sinus defects, sinus venosus defects and persistence of the foramen ovale. The ICD 9 code 747.42 and ICD 10 code Q26.3 refer to a partial anomalous pulmonary venous drainage (PAPVD). The decision to include these in the ASD cohort relates to the tendency of PAPVD to exist alongside a defect of the atrial septum and share the physiological principles of left to right shunting at atrial level (see Table 1-3). The OPCS code K10 refers to any surgical repair of the interatrial septum and K20.1 to repair of a persistent sinus venosus.

Table 4-8: Codes used to categorise ASD

	Code	Description
ICD 9	745.5	Defect of interatrial septum
	747.42	Partial anomalous pulmonary venous connection
ICD 10	Q21.1	Defect of interatrial septum
	Q26.3	Partial anomalous pulmonary venous connection
OPCS	K10	Surgical repair of interatrial septum
	K20.1	Surgical repair of persistent sinus venosus

4.4.2 PDA

The codes used to categorise PDA are summarized in Table 4-9. The code L03.2 referring to percutaneous stenting of a PDA was only available from OPCS 4.3 onwards and would therefore not be identified prior to 2006.

Table 4-9: Codes used to identify PDA

	Code	Description
ICD 9	747.0	Patent ductus arteriosus
ICD 10	Q25.0	Patent ductus arteriosus
OPCS	L02	Surgical closure of patent ductus arteriosus
	L03.1	Percutaneous occlusion of patent ductus
	L03.2	Percutaneous stent of patent ductus

4.4.3 VSD

Ventricular septal defects can be either congenital or acquired. These are dealt with by separate sections of the ICD coding system. Acquired VSDs would correctly be identified with the ICD 9 code 429.71 and ICD 10 codes I23.2 or I51.0 and were not included. The codes we used to categorise congenital ventricular septal defects are summarized in Table 4-10. Note the Gerbode defect (left ventricle to right atrial defect) is specifically included in the ICD 9 system but not ICD 10.

Table 4-10: Codes used to identify VSD

	Code	Description
ICD 9	745.4	Ventricular septal defect including Gerbode defect
ICD 10	Q21.0	Ventricular septal defect
OPCS	K11	Surgical and percutaneous repair of interventricular septum

4.4.4 Aortic lesions

Although the most common congenital lesion of the aorta is a thoracic coarctation, a broad range of anomalies may be encountered. The codes used to identify aortic lesions are summarised in Table 4-11. There is no obvious clarification between aortic coarctation and aortic stenosis, with the latter sharing an ICD code with other lesions such as a vascular ring (Kommerell's diverticulum) and sinus of Valsalva aneurysms, as such these are necessarily included together.

Table 4-11: Codes used to identify aortic lesions

	Code	Description
ICD 9	747.1	Coarctation of aorta including interrupted arch
	747.2	Other anomalies of aorta including stenosis, atresia, Kommerell's diverticulum and sinus of Valsalva aneurysms
ICD 10	Q25.1	Coarctation of aorta
	Q25.2	Atresia of aorta
	Q25.3	Stenosis of aorta
	Q25.4	Other anomalies of aorta including stenosis, atresia, vascular ring and sinus of Valsalva aneurysms
OPCS	L23.1	Repair and end to end anstamosis of aorta
	L23.2	Repair of aorta using subclavian flap

4.4.5 Ebstein's anomaly

Ebstein's anomaly is one of the few congenital lesions to have a single, well defined ICD definition and code. No OPCS code is sufficiently specific to a repair of Ebstein's anomaly to aid inclusion. Table 4-12 summarised the ICD codes used.

Table 4-12: Codes used to identify Ebstein's anomaly

	Code	Description
ICD 9	746.2	Ebstein's anomaly
ICD 10	Q22.5	Ebstein's anomaly

4.4.6 Atrioventricular septal defect

ICD coding does not discriminate between ostium primum ASDs alone and those with a ventricular component (complete AVSD). AVSD and ostium primum ASD

share features which complicate these lesions above other types of ASDs (atrioventricular valve abnormalities and atrioventricular conduction abnormalities for example). As such their inclusion in a single group is unavoidable, reasonable and conventional to the literature (9). The OPCS code K09 encompasses all repairs involving the atrioventricular septum and should therefore be specific to true AVSD. Table 4-13 summarised the codes used to classify patients with AVSD.

Table 4-13: Codes used to identify atrioventricular septal defect

	Code	Description
ICD 9	745.6	Endocardial cushion defect including ostium primum ASD, absent atrial septum and atrioventricular canal
ICD 10	Q21.2	Atrioventricularseptal defect including ostium primum defect
OPCS	K09	Repair of the atrioventricular septum including ostium primum repair

4.4.7 Tetralogy of Fallot

As with many congenital heart defects, tetralogy of Fallot represents a spectrum of disease. The degree of right ventricular outflow tract obstruction varies from minimal infundibular stenosis to complete pulmonary atresia. Likewise, the degree of aortic override may be minimal or even constitute a double outlet right ventricle. The codes used to categorise tetralogy of Fallot have been chosen to represent this spectrum of disease. Unfortunately, the ICD codes for double outlet right ventricle do not discern between Fallot type DORV and that more closely related to complete transposition of the great vessels and has therefore not been included here. OPCS coding does make this distinction and has been included here (Table 4-14).

Table 4-14: Codes used to identify tetralogy of Fallot

	Code	Description
ICD 9	745.2	Tetralogy of Fallot including with pulmonary atresia
ICD 10	Q21.3	Tetralogy of Fallot including with pulmonary atresia
OPCS	K04	Repair of Tetralogy of Fallot with or without transanular patch and with or without conduit
	K08.2	Repair of Fallot type double outlet right ventricle

4.4.8 Transposition of the great arteries with arterial switch

The physiology and long-term prospects of individuals born with transposition of the great arteries is significantly dependent upon the manner in which it is

surgically repaired. Those who undergo atrial inversion (Mustard or Senning operations) will be rendered with a systemic right ventricle and will be considered in the subsequent section. Those who undergo either arterial switch (Jatene procedure) or interventricular tunnel with RV to PA conduit (Rastelli) operations will restore physiological and anatomic function of a systemic LV and have been included together in this section. Clearly the dependence of a surgical procedure on establishing an effective diagnosis poses a problem when using ICD coding as surgical procedures are not considered and only original anatomy is accounted for. For that reason, only those who have both the ICD pertaining to TGA and an OPCS code referencing repositioning of a great vessel or the use of an RV conduit have been included in this section (Table 4-15).

Table 4-15: Codes used to identify transposition of the great arteries with arterial switch. Both an ICD code and an OPCS code must be identified to be included

	Code	Description
ICD 9	745.1	Transposition of the great vessels including double outlet right ventricle with dextraposition of the aorta
ICD 10	Q20.3	Discordant ventriculoarterial connection
&		
OPCS	K06.1	Repositioning of transposed great arteries
	K06.2	Left ventricle to aorta tunnel with right ventricle to pulmonary anastamosis
	K06.3	Left ventricle to aorta tunnel with right ventricle to pulmonary valved conduit

4.4.9 Systemic right ventricle

There are two groups of individuals for whom a systemic right ventricle would be considered the primary lesion. Those with transposition of the great arteries following atrial inversion surgery, as outlined in the prior section (4.4.8) and those with unrepaired congenitally corrected transposition of the great arteries (ccTGA).

Table 4-16 summarises the manner in which individuals were identified as having a systemic right ventricle.

Table 4-16: Codes used to identify systemic right ventricles. If the ICD code refers to complete transposition of the great arteries then a relevant OPCS code must also be identified

	Code	Description
ICD 9	745.1	Transposition of the great arteries
ICD 10	Q20.3	Discordant ventriculoarterial connection
&		
OPCS	315.3	Operation on atrial septum of heart
	K05	Reconstruction of atrium or atrial inversion for transposition of the great arteries
OR		
ICD 9	745.12	Corrected transposition of the great arteries
ICD 10	Q20.5	Discordant atrioventricular connection (ventricular inversion)

4.4.10 Fontan

Although Fontan patients represent a well-defined cohort of CHD patients, they defy categorisation by ICD methodology. In a similar manner to those with TGA, OPCS coding is essential to allow further categorisation. As Fontan patients have a vast array of underlying lesions we must rely almost solely on OPCS coding. One exception is among individuals with hypoplastic left heart syndrome, for whom the clinical phenotype is suitably severe that we have considered any individual listed with this diagnosis who has survived to adulthood to have undergone Fontan surgery as this is the only reasonable hypothesis.

Unfortunately, prior to OPCS 4, no code was suitably descriptive to confidently categorise Fontan surgery and so few will be identified prior to its inception (1989). Table 4-17 summarises the strategy for identifying Fontan lesions.

Table 4-17: Codes used to categorise as Fontan

	Code	Description
ICD 9	746.7	Hypoplastic left heart syndrome
ICD 10	Q23.4	Hypoplastic left heart syndrome
OPCS	K17.1	Total cavopulmonary connection with extracardiac connection
	K17.2	Total cavopulmonary connection with lateral atrial tunnel
	K17.7	Conversion of atrial pulmonary anastamosis to total pulmonary connection
	K18.2	Creation of valved conduit between right atrium to pulmonary artery
	K19.2	Creation of conduit between right atrium and pulmonary artery

4.4.11 Valvular lesions

OPCS codes regarding valve interventions are not specific to congenital heart disease and so cannot be included. ICD codes referring to congenital valve lesions are summarised in Table 4-3. These codes are distinct from those corresponding to acquired valve disorders which would be represented by sections 424 of ICD 9 and I34-I37 of ICD 10.

ICD codes for tricuspid stenosis and atresia, and pulmonary atresia have been included in the category of 'complex lesions' as per convention amongst similar literature (41,122). Isolated subaortic and subpulmonary lesions have been considered most appropriately amongst valvular lesions due to the shared indications for intervention and physiological similarities with stenotic valve lesions.

Table 4-18: Codes used to identify valvular lesions

	Code	Description
ICD 9	746.0	Anomalies of pulmonary valve
	746.3	Stenosis of aortic valve
	746.4	Insufficiency of aortic valve and bicuspid valve
	746.5	Mitral stenosis
	746.6	Mitral insufficiency
	746.81	Subaortic stenosis
	746.83	Infundibular pulmonary stenosis
	Q22.1	Pulmonary stenosis
	Q22.2	Pulmonary insufficiency
	Q22.3	Other malformation of pulmonary valve
	Q22.8	Other malformation of tricuspid valve
	Q22.9	Malformation of tricuspid valve, unspecified
ICD 10	Q23.0	Stenosis of aortic valve
	Q23.1	Insufficiency of aortic valve and bicuspid valve
	Q23.2	Mitral stenosis
	Q23.3	Mitral insufficiency
	Q23.8	Other malformation of mitral and aortic valve
	Q23.9	Malformation of aortic and mitral valve, unspecified
	Q24.3	Infundibular pulmonary stenosis
	Q24.4	Subaortic stenosis

4.4.12 Complex lesions

Many of the codes included under the category of complex lesions are encountered in more specific categories and will only default to this category if no procedural information is known. For instance, complete transposition of the great arteries will only be included in this category if no OPCS code pertaining to atrial or arterial inversion can be identified. A further example would be an individual with tricuspid atresia would default to 'complex lesions' if no identifying OPCS code for a Fontan type operation could be identified.

There are a few examples of complex lesions identifiable by ICD 10 coding which were not identifiable by ICD 9, such as hypoplastic right heart syndrome and aortopulmonary septal defect. As such, these exceptionally rare lesions would be coded with non-specific lesion codes and would be likely to be included in the 'other lesions' category if coded prior to April 1st 1996.

Unifocalisation procedures (recruitment of aortopulmonary collaterals into a neo-pulmonary trunk) have been included here as they are most commonly encountered as a surgical strategy for pulmonary atresia with major aortopulmonary collateral arteries. The truncated form of the OPCS code for repairs of double outlet right ventricles (K08) has been included with complex lesions but will only default to this category if the more specific form of the code (K08.2), relating to Fallot type DORV is absent. The double switch operation may be used in some individuals with ccTGA, particularly when complicated by additional lesions which mandate surgical intervention and these individuals have been included in this, complex category.

Table 4-19: Codes used to identify complex lesions

	Code	Description
ICD 9	745.0	Common truncus
	745.19	Other transposition complexes
	745.11	Double outlet right ventricle
	745.3	Single ventricle
	745.7	Cor biloculare
	746.1	Tricuspid atresia and stenosis
	746.7	Hypoplastic left heart syndrome
	747.3	Anomalies of the pulmonary artery (hypoplasia, stenosis and atresia)
	746.01	Pulmoary valve atresia
	747.41	Total anomalous pulmonary venous connection
	745.10	Complete transposiion of the great areteries
ICD 10	Q20.0	Common arterial trunk
	Q20.1	Double outlet righ ventricle (Taussig-Bing syndrome)
	Q22.4	Tricuspid atresia and stenosis
	Q23.4	Hypoplastic left heart syndrome
	Q25.5	Pulmoary atresia
	Q26.2	Total anomalous pulmonary venous connection
	Q20.2	Double outlet left ventricle
	Q20.4	Double inlet ventricle (single ventricle)
	Q20.6	Isomerism of atrial appendages (with asplenia or polysplenia)
	Q21.4	Aortopulmonary septal defect
	Q22.6	Hypoplastic right heart syndrome
	Q20.3	Discordant ventriculoarterial connections
OPCS	L01.1	Correction of persistent truncus arteriosus
	K06.4	Atrial inversion and repositioning of transposed great artery (double switch)
	L69.2	Pulmonary unifocalisation
	K07	Correction or intervention to total anomalous pulmoary venous connection
	K08	Repair of double outlet right ventricle

4.4.13 Other lesions

Categorisation will default to ‘other lesions’ when either the code description is non-specific, referring to ‘other obstructive anomalies of the heart’ (ICD 9 code 746.84) for example, or when the code used is non-specific (shortened/truncated codes), often referring to abnormalities of a region of the heart. Similarly, procedural coding may reflect interventions which may be used for an array of CHD such as atrial septostomies or again be included in truncated form, preventing more specific categorisation.

Table 4-20: Codes used to categories as 'other lesions'

	Code	Description
ICD 9	745.8	Other bulbus cordis and cardiac septal closure defects
	745.9	Unspecified defect of septal closure
	746.82	Cor triatriatum
	746.84	Other obstructive anomalies of the heart
	746.85	Coronary artery anomalies
	746.9	Unspecified anomaly of heart
	747.4	Anomalies of great veins (absence and persistence of cavae)
ICD 10	Q20.8	Other malformations of cardiac chambers and connections
	Q20.9	Malformation of cardiac chambers and connections, unspecified
	Q21.8	Other malformation of cardiac septa
	Q21.9	Malformation of cardiac septa, unspecified
	Q25.8	Other malformation of great arteries
	Q25.9	Malformation of great arteries, unspecified
	Q26.1	Persistent left superior vena cava
	Q26.4	Anomalous pulmonary venous connection, unspecified
	Q24.5	Malformation of coronary vessels
OPCS	K12	Surgical and percutaneous closure of unspecified septum
	K13	Percutaneous repair of unspecified septum
	K14	Open atrial septostomy or septectomy
	K15	Closed atrial septostomy or septectomy
	K18	Creation and revision of varius cardiac conduits
	K19	Creation or intervention to cariac conduit and Rastelli type repair
	L05	Systemic arterial to pulmonary arterial shunt, various
	L06	Creation or takedown of aorta to pulmonary arterial connection
	L07	Creation, closure or dilation of subclavian artery to pulmonary arterial shunt
	L08	Creation or percutaneous intervention to subclavian artery to pulmonary artery shunt
	L12.1	Application of band to pulmonary artery
	L12.2	Adjustment of band to pulmonary artery
	L12.3	Removal of band to pulmonary artery
	L69	Intervention to major systemic to pulmonary collateral
	L70.8	Intervention to major systemic to pulmonary collateral and unifocalisation
	K20.3	Repair of cor triatriatum
	K20.8	Repair of septum or coronary sinus
	K20.9	Unspecified refashioning of septum
	K20.4	Repair of coronary sinus abnormality

4.4.14 Hierarchy of lesion categories

Those individuals assigned to more than one lesion category were recoded in a hierarchical manner until each individual was assigned a single 'major diagnosis' group. This was done to reflect specificity of grouping; an individual coded as both 'complex' and 'Fontan' would be recoded to Fontan only, as well as complexity of lesion; an individual coded as both ASD and TOF would be recoded as TOF.

Figure 4-1 summarises the hierarchy of lesion categorisation. Although similar methods of categorising lesions have been used previously (9) no convention exists. As per **Figure 4-1**, the hierarchy corresponds to increasing lesion complexity, with simple lesions at the bottom and complex lesions at the top. The exception to this is with Tetralogy of Fallot which is considered to be of moderate complexity however lies above TGA with arterial switch, systemic RV and otherwise unspecified complex lesions. This is to reflect the specificity of the procedural codes for TOF. This may be of importance as both TOF and TGA may have DORV type morphology. If the repair of DORV is of tetralogy 'type' this is specifically referenced by the OPCS code and therefore more reliably identified as TOF. If the repair does not specify TOF type (or no OPCS code is identified) then the lesion will default to complex and not be 'upgraded' to TOF.

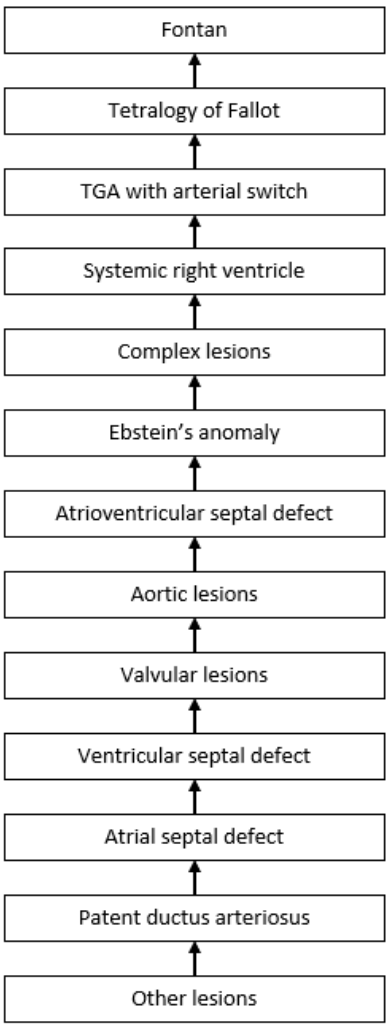


Figure 4-1: Hierarchy of lesion categories

4.5 Classifying lesion complexity

Attempts to classify CHD by complexity most commonly use or approximate the system outlined by Task Force 1 of the 32nd Bethesda Conference (122). As our data is stratified solely by electronic record coding our approximation of this system is matched as closely as this allows and is very similar to published literature (73).

Table 4-21 outlines the lesions included in the three strata of CHD complexity. As compared to the Bethesda classification ours is somewhat simplified. This is a consequence of two main limitations to our data set. Firstly, we are unable to clarify the severity of valvular lesions as we did not have access to imaging results and severity is not considered by ICD coding. For this reason, we have categorised all isolated pulmonary valve stenosis as simple where the Bethesda system would include moderate and severe pulmonary stenosis as moderately complex. The second reason is that our inability to individually corroborate electronic records with medical notes means we are unable to rule out if a defect has received an intervention. OPCS coding will allow identification of when a procedure has definitely occurred however the absence of a code does not rule out that the same intervention has occurred at some point, either prior to the data period (or prior to the code's inception) or out with Scotland (which has occurred with certain CHD procedures over the years). As such we have categorised all PDAs as simple where the Bethesda system would categorise those without intervention as moderately complex.

Table 4-21: Categorisation of lesions by lesion complexity

Complexity	Lesion
Simple	ASD (secundum septum)
	Isolated congenital aortic valve disease
	Isolated congenital pulmonary stenosis
Moderate	Anomalous pulmonary venous drainage
	Atrioventricular septal defect
	Tetralogy of Fallot
	Ebstein's anomaly
	Valvular lesions (unless isolated pulmonary stenosis or aortic valve disease)
	Aortic coarctation
	Sub and supravalvular aortic stenosis
Severe	Transposition of the great ateries (irrespective of repair)
	Congenitally corrected transposition of the great arteries
	Fontan
	Eisenmenger syndrome
	Truncus arteriosus
	Univentricular heart
	Hypoplatic left heart syndrome
	Tricuspid atresia
	Pulmonary atresia
	Aortopulmonary window

4.6 Classifying cause of death

4.6.1 Major groupings

It was identified that 80.0% of the deaths amongst the study cohort could be categorised under seven major headings, corresponding to ICD 9 and 10 codes. These headings are also used in the reporting of deaths as recorded by the NRS and as reported in the annual report of vital statistics at a population level (123). The headings used were: death attributed to congenital heart disease, ischaemic heart disease, cerebrovascular and peripheral vascular disease, other cardiovascular disease, malignancy, respiratory, and infection. The remaining deaths were grouped together as ‘other’.

The codes used to categorise causes of death into major groups are described in Table 4-22.

Table 4-22: Major groupings of causes of death, ICD codes and description.

Cause of death	ICD 9 codes	ICD 10 codes	Description
CHD	745, 746, 747.0, 747.1, 747.2, 747.3, 747.4	Q20 - Q25	Congenital malformation of cardiac chambers and connections Congenital malformation of cardiac septa Congenital malformation of pulmonary and tricuspid valves Congenital malformation of aortic and mitral valves Other congenital malformations of the heart Congenital malformations of the great arteries
IHD	410 - 414	I20 - I25	Ischaemic heart disease
CVD/PVD	43 - 44	I6 - I7, K55	Cerebrovascular disease (ischaemic or atraumatic haemorrhage) Disease of the arteries, arterioles and capilliaries Vascular disorders of the intestine
Other cardiac	39 - 40, 420, 425-429, 458, 514	I0-I1, I30-31, I40, I42, I44 - I51, I81, I95	Rheumatic heart disease Hypertensive diseae Pericarditis and other pericardial disease Myocarditis Cardiomyopathy Conduction disorders of the heart Cardiac arrhythmias Heart failure
Malignancy	14 - 23	C, D0 - D4	Malignant neoplasms Neoplasms in situ
Infection	0, 10 - 13, 320 - 322, 324 - 326, 46, 48, 68, 510, 513, 711, 771, 421, 422	A - B, G00, G03, J0 - J2, J85 - J86, L00, L02, L03, L08, M00, P36, P39, I33, I38	Bacterial infections and parasitic diseases Bacterial meningitis Infective encephalitis Lung absces, pyothorax and acute and chronic pneumonias Infections of the skin and subcutaneous tissue Acute and subacute endocarditis Infectious arthropathies Infections of the perinatal period
Respiratory	415-417, 453, 511-512, 515-519, 49-50	I26-I28, J3-J7, J80, J82, J84, J9	Pulmonary heart disase Diseases of pulmonary circulation Diseases of the upper respiratory tract Chronic lower respiratory tract disorders Pleural disorders

4.6.2 Cardiovascular and non-cardiovascular death

Deaths were also categorised as by cardiovascular and non-cardiovascular causes. CV deaths included all CHD, IHD, CVD/PVD and 'other cardiac' deaths as defined in Table 4-22. Additionally, for the purposes of analysis by CV and non-CV deaths, pulmonary embolus was included as CV (ICD 9 code 415, ICD 10 code I26). All other deaths were categorised as by non-CV causes however deaths where the cause could not be determined were excluded from this system of categorisation (ICD 9 code 798, ICD 10 code R99). This definition of cardiovascular mortality has been used previously when ICD coding via death certification has been relied upon (124–126). A notable exception or perhaps oversight in previous work where congenital heart disease is not the focus, is

that deaths due to congenital heart disease are not generally included into the definition of CV mortality.

4.7 Follow up and time to censorship

An individual's follow up period was defined as starting at the 1st day of their first CIS which was discharge coded after January 1st, 1986 (ergo, follow up may start prior to January 1st, 1986). This was true even if none of the inclusion codes as defined in Table 4-3 were encountered during that particular CIS. By the nature of CHD it is present from birth and so utilising data linkage to identify all episodes for an individual and extending the period of follow up back to the earliest encounter within the data period was felt to be appropriate.

As explained in section 4.3, dates were limited to month and year only for reasons of anonymisation and so the start of follow up was approximated to the 1st of the month in question. For those individuals who were first encountered prior to age 16, their follow up start was determined to be the 1st of January of the year in which they turned 16. Again, this approximation was due to the necessary anonymisation as recommended by the privacy panel, prohibiting access to dates of birth as explained in section 4.3.

Follow up was continued until either death or administrative censorship on the 30th September 2017. ISD data is unable to account for other forms of censorship, such as by emigration.

4.8 Statistics

This section describes the statistical methodology common throughout this thesis. Where deviations or significant alterations to these methods was necessary, they will be outlined in the relevant results Chapter.

4.8.1 Preamble, descriptives and significance

All statistical tests were carried out using STATA 14 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP). Continuous variables are presented as mean with standard deviation where the distribution is normal and by median and interquartile range (IQR) when non-normal. Comparison between groups was carried out by way of independent sample T-test, Pearson's Chi squared test or Mann Whitney U test as appropriate. Comparison of rates of change were carried out using the proportion Chi squared test, in the manner previously advocated by Fan *et al* (127). For all statistical methods a two-tailed p value of <0.05 was considered to be of statistical significance.

4.8.2 Population data

Population numbers, deprivation statistics and cause of death data were derived from the NRS table of vital events 6.4 for each year between 1986 and 2017. This information is freely available in online form from 2001 and in print prior to 2001.

4.8.3 Kaplan Meier

Kaplan Meier estimates were left truncated at the point of first episode within the data period. At times it was considered appropriate to extend left back to age 16 and where this was the case it will be highlighted in the appropriate result Chapter. As all Kaplan Meier estimates in this work concern mortality, estimates are right censored.

4.8.4 Cox regression

Uni and multivariate models of survival were calculated using Cox regression and output presented as hazard ratios with 95% confidence intervals. The Breslow method was used to account for ties and the assumption of proportional hazard was checked visually using log(-log(survival)), “log-minus-log” plots.

4.8.5 Standardised mortality ratios

Where appropriate, age standardised mortality ratios were calculated by dividing the observed number of deaths amongst the ACHD population by the expected number of deaths calculated using population mortality rates. As the duration of follow up was highly variable between individuals and each person may contribute to multiple age cohorts throughout the data set, these calculations were limited to mortality occurring within the first year of inclusion into the data set. Expected mortality was calculated using the mean of the yearly population mortality rates for each age cohort during the time period in question (the total data-period, the first half of the data period and the second half of the data period) as obtained via the NRS table of vital events 6.4 (as outlined in section 4.8.2).

5 Circumstances of death and survival for all ACHD lesions and changes over time

5.1 Introduction

As established by the preceding literature review, survival for all ACHD and according to underlying lesion is the most established method of reporting in the published data. Population level data however remains scarce and has never been established for the Scottish population. Data regarding cause of death is more sparse still and temporal changes are not reported in the identified literature.

In clinical practice patients are most commonly categorised according to their underlying congenital heart lesion, often in combination with their surgical and interventional history. This allows the clinician to consider common and important problems specific to this group upon review or when presented with a change in symptoms or signs. The nature of congenital heart disease however is that although the majority of patients are easily characterised by a lesion or a dominant lesion if multiple coexist, many other rare lesions do exist and some congenital heart disease defies classification in this manner altogether. For this reason, reporting data at an individual lesion level would neither be practical nor useful. The 13 major groupings described in this Chapter have been explained in section 4.4 and are broadly according to convention as described in the existing literature (50,51,75) and according to my experience in clinical practice.

This Chapter will establish the baseline characteristics of the total study population and according to their major underlying congenital lesion. Temporal changes in survival and causes of death will be outlined.

5.2 Methods

The preceding Chapters have described the methods by which patients are identified using ICD and OPCS coding. As these coding systems have evolved and exist in several iterations across my data period comparisons over time at lesion level is affected. Due to the particular heterogeneity within the OPCS system, lesions dependant on this method of coding (Fontan and TGA arterial switch) are not readily identified by the earliest version (OPCS3). Consequently, these lesions are not individually reported in temporal analyses within this Chapter.

Due to the significant variation in age at first encounter, this Chapter has presented Kaplan Meier curves not as observed, left truncated graphics but rather as being extended left to start at age 16 and then using age at death or age at censorship to illustrate survivorship. The alternative, to present fully left truncated estimates would misleadingly suggest those who present to the data set in later life (as you might expect with less severe CHD such as ASDs) to experience relatively poorer survival. As these lesions have been present from birth and it is time to presentation or recognition by the data set which is altered, extending survival leftward was preferred in this Chapter. As a result, these graphs should not be used to truly estimate the real-life survival for each lesion as this would be an over-estimate due to a survivor bias, as comparable individuals may have died during the 'left extended' phase and hence would be hidden from this data set. The Kaplan-Meier analyses are thus meant as a relative guide as to the univariate survival of each lesion when compared to CHD as a whole.

Section 5.3.4 describes deaths where a CHD code was identified from death records (having been listed as a cause on the MCCD) but the individual does not have an SMR01 record during the data period. As death recording has no place for procedural coding (OPCS) only ICD coding is utilised for patient identification and lesion grouping. As such, for this section only, the lesions which require procedural data will not be delineated. Fontan, TGA with arterial switch and the TGA with atrial switch are the groups affected and will be included in the 'complex' category.

5.3 Results

5.3.1 Demographics and baseline characteristics

A total of 16,210 patients were identified from 1986 to 2015 of which 4162 (25.7%) died. The baseline characteristics of the total study population, those who survived the data period and those who died are summarized in Table 5-1.

More women than men were identified (50.9% and 49.2%, p=0.03) and mean age at inclusion was higher for women than men (40.6, SD 24.4 and 37.6, SD 22.4), p<0.01). A higher proportion of women than men died during follow up (27.2% and 24.2%, p<0.01).

Those with shunt lesions; ASD, PDA, and AVSD as well as Ebstein's anomaly were predominantly women, whereas those with conotruncal lesions (TOF and systemic RV) as well as aortic and Fontan cohorts were predominantly men. For the combined cohorts of 'complex lesions' and 'other lesions' there was no significant difference in sex distribution (49.7% (p=0.85)and 48.5% (p=0.23) female respectively) (Table 5-2).

A quintile group of SIMD could be assigned for 16,045 (99.0%) individuals. Among the 165 individuals for which SIMD data was not available, more were male (55.8%) and they were younger (median 23, IQR 16-49) when compared to the total study population. The most common SIMD quintile observed was 1-most deprived (4355 (27.1%) individuals) and least common was 5-least deprived (2516 (15.7%) individuals). A higher proportion of individuals in the more deprived socioeconomic quintiles died during follow up (26.2% and 28.0% for SIMD 1 and 2 respectively) when compared with the least deprived (24.5% and 22.5% for SIMD 4 and 5 respectively), p<0.01.

AF (9.9%) and ischaemic heart disease without myocardial infarction (10.0%) were the most commonly observed comorbidities. Cancer (2.5%) and diabetes (3.7%) were less commonly observed. The majority of patients with diabetes (58.8%), cancer (73.1%), AF (54.7%) and prior myocardial infarction (65.6%) died during the data period.

Atrial septal defect was the most common lesion identified, representing 25.7% of the total study cohort. TGA with arterial switch and Ebstein's anomaly were the least frequently observed lesions, representing 0.2% and 0.7% of the total study cohort respectively. Patients with aortic lesions were the most frequently observed to die (52.5%) during the study period. Few patients with PDA (5.7%) and no patients with TGA arterial switch died during follow up.

Table 5-1: Baseline characteristics for all patients and for those alive and dead at the end of follow up

	All (%)	Alive (%)	Dead (%)
All	16210	12048 (74.3)	4162 (25.7)
Age at inclusion (IQR)	34 (16-59)	19 (16-45)	67 (52-77)
Female	8242 (50.9)	6004 (72.9)	2238 (27.2)
Male	7968 (49.2)	6044 (75.9)	1924 (24.2)
SIMD quintile	16045		
1 most deprived	4355 (27.1)	3215 (73.8)	1140 (26.2)
2	3441 (21.5)	2474 (71.9)	967 (28.1)
3	2997 (18.7)	2222 (74.1)	775 (25.9)
4	2736 (17.1)	2066 (75.5)	670 (24.5)
5 least deprived	2516 (15.7)	1950 (77.5)	566 (22.5)
Comorbidity			
Diabetes	606 (3.7)	250 (41.3)	356 (58.8)
Cancer	401 (2.5)	108 (26.9)	293 (73.1)
AF	1609 (9.9)	728 (45.3)	881 (54.8)
CVD	931 (5.7)	613 (65.8)	318 (34.2)
HTN	946 (5.8)	572 (60.5)	374 (39.5)
AMI	896 (5.5)	308 (34.4)	588 (65.6)
other IHD	1619 (10.0)	843 (52.1)	776 (47.9)
Lesion			
ASD	4172 (25.7)	3365 (80.7)	807 (19.3)
PDA	983 (6.1)	927 (94.3)	56 (5.7)
VSD	2244 (13.8)	1584 (70.6)	660 (29.4)
Aortic	2143 (13.2)	1017 (47.5)	1126 (52.5)
Ebstein's	105 (0.7)	71 (67.6)	34 (32.4)
AVSD	600 (3.7)	491 (81.8)	109 (18.2)
TOF	564 (3.5)	495 (87.8)	69 (12.2)
TGA arterial switch	35 (0.2)	35 (100)	-
Systemic RV	133 (0.8)	115 (86.5)	18 (13.5)
Complex	1285 (7.9)	1042 (81.1)	243 (18.9)
Fontan	167 (1.0)	151 (89.4)	16 (9.6)
Valvular	2163 (13.3)	1598 (73.9)	565 (26.1)
Other	1616 (10.0)	1157 (71.6)	459 (28.4)

5.3.2 Follow up, mortality and age at death

A total of 168,177 person years of follow up were observed across the entire study population. Cumulative follow up ranged from 196 person years for TGA arterial switch, to 43,483 person years for ASD. Cumulative follow up and mortality rates for each CHD lesion are summarised in Table 5-2.

Mean age at inclusion varied from 16 (SD 0) for TGA with arterial switch to 51.5 (SD 27.9) for aortic lesions. Mean age at death for the total study cohort was 68.1 (SD 19.1) years and varied from 22.2 (SD 5.1) years for the systemic RV cohort to 77.0 (SD 14.8) years for aortic lesions. For comparison, the population estimates of age at death from 2016-2018 in Scotland were 77.0 for men and 81.1 for women.

The observed mortality rate for the total study population was 24.7 (95% CI 24.0-25.5) deaths per 1000 person years. No deaths were observed for the TGA arterial switch group but otherwise the mortality rate ranged from 5.0 (95% CI 3.8-6.5) for PDA to 57.6 (95% CI 54.3-61.0) deaths per 1000 person years for the aortic lesion cohort.

Table 5-2: Follow up and mortality rate for all CHD and all lesion groups

Lesion	n	Women, % (compared to men)	Dead, n (%)	Age, median (IQR)	Age at death, median (IQR)	Cummulative follow-up, years	Mortality rate per 1000 person years (95% CI)
All	16210	50.9 (p=0.03)	4162 (25.7)	34 (16-59)	74 (58-82)	168177	24.7 (24.0-25.5)
ASD	4172	57.5 (p<0.01)	807 (19.3)	43 (26-59)	73 (61-81)	43483	18.6 (17.3-19.9)
PDA	983	62.2 (p<0.01)	56 (5.7)	16 (16-16)	69.5 (50.5-78)	11194	5.0 (3.8-6.5)
VSD	2244	50.4 (p=0.70)	660 (29.4)	17 (16-56)	70 (56-79)	23080	28.6 (26.5-30.9)
Aortic	2143	47.7 (p=0.03)	1126 (52.5)	59 (16-77)	81 (73-86)	19563	57.6 (54.3-61.0)
Ebstein's	105	60.0 (p=0.04)	34 (32.4)	35 (19-50)	55 (37-66)	1171	29.0 (20.7-40.6)
AVSD	600	55.2 (p=0.01)	109 (18.2)	16 (16-40)	63 (41-74)	6785	16.1 (13.3-19.4)
TOF	564	42.0 (p<0.01)	69 (12.2)	16 (16-17.5)	42 (30-57)	7250	9.5 (7.5-12.1)
TGA switch	35	42.9 (p=0.40)	0	16 (16-16)	NA	196	NA
Systemic RV	133	33.1 (p<0.01)	18 (13.5)	16 (16-16)	20.5 (17-27)	1735	10.4 (6.5-16.5)
Complex	1285	49.7 (p=0.85)	243 (18.9)	16 (16-31)	54 (31-72)	16148	16.1 (13.3-17.1)
Fontan	167	40.1 (p<0.01)	16 (9.6)	16 (16-16)	22 (19.5-30)	1730	9.3 (5.7-15.1)
Valvular	2163	41.7 (p<0.01)	565 (26.1)	44 (16-65)	76 (62-83)	20319	27.8 (25.6-30.2)
Other	1616	48.5 (p=0.23)	459 (28.4)	49 (28-63)	67 (51-78)	15518	29.6 (27.0-32.4)

Mean age at death during the earliest study cohort (1986-1990) was 61.4 (SD 19.3) compared to 68.5 (SD 19.5) during the most recent study period (2015-2017), p<0.01. The breakdown of distribution of deaths according to 5 year age cohorts for the earliest and most recent time period studied are summarised in Figure 5-1. A cohort from the general population of Scotland covering the same time period is shown for comparison. From 1986 - 1990 death was most frequently encountered in the 75-79 years age bracket (13.3% of all deaths). In the most recent time period >84 years was the most common age at death for all CHD (20.44%), as it is in the general population.

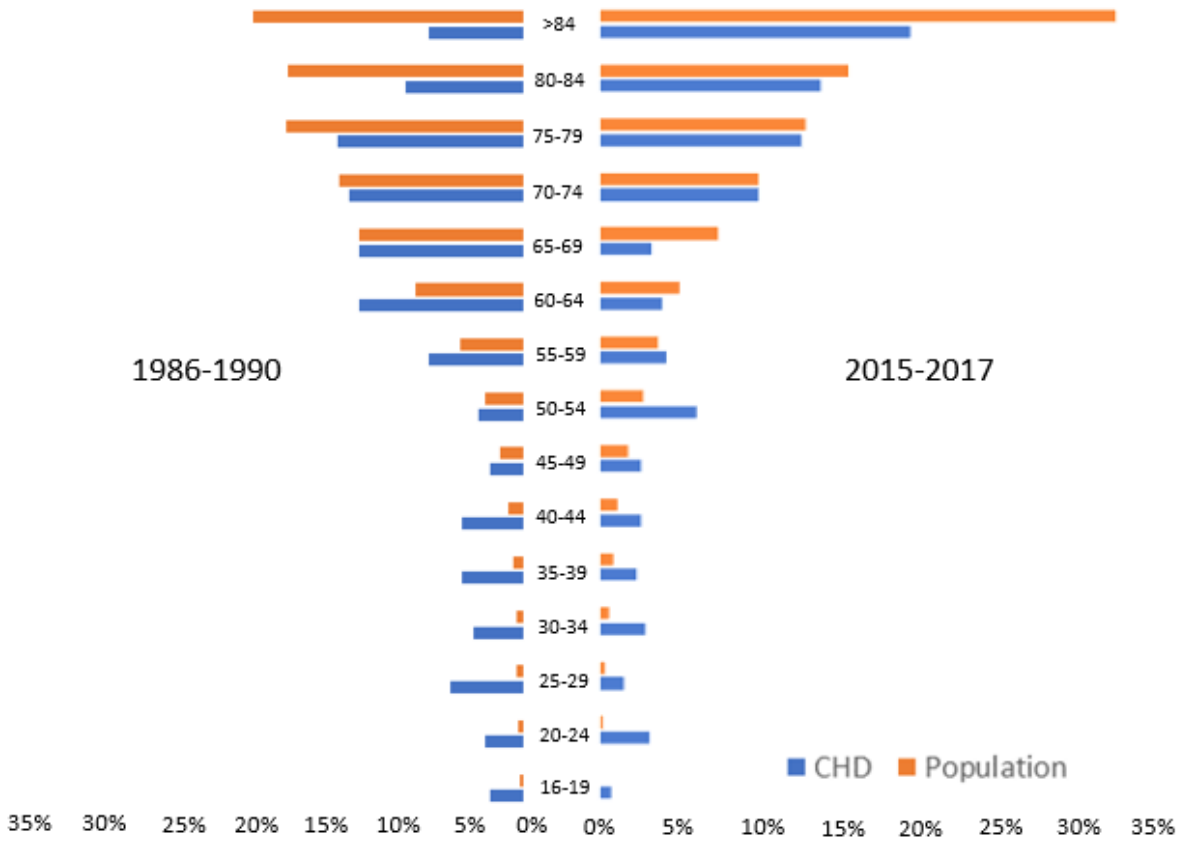


Figure 5-1: Distribution of age at death cohorts compared to the general population for the earliest (1986-1990) and most recent (2015-2017) time periods

Deaths in early adulthood are more clearly shown in Figure 5-2. In total, 23.0% of all deaths from 1986-1990 were in those under the age of 45. This is compared to 14.1% of deaths from 2015-2017. A higher percentage of deaths were witnessed for all age cohorts below 45 years in the earliest compared to most recent time period except amongst death at age 20-24.

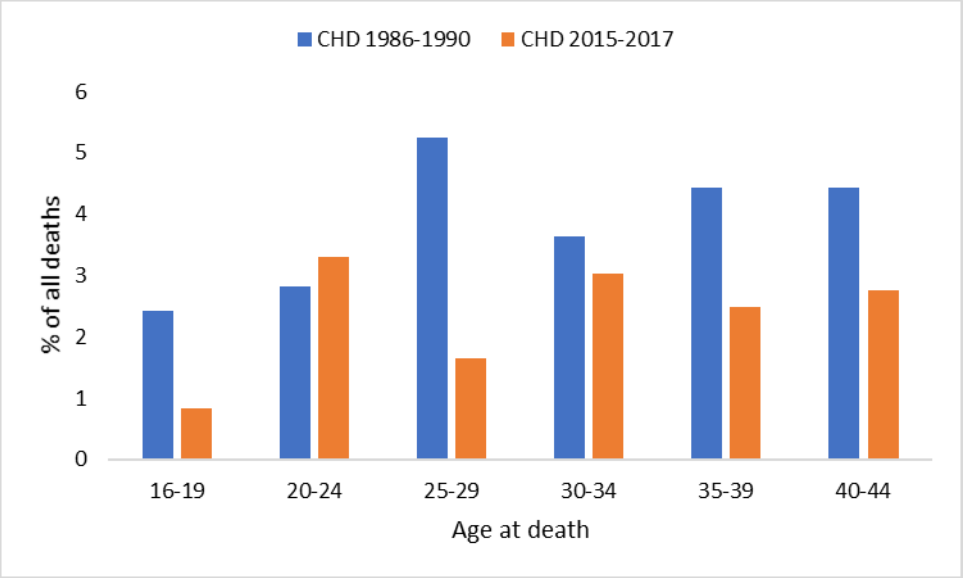


Figure 5-2: Comparison of age at death between the earliest and most recent time cohorts for all congenital heart disease (CHD) lesions

Overall, the median age at death increased from 72 (IQR 59-81) to 74 (IQR 58-83) years between the first and second half of the data period (p<0.01). Significant increases in age at death were seen for ASD (68 (IQR 58-77) to 74 (IQR 62-82)), p<0.01, and VSD (68.5 (IQR 57-76) to 73(IQR 55-83), p<0.01). Point estimates of age at death increased for all other lesions except PDA however statistical significance was not achieved.

The unadjusted survival of individual lesions from age 16 is demonstrated in Figure 5-3, Figure 5-4 and Figure 5-5. When compared to the total patient cohort, survival was greater for ASD (HR 0.81, 95% CI 0.75-0.88 p<0.01), valvular (HR 0.82, 95% CI 0.75-0.90 p<0.01) and aortic lesions (HR 0.78, 95% CI 0.72-0.83 p<0.01). It was lower for VSD (HR 1.78, 95% CI 1.36-1.61 p<0.01), Ebstein's anomaly (HR 2.74, 95% CI 1.95-3.84 p<0.01), AVSD (HR 1.67, 95% CI 1.38-2.02, p<0.01), TOF (HR 3.24, 95% CI 2.54-4.12 p<0.01), systemic RV (HR 6.72, 95% CI 4.20-10.76 p<0.01), Fontan (HR 3.53, 95% CI 2.16-5.79 p<0.01) and complex lesion (HR 1.89, 95% CI 1.67-2.14 p<0.01). There was no significant difference in survival when compared to the reference group for PDA (HR 1.04, 95% CI 0.80-1.36 p=0.77) and 'other' lesions (HR 1.04, 95% CI 0.95-1.15 p=0.38)

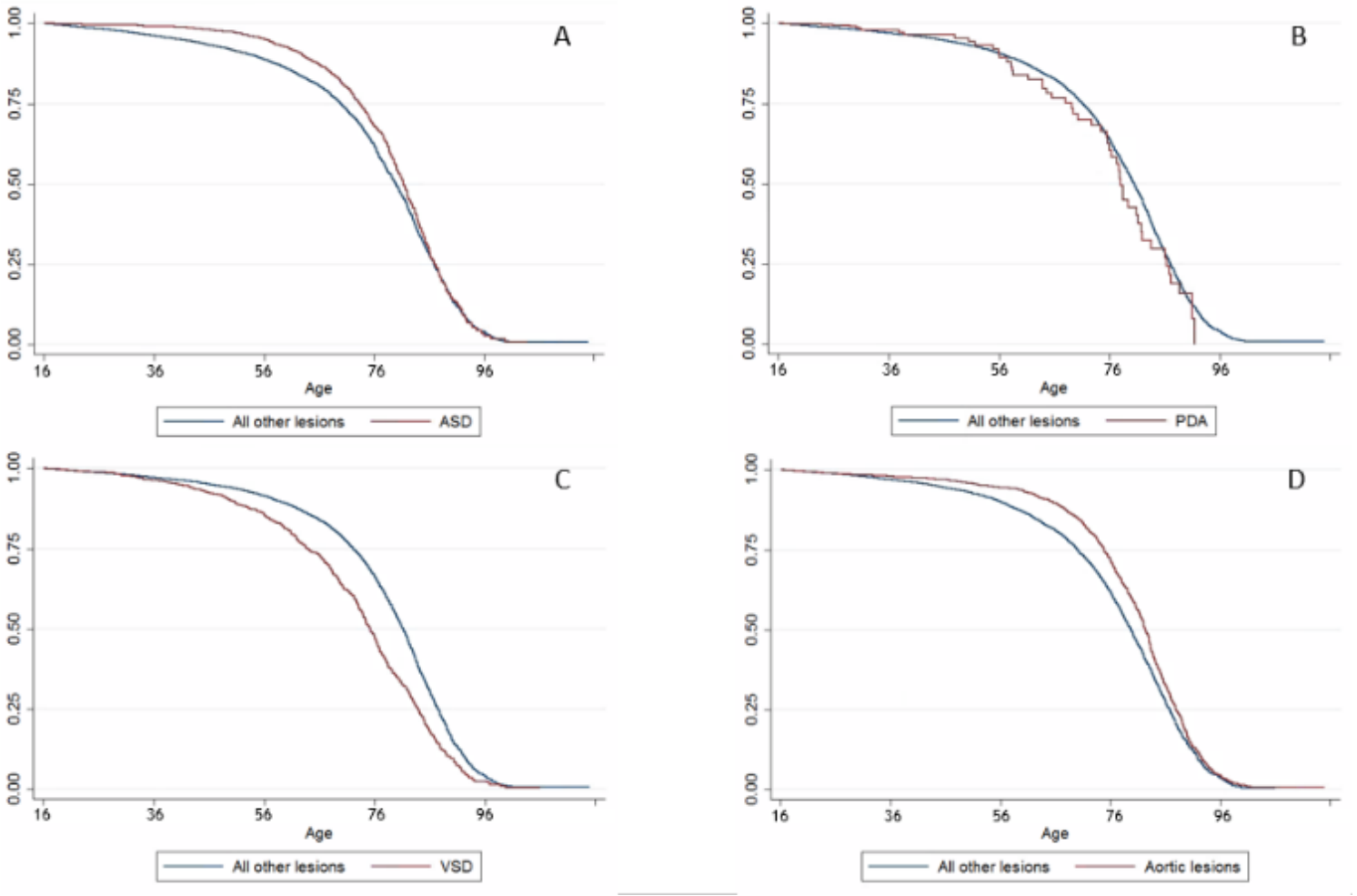


Figure 5-3: Kaplan Meier survival curves (ASD, PDA, VSD and aortic lesions)
A – ASD compared to all other lesions, B – PDA compared to all other lesions, C- VSD compared to all other lesions, D – Aortic compared to all other lesions

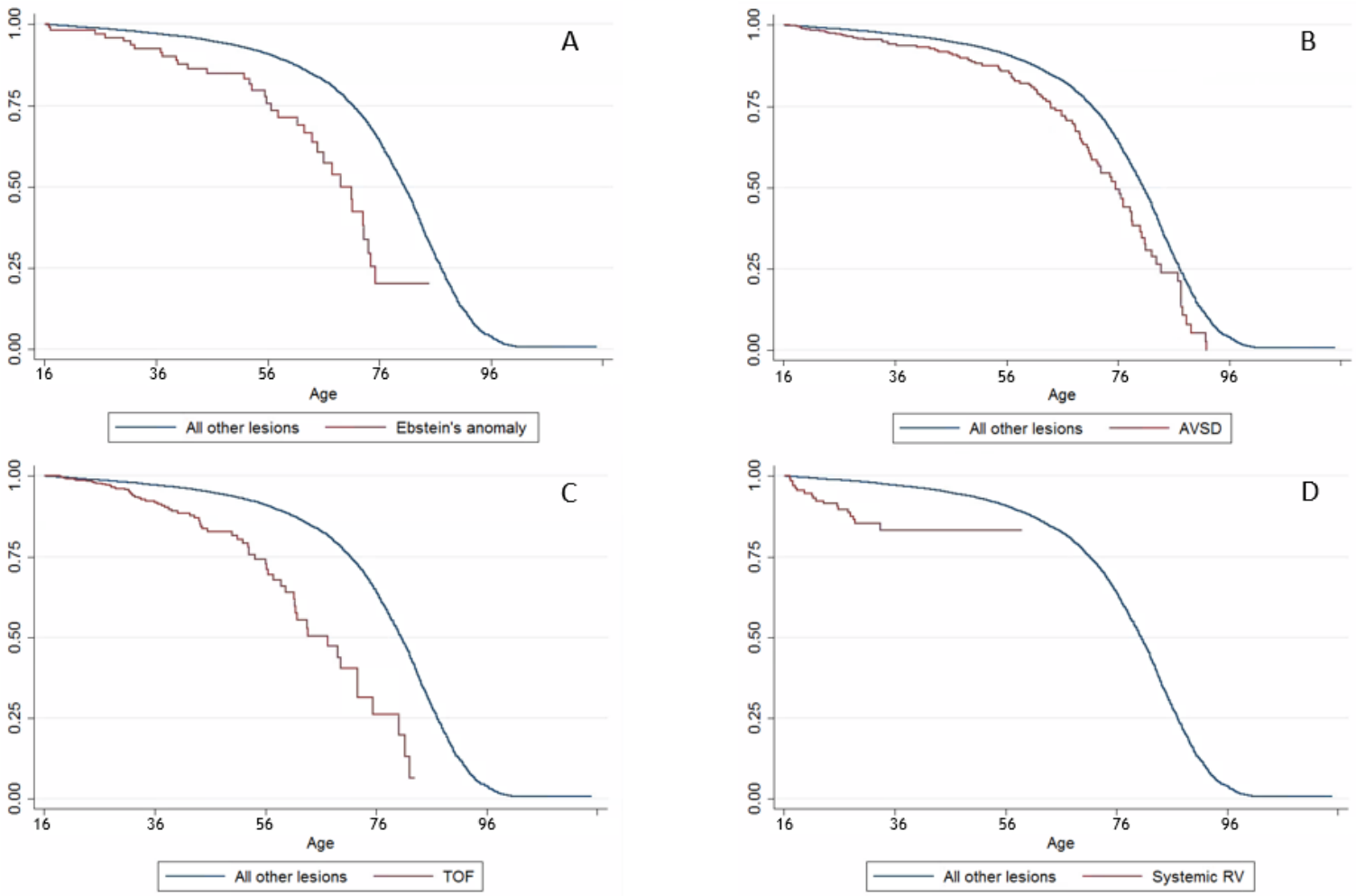


Figure 5-4: Kaplan Meier survival curves (Ebstein's anomaly, AVSD, TOF, Systemic RV)
A – Ebstein's anomaly compared to all other lesions, B – AVSD compared to all other lesions, C – TOF compared to all other lesions, D – Systemic RV compared to all other lesions

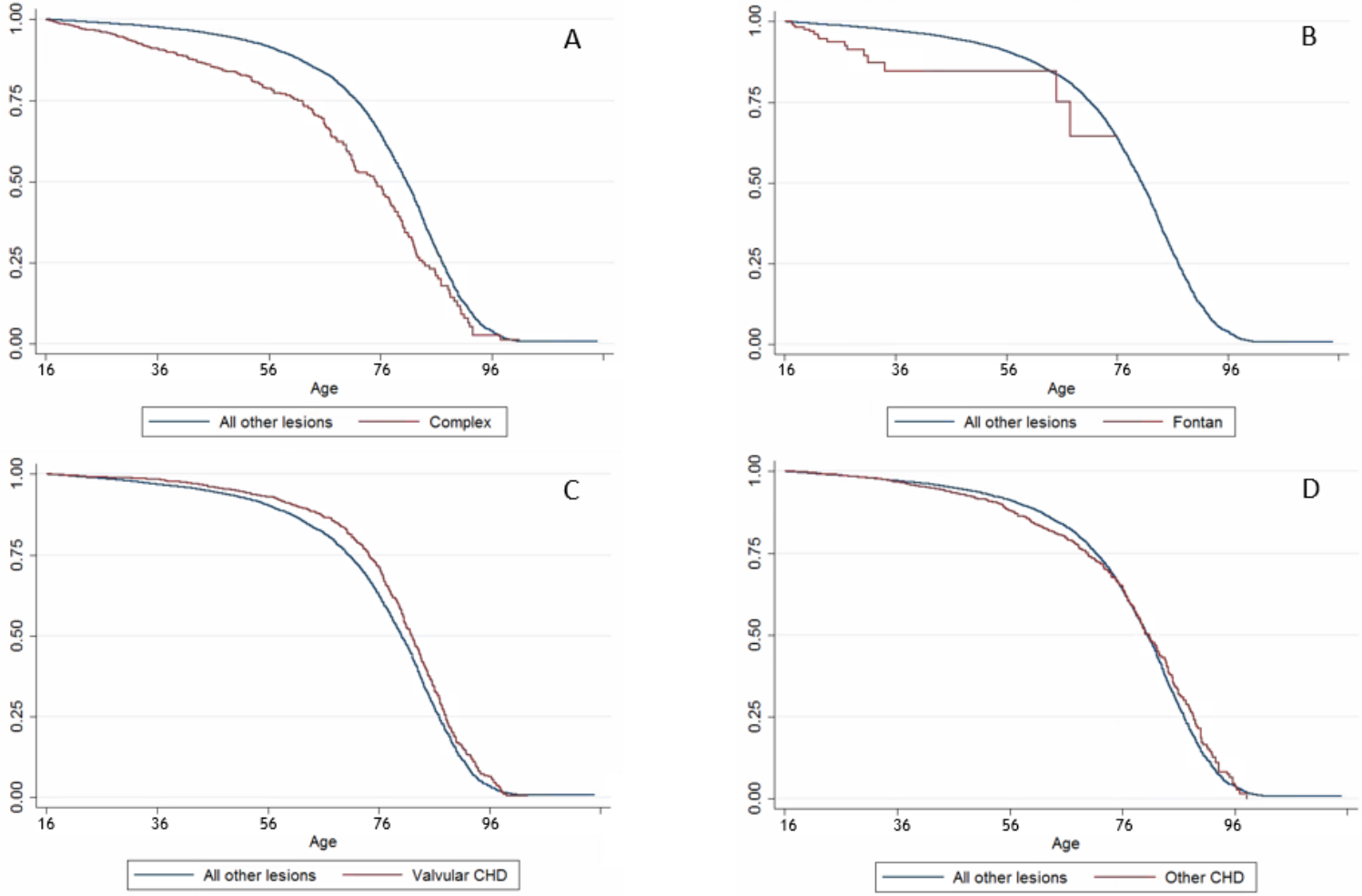


Figure 5-5: Kaplan Meier survival curves (complex lesions, Fontan, valvular and 'other' CHD)
A – Complex lesions compared to all other lesions, B – Fontan compared to all other lesions, C – valvular compared to all other lesions, D – 'other' CHD compared with all other lesions

Standardised mortality ratios were calculated from the 1 year mortality rate observed for age cohorted ACHD patients as compared with the expected mortality calculated from the age equivalent general population. Table 5-3, Table 5-4, and Table 5-5 outline the observed as well as the expected mortality for each age cohort as well as the standardised MR for; the total data period; the first half of the data period; and the second half of the data period respectively. For the total data period the one-year age standardised MR as compared to the general population was 5.22 (95% CI 4.92-5.52). This is accounted for by the equivalent standardised MR of 6.71 (95% CI 6.23-7.22) for the first half of the data period, significantly higher than the second half of the data period (4.05, 95% CI 3.69-4.43, $p<0.01$).

Table 5-3: Observed and expected deaths according to age cohorts for adult congenital heart disease, standardised using population mortality rates. Standardised mortality ratio is observed/expected ACHD deaths.

Age group	ACHD No.	ACHD deaths	ACHD mortality rate per 1000	Population mortality rate per 1000	Expected deaths	Standardised MR
15-24	6897	35	5.07	0.58	4.00	8.75 (6.19-12.03)
25-34	1280	27	21.09	0.93	1.19	22.68 (15.26-32.56)
35-44	1551	55	35.46	1.75	2.71	20.26 (15.44-26.22)
45-54	1656	75	45.29	4.18	6.92	10.84 (8.59-13.51)
55-64	1621	145	89.45	10.97	17.78	8.16 (6.91-9.57)
65-74	1619	274	169.24	27.64	44.75	6.12 (5.43-6.88)
75-84	1145	366	319.65	67.44	77.22	4.74 (4.27-5.24)
85-89	311	132	424.44	141.48	44.00	3 (2.52-3.55)
90+	101	51	504.95	235.79	23.81	2.14 (1.61-2.79)
Total		1160			222.39	5.22 (4.92-5.52)

Table 5-4: Observed and expected deaths during the first half of the data period (1986-2000) according to age cohorts for adult congenital heart disease, standardised using population mortality rates. Standardised mortality ratio is observed/expected ACHD deaths.

Age group	ACHD No.	ACHD deaths	ACHD mortality rate per 1000	Population mortality rate per 1000	Expected deaths	Standardised MR
15-24	1747	26	14.88	0.66	1.15	22.61 (15.08-32.65)
25-34	528	18	34.09	0.93	0.49	36.73 (22.46-56.93)
35-44	444	32	72.07	1.74	0.77	41.56 (28.91-57.97)
45-54	460	32	69.57	4.73	2.18	14.68 (10.21-20.47)
55-64	559	88	157.42	13.33	7.45	11.81 (9.53-14.48)
65-74	640	185	289.06	33.68	21.56	8.58 (7.41-9.89)
75-84	511	228	446.18	77.36	39.53	5.77 (5.06-6.55)
85-89	138	68	492.75	158.63	21.89	3.11 (2.43-3.91)
90+	41	23	560.98	225.57	9.25	2.49 (1.61-3.67)
Total		700			104.27	6.71 (6.23-7.22)

Table 5-5: Observed and expected deaths during the second half of the data period (2001-2017) according to age cohorts for adult congenital heart disease, standardised using population mortality rates. Standardised mortality ratio is observed/expected ACHD deaths.

Age group	ACHD No.	ACHD deaths	ACHD mortality rate per 1000	Population mortality rate per 1000	Expected deaths	Standardised MR
15-24	5150	9	1.75	0.511	2.63	3.42 (1.67-6.28)
25-34	752	9	11.97	0.93	0.70	12.86 (6.27-23.59)
35-44	1170	23	19.66	1.76	2.06	11.17 (7.25-16.49)
45-54	1196	43	35.95	3.7	4.43	9.71 (7.11-12.95)
55-64	1062	57	53.67	8.89	9.44	6.04 (4.62-7.77)
65-74	979	89	90.91	22.32	21.85	4.07 (3.29-4.99)
75-84	634	138	217.67	58.7	37.22	3.71 (3.13-4.37)
85-89	173	64	369.94	126.35	21.86	2.93 (2.27-3.71)
90+	60	28	466.67	224.81	13.49	2.08 (1.41-2.96)
Total		460			113.67	4.05 (3.69-4.43)

A multivariate regression model for all-cause mortality, adjusted for sex, age, year of presentation, comorbidity (diabetes, cancer, AF, CVD, HTN, AMI and other IHD), congenital lesion and socioeconomic group, is summarized in Table 5-6.

Male sex confers a small increased risk of all-cause mortality (HR 1.14, 95% CI 1.07-1.21, p<0.01) compared with female. When stratifying risk of mortality according to underlying lesion, the largest patient cohort of ASD was used as the reference and HRs for other lesions are relative to this. Figure 5-6 illustrates the relative hazard of each lesion as well as sex. Overall the lowest risk was noted for PDA (HR 0.88, 95% CI 0.67-0.16, p=0.36) and the highest for Fontan circulations (HR 2.20, 95% CI 1.34-3.63, p<0.01) and Ebstein's anomaly (HR 2.45, 95% CI 1.74-3.46, p<0.01).

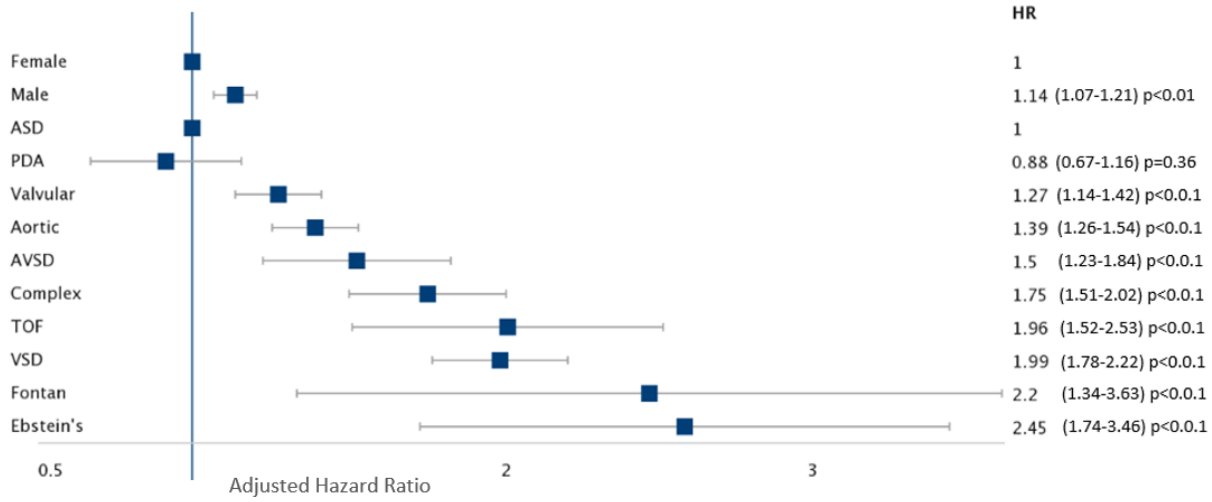


Figure 5-6: Forest plot of multivariate hazard ratios for all-cause mortality according to sex and individual lesion

The risk of all-cause mortality decreased as year of first presentation increased. As is illustrated in Figure 5-7, a reduction in hazard occurred between each of the six time cohorts and amount to a 65% reduction in instantaneous risk of all-cause mortality between the earliest and most recent data periods.

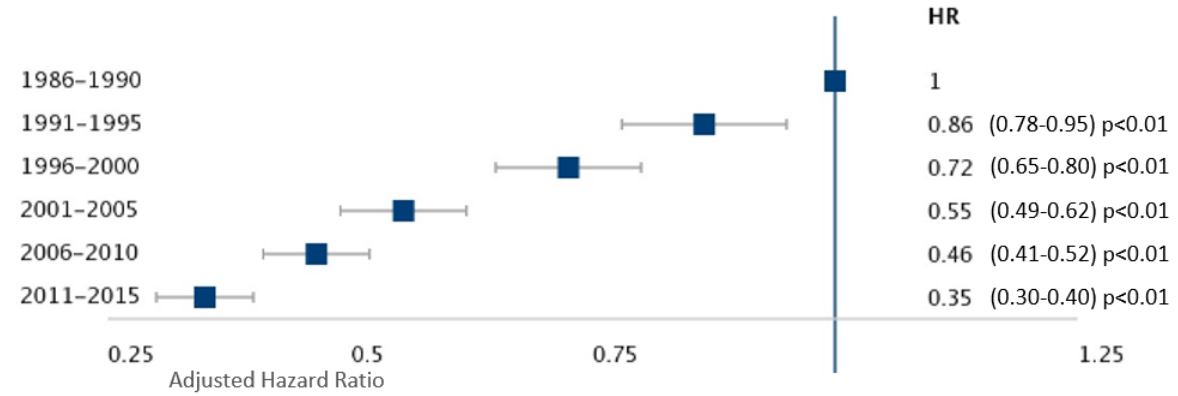


Figure 5-7: Forrest plot of multivariate hazard ratios for all-cause mortality according to year of inclusion to data set

Mortality was higher in the presence of diabetes (HR 1.71, 95% CI 1.53-1.91, p<0.01), cancer (HR 1.79, 95% CI 1.58-2.02, p<0.01), acute myocardial infarction (HR 1.39, 95% CI 1.26-1.52, p<0.01), and atrial fibrillation (HR 1.24, 95% CI 1.15-1.35, p<0.01). No significant difference in mortality was observed in the presence of hypertension (HR 0.96, 95% CI 0.86-1.07, p=0.44), cerebrovascular disease (HR 1.09, 95% CI 0.97-1.22, p=0.17) or ischaemic heart disease without myocardial infarction (HR 0.93, 95% CI 0.86-1.01, p=0.08).

Table 5-6: Breakdown of death according to demographics, lesion, data period and deprivation with multivariate hazard ratios for all-cause mortality

	All (%)	Dead (%)	HR [95% CI] (p value)
Female	8169 (50.9)	2216 (27.1)	1
Male	7876 (49.1)	1902 (24.2)	1.14 [1.07-1.21] (<0.01)
Age			1.07 [1.07-1.07] (<0.01)
Year of Presentation			
1986-1990	3206 (20.0)	834 (26.0)	1
1991-1995	2892 (18.0)	892 (30.8)	0.86 [0.78-0.95] (<0.01)
1996-2000	2978 (18.6)	842 (28.3)	0.72 [0.65-0.80] (<0.01)
2001-2005	2158 (13.5)	641 (29.7)	0.55 [0.49-0.62] (<0.01)
2006-2010	2453 (15.3)	576 (23.5)	0.46 [0.41-0.52] (<0.01)
2011-2015	2358 (14.7)	333 (14.1)	0.35 [0.30-0.40] (<0.01)
Comorbidity			
Diabetes	605 (3.8)	356 (58.8)	1.71 [1.53-1.91] (<0.01)
Cancer	401 (2.5)	293 (73.1)	1.79 [1.58-2.02] (<0.01)
AF	1593 (9.9)	872 (54.7)	1.24 [1.15-1.35] (<0.01)
CVD	925 (5.8)	315 (34.1)	1.09 [0.97-1.22] (0.17)
HTN	940 (5.9)	372 (39.6)	0.96 [0.86-1.07] (0.44)
AMI	885 (5.5)	580 (65.5)	1.39 [1.26-1.52] (<0.01)
Other IHD	1613 (10.1)	773 (47.9)	0.93 [0.86-1.01] (0.08)
Lesion			
ASD	4141	801 (19.3)	1
PDA	972	54 (5.6)	0.88 [0.67-1.16] (0.36)
VSD	2210	648 (29.3)	1.99 [1.78-2.22] (<0.01)
Aortic	2123	1117 (52.6)	1.39 [1.26-1.54] (<0.01)
Ebstein's	104	34 (32.7)	2.45 [1.74-3.46] (<0.01)
AVSD	596	108 (18.1)	1.50 [1.23-1.84] (<0.01)
TOF	552	68 (12.3)	1.96 [1.52-2.53] (<0.01)
Complex	1432	257 (18.0)	1.75 [1.51-2.02] (<0.01)
Fontan	166	16 (9.6)	2.20 [1.34-3.63] (<0.01)
Valvular	2144	561 (26.2)	1.27 [1.14-1.42] (<0.01)
Other	1605	454 (28.3)	1.37 [1.22-1.54] (<0.01)
SIMD Quintile			
1 - most deprived	4355	1140 (26.2)	1
2	3441	967 (28.1)	0.91 [0.84-0.99] (0.04)
3	2997	775 (25.9)	0.87 [0.79-0.95] (<0.01)
4	2736	670 (24.5)	0.76 [0.69-0.84] (<0.01)
5 - least deprived	2516	566 (22.5)	0.67 [0.60-0.74] (<0.01)

5.3.3 Cause of death

Seven diagnoses of cause of death accounted for 80.0% of deaths amongst the study population and 70.9% of deaths in the general population. The proportional distribution of cause of death for the entire study population, as well as for individual CHD lesion, and compared to the Scottish population for each of these seven diagnoses (congenital heart disease, ischaemic heart disease, peripheral and cerebrovascular disease, other cardiac disease, respiratory disease, infection and malignancy) and by all 'other' causes, are summarised in Figure 5-8.

Amongst the general population, malignancy was the most frequent cause of death, representing 28.7% of all deaths. In the study population, malignancy was the most frequent cause of death amongst the PDA cohort alone, representing 21.4% of deaths.

Across the study population, IHD was the most frequent cause of death (24.1% of all deaths). IHD was also the predominant cause of death for VSD (41.8%), AVSD (19.3%), ASD (17.0%), aortic lesions (28.1%), valvular lesions (21.2%) and 'other' CHD (20.5%). IHD was the second most frequent cause of death in the general population (11.9%) and significantly less frequent than in the study population ($p<0.01$).

Death directly attributed to congenital heart disease predominated for more complex lesions; accounting for 77.8% of deaths in systemic RV patients, 55.1% in the TOF cohort, 52.9% for Ebstein's anomaly, 50.0% in the Fontan group and 32.5% of deaths in the complex CHD cohort. In the general population, death due to congenital heart disease represented only 0.03% of total deaths in adults

Peripheral and cerebrovascular disease related death was most commonly observed for Fontan circulations (12.5%), PDA (12.5%) and aortic lesions (12.0%). Infection deaths were most highly represented in valvular CHD, representing 9% of the total in that cohort and are significantly more frequent than the 5.6% in the general population ($p<0.01$).

Over the total data period the majority (53.9%) of deaths were due to cardiovascular causes, p<0.01. This is significantly greater than for the general population (39.2%) over the same time period (p<0.01).

Cardiovascular death predominates for most congenital lesions, achieving statistical significance for; systemic RV (77.8%, p=0.02), Ebstein's anomaly (76.5%, p<0.01), VSD (65.3%, p<0.01), and aortic lesions (56.0%, p<0.01). And approaching statistical significance for; complex lesions (56.4%, p=0.05), Fontan circulation (68.8%, p=0.13), AVSD (56.9%, p=0.15), and valvular lesions (51.3%, p=0.53).

Non-cardiovascular death was more common for; ASD (56.9%, p,0.01), 'other' CHD (52.3%, p=0.33) and PDA (51.9%, p=0.79), achieving statistical significance for ASD only.

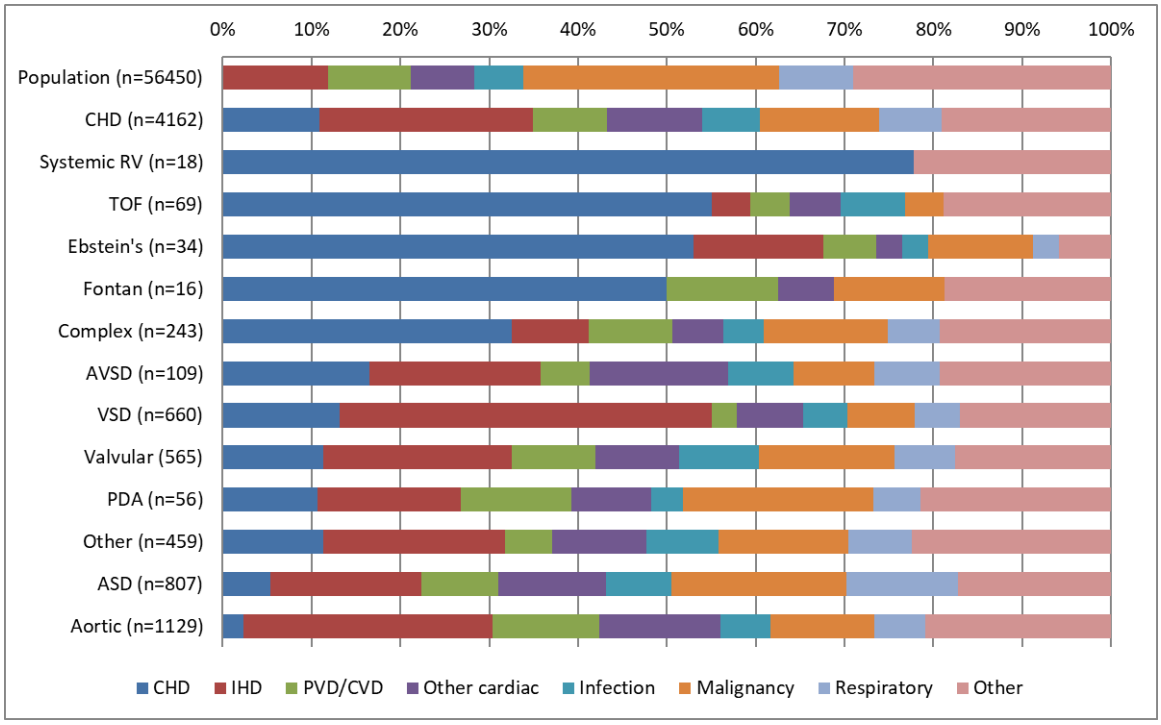
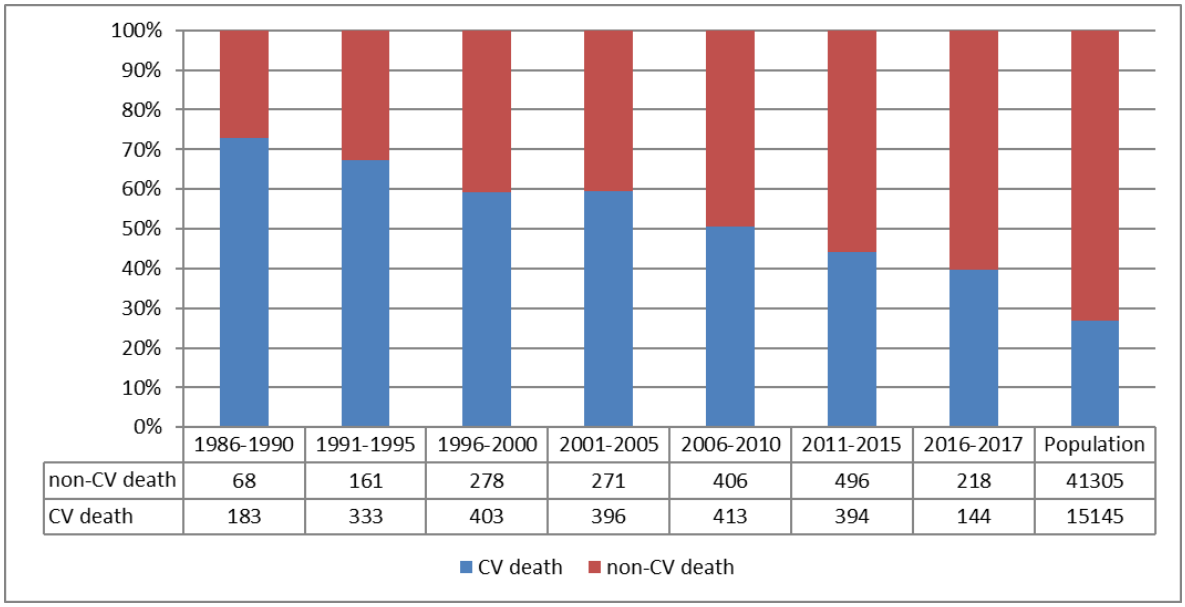


Figure 5-8: Proportional distribution of causes of death for all CHD, by individual lesion, and compared to the general population.

The proportion of cardiovascular deaths reduced over time. Figure 5-9 shows the changing proportion of cardiovascular to non-cardiovascular deaths throughout the study period.

During the earliest data period of 1986-1990, 72.9% of deaths among the study population were due to cardiovascular causes. By 2006-2010, the proportion of cardiovascular and non-cardiovascular deaths were equal (50.4% and 49.6%, p=0.83). By the most recent data period of 2016-2017, only 40% of deaths were due to cardiovascular causes. This remains significantly greater than the 26% of deaths among the general population of Scotland in 2016, p<0.01.



	1986-1990	1991-1995	1996-2000	2001-2005	2006-2010	2011-2015	2016-2017	Population
non-CV death	68	161	278	271	406	496	218	41305
CV death	183	333	403	396	413	394	144	15145

Figure 5-9: Proportional distribution of cardiovascular and non-cardiovascular death according to year of death and compared to the general population (as reported in 2016).

Figure 5-10 compares the proportion of cardiovascular deaths in the study population and the general population during each time period.

From the first to the most recent data period, the proportion of cardiovascular deaths in the ACHD population fell by 33.1%, and in the general population by 22.7%, p<0.01. This corresponds to a 1.07% reduction in cardiovascular death per year in the ACHD population and a 0.73% reduction per year in the general population p=0.02.

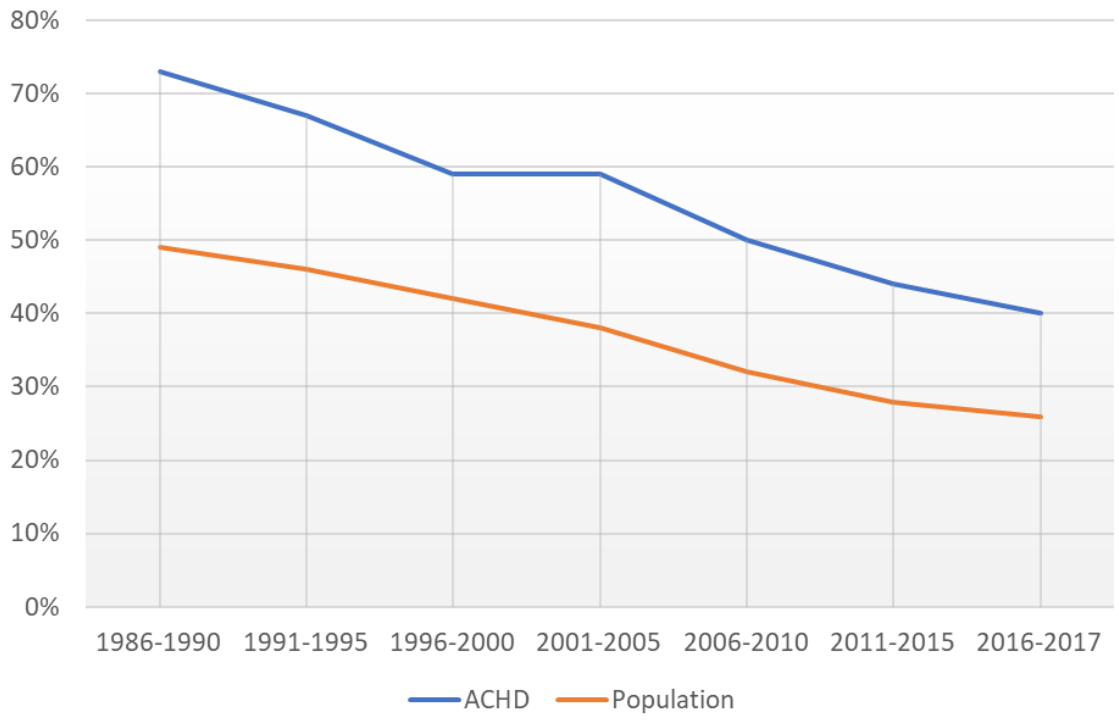


Figure 5-10: Percentage of cardiovascular deaths according to year of death for adult congenital heart disease (ACHD) and the general population

5.3.4 Deaths occurring without an SMR01 record

From the time point where this information was available (after Dec 1999), 198 individuals were identified as having CHD from death records. Median age at death was 52.5 years (IQR 40-68). Age at death did not change significantly between the first half (median 51, IQR 39-68) and second half (median 52.5, IQR 40-67) of the data period (1999-2007 and 2008-2015), p=0.72. When combined with deaths identified by SMR01 records, these 198 deaths represent 4.5% of the total deaths amongst those with CHD. To breakdown these results by all

individual congenital lesions or demographics may jeopardise confidentiality however, valvular or ‘other CHD lesions’ were implicated in the majority (122, 61.6%) of these deaths.

Valvular CHD was implicated in 52 deaths identified from death records. All but 2 of these individuals were found to have lesions of the aortic valve. The majority (38, 73.1%) of deaths were attributed to the valve lesion and all but 7 (86.5%) were by CV causes. The mean age at death amongst these individuals was 54.8 (SD 16.5) years. These 52 deaths represent 8.4% of the total deaths amongst individuals with valvular CHD when inclusive of those with an SMR01 record.

A total of 70 individual were coded with ‘other’ CHD on death certification alone. The majority of these codes pertain to ill-defined and unspecified congenital anomalies of the heart, however 22 (31.4%) had congenital anomalies of the coronary arteries. Mean age at death for the whole cohort was 50.0 (SD 18.7) years and 52.3 (SD 19.5) years amongst those with coronary anomalies. The 70 deaths presented here corresponds to 13.2% of the total number of deaths included for ‘other’ CHD lesions when inclusive of those with an SMR01 record.

5.4 Discussion

5.4.1 Baseline characteristics and follow up

A total patient cohort of 16,210 followed for 168,177 years represents a substantial study population. Although this does not represent the entire ACHD cohort in Scotland, only those who generated an SMR01 record via an in patient stay, no larger Scottish cohort has been reported. When compared with other non-selected adult studies world-wide, only one article reports a larger patient cohort (51) and total follow up. Although these studies were not designed to estimate the prevalence of ACHD in Scotland, 16,210 individuals equates to 0.36% or 3.59 per 1000 of the adult Scottish population based on 2018 figures. This is similar to previous estimates of prevalence including that by Marelli *et al* (9) of 4.09 per 1000 in the adult Quebec population. This would suggest that a substantial, albeit not a complete representation of the ACHD population of Scotland was achieved. The future ability to cross reference this with local databases would prove useful to capture the magnitude of missed cases or any bias this may impose.

A marginal but statistically significant female preponderance was observed (50.9%, p=0.03) and again this is common in the reported literature (41,44,128) with no identified comparable published article presenting a population with significantly more men. Similar to the articles discussed in the preceding literature review, sex distribution was highly variable depending upon lesion. The pattern of sex distribution in our study cohort matches that reported in the previously analysed literature other than for Fontan patients which was equally represented between the sexes in the literature but predominantly male in our cohort (59.9%, p=0.01).

As with CHD diagnoses, co-morbidity was established by ICD coding as recorded upon discharge from a hospital episode. As such it will represent an underestimate of the true prevalence of the condition within the cohort. If the individual has not had an admission where the co-morbidity in question was the primary diagnosis, should it not be deemed significant, or if was simply missed on admission, then it is conceivable that it would not be coded. For instance a previous estimate of the prevalence of diabetes in the Scottish population

quoted 5.4% (129) but was only 3.7% in our cohort. In contrast our study prevalence of AF at 9.9% is significantly greater than the 3-6% identified from acute hospital admissions in the UK population previously (130,131), with the upper value of 6% established from a regional Scottish population. Despite this, for the reasons mentioned above, the true prevalence of AF in the ACHD population is likely to be even higher as it is inevitable that some instances were missed by clinical coding. It has previously been established that AF and atrial flutter become increasingly prevalent in the ACHD population as age increases, as age at time of repair increases and as complexity of lesion increases (132). Unfortunately, National Records of Scotland do not collate data regarding comorbidity prevalence and so estimates as above can only be extrapolated from the journal literature. As such, comparison of the effect of co-morbidity on mortality with that of the general population is not possible. Future studies would benefit from a population matched cohort to allow direct comparison. Comorbidities were more common amongst the study population as age increases. Coupled with finding of improved temporal survival in this cohort (equating to an aging patient population) this would suggest an increasingly complex and multimorbid patient cohort.

Socioeconomic classification as determined by SIMD is not equally distributed throughout the study cohort. The highest quintile of deprivation is disproportionately represented, being observed for 27.1% of the ACHD population, significantly greater than the 20.0% population determined quintile, $p<0.01$. No data regarding socioeconomic status has been identified in the literature for adults with CHD but one article has reported similar findings in children (133), however outcomes were not reported.

5.4.2 Survival and mortality

Over the total study period 25.2% of the entire cohort died. This is higher than in the previously reported literature. It may be that our study population is comprised of more severe disease phenotypes as inclusion is dependent on a hospital admission. In many other cohorts, mild disease which is simply followed in clinic, but never requires admission will also be included in the denominator. Another reason would be that the median baseline age in our study cohort of 34

years is higher than the comparable literature as reported in the previous Chapter where the average age on all accounts was below 30 years.

Age at death increased throughout the study period. Although the increase in age at death between the earliest and most recent study period, and from the first to the second half of the study period was highly statistically significant for the entire study cohort, this was not the case for each individual lesion. Once divided into 13 diagnostic groups, too few deaths were observed in each of the seven time cohorts to allow accurate comparison. For this reason, lesion specific age at death was limited to the first and second half of the data period. Necessarily this limited the magnitude of change between the two time periods. Increased mean and median age at death was nevertheless observed for the two largest patient cohorts: ASD and VSD. Increases in point estimates amongst the smaller lesion cohorts did not achieve statistical significance.

Death occurred more frequently throughout the data period when co-morbidity was present. Once adjusted for demographics, lesion, age and socioeconomic deprivation the conferred risk persisted for diabetes, AF, cancer and myocardial infarction. The risk associated with AF is worthy of particular mention as the observed prevalence within our cohort was certainly higher than the general population. This is no surprise as the CHD population have unique exposure to conditions which predispose to the development of AF. Atrial enlargement in conditions such as ASD, or as a haemodynamic consequence of surgical interventions such as Fontan palliation provide a substrate for the development of AF. It is equally known that scar and suture in the atria such as occurs after atrial switch procedures and anomalous pulmonary vein repairs, increase the risk of AF and other atrial tachyarrhythmias (132,134). The increased mortality observed in patients with AF could be explained in two ways:

- AF increases in prevalence as the disease progresses and is a marker of disease. This is particularly true of Fontan and atrial switch patients where AF is frequently a marker of the broader problem of failing haemodynamics
- AF directly increases mortality

Benjamin et al. have previously described a 1.5 to 1.9 fold increase in mortality associated with AF even after adjusting for underlying heart disease, inferring

causality of AF itself (135). This did not however include adjustment for congenital heart disease, and it seems likely that AF as a marker of disease severity is at least partially responsible for the increased mortality that we observed. This may be further supported by the lack of increased risk we witnessed for stroke, classically considered to be a key mechanism of excess mortality associated with AF.

Neither hypertension nor ischaemic heart disease in the absence of acute myocardial infarction increased the risk of mortality following adjustment. This may be explained as the recognition of these common and well-established risk factors allows treatment and therefore risk reduction compared to the comparator group where unchecked risk may be a feature.

Age standardised mortality for those with ACHD was dramatically higher than the general population. Deaths were observed at a rate of more than five times what would be expected from the population mean throughout the data period. Although this clearly represents excess mortality amongst those with ACHD, the true SMR may be slightly less. As the SMRs are based on mortality observed during a single year of follow up from the point that an individual is first recognised to the data set, there may be a bias towards an excess risk of mortality. This results from inclusion to the data set most commonly occurring as a result of a hospital admission, an inherently 'risky' point in time. What is clear however is that the age standardised mortality ratio decreased in the second half of the data period. This is reflected by a statistically significant reduction in robustly adjusted mortality hazard for those presenting in more contemporaneous time periods. This is a finding echoed in prior studies (51) however the magnitude of improvement we demonstrated is even greater, likely due at least in part to our longer follow up period and therefore greater time differential from the start to the end of follow up.

Socioeconomic deprivation was not only disproportionately high amongst our study population but was associated with a significantly increased mortality risk. This will be explored in detail in subsequent Chapters.

5.4.3 Cause of death

Ischaemic heart disease was the most common cause of death in the study population and was significantly more common than for the general population. Acute coronary syndrome has previously been demonstrated to be increased in the CHD population (136,137). There has been some speculation as to causality in the previously published literature, however mechanisms remain speculative. Previous epidemiological studies have suggested higher rates of hypertensions and diabetes amongst ACHD patients as a potential contributor (138). Other feasible physiological mechanisms may include cyanosis increasing the vulnerability of the myocardium despite compensatory mechanisms, and higher rates of atrial arrhythmia and the presence of shunts increasing the possibility of coronary embolic events.

The best-established association between CHD and IHD stems from the increased risk with aortic coarctation (139), although more contemporary evidence has questioned the direct causal relationship. Roifman *et al*(140) state that the increased risk is nullified when traditional risk factors, particularly hypertension, are adjusted for. Irrespective of the mode of association there is agreement in the literature that this population suffer disproportionately with IHD. Indeed, this was one of the lesions where IHD death was most highly represented in our cohort. What is less easily explained is the exceptionally high frequency of IHD deaths among the VSD cohort. An increased rate of IHD in the VSD population has previously been noted (136) but a relative abundance compared with aortic lesions is contrary to published literature (140). It must be considered that an error of diagnostic coding at source may be responsible for a proportion of this excess. Ventricular septal defects are a well-recognised and frequently fatal consequence of myocardial infarction. As such it is feasible that a proportion of deaths due to ischaemic heart disease where non-congenital VSD was a feature were incorrectly coded as Q21.0 (congenital ventricular septal defect) rather than the correct code, I23.2 (ventricular septal defect complicating a myocardial infarction). It is also noted that the median age of inclusion to the data set for those with VSD who died due to IHD was 71.5 (IQR 64-76.5) and for those who died of non IHD causes the age at first inclusion to the data was 57 (IQR 35-71.5) $p<0.01$.This would suggest two heterogenous groups. Also, during the first half of the data period, 55.0% of deaths in those with VSD were due to IHD, however

during the second half of the data period only 30.8% were due to IHD. It could be suggested that this represents a general decline in population deaths associated with ischaemic VSDs as a result of more widespread availability of primary percutaneous coronary intervention in more recent years (141), further suggesting a coding discrepancy as at least part of the reason for the unexpectedly hight rate of IHD deaths in those with VSD.

Although IHD is the overall predominant cause of death, for lesions of greater complexity (Fontan, systemic RV, TOF, Ebstein's anomaly and 'complex'), death directly attributed to congenital heart disease was clearly predominant (Figure 5-8). The specific mode of death amongst these patients cannot be further determined due to the epidemiological and anonymised nature of the study. Previous non-population studies which have allowed for case note review to further determine cause of death in circumstances such as this have determined heart failure and sudden cardiac death to predominate when death as a result of congenital heart disease is documented (50,75).

Cause of death among less complex lesions such as ASD and PDA more closely mirror those of the general population (Figure 5-8) where, for instance, malignancy represents a larger proportion. Age at death in these lesions is also higher and it is logical that cause of death is less influenced by the underlying congenital defect.

Interestingly, the congenital lesion which expressed the highest proportion of deaths related to infection was the valvular cohort at 9.0%, which is also more than in the general population (5.6%). Valvular congenital heart disease has been shown previously to confer a particularly high risk of infective endocarditis (142,143) which likely outstrips other forms of CHD; even when prosthetic material is used for surgical repair (142). It is therefore expected that a proportion of the excess of infectious deaths in this cohort will be related to infective endocarditis.

Although CV death predominates over the course of the entire study period this is significantly reduced in more contemporary analyses. The rate of reduction in cardiovascular deaths in the study population outstrips that of the general population. Although trends in cardiovascular deaths have not previously been

reported in the published literature, time point estimates in the proportion of cardiovascular deaths appears similar to previous studies (Section 2.3.3). For instance Diller *et al* (50) reported 63.5% of deaths by CV causes at a study mid-point of 2002 in an English cohort, this is compared with 59.4% during the corresponding time cohort in my analyses.

CHD was identified from death records in 198 individuals (4.5% of all deaths). Although it is likely that some of these individuals were known to have CHD, having simply not generated an in-patient episode during the data period, sudden death in CHD remains of significant importance and has previously been implicated in as many as 20% of cases (144). The frequency by which CHD presents post-mortem in adulthood is not established. In one study of 182 post-mortem examinations resulting from sudden death at 35 years or less, 12.1% had previously unknown CHD, more than half of which were coronary anomalies and the majority of the remainder were anomalies of the aortic valve (145). This appears to be in line with our findings. Although only 4% of the total number of CHD deaths in this document occurred without an SMR01 record, a disproportionate number were due to valvular CHD (representing 8.4% of the total valvular CHD deaths), or 'other' CHD lesions (representing 13.2% of the total mortality) amongst which coronary anomalies were prominent.

Median age at death was drastically lower amongst this patient cohort when compared to those with SMR01 records (median 52.5 and 74 years respectively). This was consistent across all CHD subtypes including when valvular and coronary anomalies were implicated. This would suggest that sudden, premature death amongst previously unidentified CHD lesions, particularly of valvular and coronary aetiologies are noteworthy and may merit further study.

The proportion of cardiovascular deaths decreased throughout the data period. Although the proportion of cardiovascular deaths also decrease in the general population over the same time period, the rate of change observed for the study population is greater. This important observation is additive to the finding of improved survival which we have demonstrated for the ACHD patients of Scotland. Not only are patients living longer but the progressive convergence of cause of death with that of the general population would suggest a more generalised homogenisation. This is likely to reflect more holistic improvements

in care, monitoring, and support than with survival benefit alone, which has thus far been primarily attributed to surgical advances.

6 Survival and causes of death according to sex

6.1 Introduction

It has long been established that sex plays an important role in non-congenital cardiovascular disease. Over recent decades temporal shifts in the sex distribution of deaths attributable to cardiovascular disease have been reported (most extensively for the US population). In general, women have fared poorly compared to men who have seen a gradual decline in deaths due to cardiovascular disease since the early 1980s. Similar improvements were not seen for women until around the year 2000. Since this time however, improvements for women appear to be dramatic and have fallen into line with those seen for men (Figure 6-1) (61).

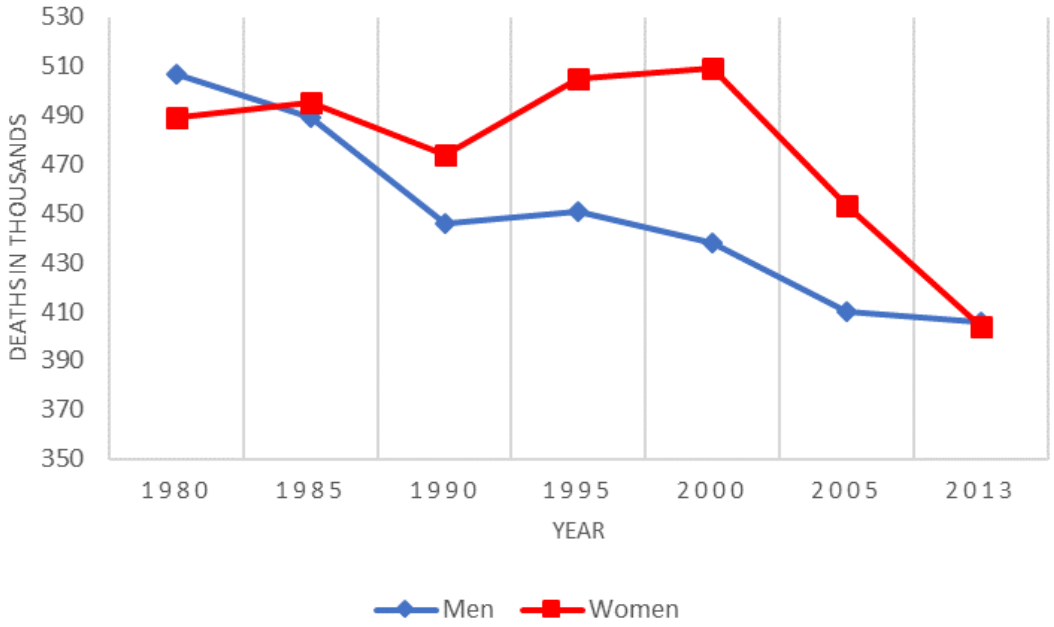


Figure 6-1: Cardiovascular deaths in the US population adapted from data reported by the American Heart Association (61)**.**

Despite the well-established differences in outcomes for men and women with non-congenital cardiovascular disease and the obviously important role that sex plays in the prevalence of underlying congenital defects, as touched on in the preceding literature review and results Chapter; the paucity of published literature dedicated to examining sex and mortality in congenital heart disease is striking.

Historically, the sex differences in outcomes for men and women with congenital heart disease have been documented according to clinical experience and expert consensus. A published lecture by Prof Jane Somerville was the first to concentrate specifically on the gender differences in outcomes for ACHD patients. Although sparse in the available data at the time, a higher incidence and mortality associated with Eisenmenger's syndrome and a reduced mortality associated with aortic valve disorders among women was proposed (146).

In more recent years three articles from prominent research groups have examined sex and outcomes among adults with congenital heart disease, however mortality findings have been contradictory; Oliver et al suggests excess mortality among women in their large, single centre study (147); Engelfriet et al found that men experienced greater mortality in their examination of the multinational European Heart Survey database (62); and Verheugt et al demonstrated no statistically significant difference in mortality for men and women via the Dutch national CONCOR registry (63). It seems reasonable to state with some confidence that the relationship between sex and mortality in adults with congenital heart disease has not yet been well-established.

6.2 Results

6.2.1 Baseline demographics according to sex

Of the 16,210 individuals identified between 1986 and 2015, more were female (50.9%) than male (49.2%), p=0.03. Throughout the entire data period the mean adult population of Scotland was 1,982,089 men and 2,186,207 women. Therefore, adjusted for the general population distribution males with ACHD represent 4.02 per 1000 population, compared with 3.77 per 1000 amongst women. The distribution of baseline characteristics according to sex are summarised in Table 6-1. Women were older at first inclusion into the data set (40.6, SD 24.4 compared with 36.7, SD 22.2, p<0.01).

Regarding comorbidity, more men than women were diagnosed with diabetes (4.1% and 3.4% respectively), p=0.01. Ischaemic heart disease without myocardial infarction was also significantly more common in men than women (11.4% and 8.7% respectively), p<0.01. Cancer (male 2.6%, female 2.4%, p=0.55), AF (male 9.8%, female 10.0%, p=0.62), CVD (male 5.6%, female 5.9%, p=0.36) AMI (male 5.8%, female 5.3%, p=0.16) and hypertension (male 5.7%, female 6.0%, p=0.35) were equally represented in the male and female cohorts.

A significantly higher proportion of women than men reside in areas of high-level socioeconomic deprivation. A breakdown of sex distribution according to SIMD quintile is provided in Table 6-1 and is graphically illustrated by Figure 6-2. Figure 6-3 shows the absolute percentage of each sex residing within postcode sectors of each SIMD quintile. In total 43.4% of men reside in the top half (more affluent) of SIMD sectors compared with only 40.2% of women (p<0.01).

The distribution of underlying congenital lesions according to sex has been touched on in the previous Chapter. Briefly, a statistically significant male predisposition is observed for; aortic lesions (52.3%, p<0.01), TOF (58.0%, p<0.01), systemic RV (66.9%, p<0.01), valvular lesions (58.3%, p<0.01) and Fontan circulations (59.9%, p<0.01). A significant female predisposition exists for; ASD (57.5%, p<0.01), PDA (62.2%, p<0.01) and AVSD (55.2%, p=0.03). Ebstein's anomaly (female 60%, male 40%, p=0.06), TGA arterial switch (female 42.9%, male 57.1%, p=0.34), VSD (female 50.4%, male 49.6% p=0.65) and

complex but not otherwise classified (female 49.7%, male 50.4%, p=0.80) lesions are not significantly different between sex.

Table 6-1: Baseline characteristics and demographics according to sex Percentages for all patients are given as column percentages. Male and female percentages refer to row percentages i.e. male:female proportion. P values refers to the male:female proportion.

	All (%)	Male (%)	Female (%)	p value
All	16210	7968 (49.2)	8242 (50.9)	0.03
Age at entry, mean (SD)	39.1 (23.5)	36.7 (22.2)	40.6 (24.4)	<0.01
SIMD quintile				
1-most	4355 (27.1)	2031 (46.6)	2324 (53.4)	<0.01
2	3441 (21.5)	1648 (47.9)	1793 (52.1)	0.10
3	2997 (18.7)	1506 (50.3)	1491 (49.8)	0.18
4	2736 (17.1)	1410 (51.5)	1326 (48.5)	0.01
5-least	2516 (15.7)	1281 (50.9)	1235 (49.1)	0.06
Comorbidity				
Diabetes	606 (3.7)	328 (54.1)	278 (45.9)	0.01
Cancer	401 (2.5)	203 (50.6)	198 (49.4)	0.55
AF	1608 (9.9)	781 (48.6)	827 (51.4)	0.62
CVD	931 (5.7)	444 (47.7)	487 (52.3)	0.36
HTN	946 (5.8)	451 (47.7)	495 (52.3)	0.35
AMI	896 (5.5)	461 (51.5)	435 (48.6)	0.16
Other IHD	1619 (10.0)	906 (56.0)	713 (44.0)	<0.01
Lesion				
ASD	4172 (25.7)	1774 (42.5)	2398 (57.5)	<0.01
PDA	983 (6.1)	372 (37.8)	611 (62.2)	<0.01
VSD	2244 (13.8)	1113 (49.6)	1131 (50.4)	0.65
Aortic	2143 (13.2)	1120 (52.3)	1023 (47.7)	<0.01
Ebstein's	105 (0.7)	42 (40.0)	63 (60.0)	0.06
AVSD	600 (3.7)	269 (44.8)	331 (55.2)	0.03
TOF	564 (3.5)	327 (58.0)	237 (42.0)	<0.01
TGA switch	35 (0.2)	20 (57.1)	15 (42.9)	0.34
Systemic RV	133 (0.8)	89 (66.9)	44 (33.1)	<0.01
Complex	1285 (7.9)	647 (50.4)	638 (49.7)	0.80
Fontan	167 (1.0)	100 (59.9)	67 (40.1)	<0.01
Valvular	2163 (13.3)	1262 (58.3)	901 (41.7)	<0.01
Other	1616 (10.0)	833 (51.6)	783 (48.5)	0.04

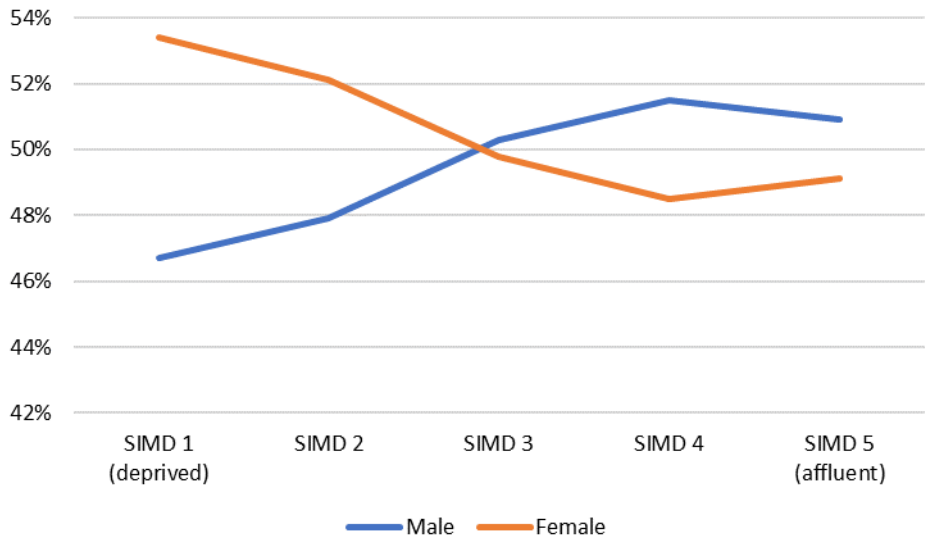


Figure 6-2: Proportional distribution of male and female sex within each quintile of socioeconomic deprivation Percentages are given as proportional distribution of males and females within each quintile group i.e. total to 100% within each SIMD quintile.

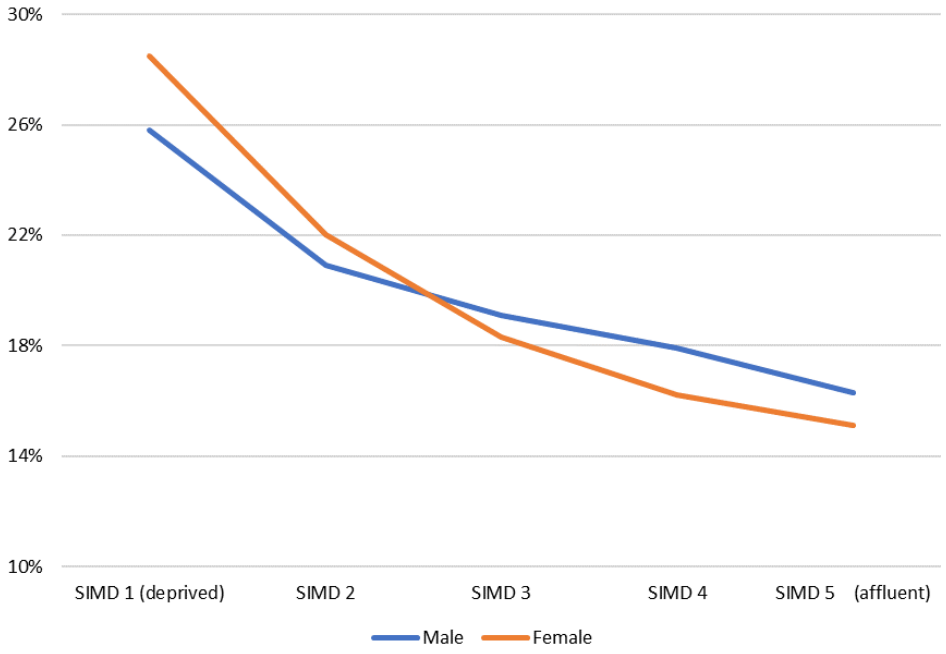


Figure 6-3: Proportional distribution of SIMD quintiles for male and female sex Percentages are given as absolute proportion of each sex in the quintile group i.e. total to 100% within each sex category

6.2.2 Follow up, mortality and age at death according to sex

6.2.2.1 Observed mortality and age at death

A higher proportion of women than men died during follow up (27.2% and 24.2%, p<0.01). Table 6-2 compares those individuals who survived and those who died during the data period and compares males and females.

Women who died during the data period were significantly older at inclusion into the data set than men who died (65.8, SD 19.5 and 57.7, SD 20.9 years, p<0.01).

For each recorded comorbidity a higher proportion of women died than men. This achieved statistical significance for all except cancer and cerebrovascular disease. A particular excess of female death was noted when AMI was diagnosed (73.6% compared with 58.1% for men, p<0.01), ischaemic heart disease without acute myocardial infarction was present (53.9% compared with 43.3% for men, p<0.01), when AF was diagnosed (60.7% compared with 48.4%, p<0.01), or if hypertension was coexistent with ACHD (47.5% compared with 30.8%, p<0.01).

The relative distribution of socioeconomic deprivation between men and women is described above. A higher proportion of women than men died in each SIMD quintile and the magnitude of difference was relatively consistent across the quintile groups, achieving statistical significance in only the second most deprive (SIMD 2) quintile (30.1% females died compared with 26.2% of men, p=0.01).

The distribution of deaths by sex according to underlying lesion is also summarised in Table 6-2. A greater proportion of women than men with aortic lesions died during follow up (62.0% and 43.9%, p<0.01). This was also true for valvular lesions (33.7% and 20.7%, p<0.01) and the combined cohort of ‘other’ CHD (31.6% and 25.5%, p=0.01).

Table 6-2: Comparison of baseline characteristics according to sex for those who survived and those who died during the data period. p values refer to comparison of percentages of deaths between men and women

	Male		Female		
	Alive (%)	Dead (%)	Alive (%)	Dead (%)	p value
All	6044 (75.9)	1924 (24.2)	6004 (72.3)	2238 (27.2)	<0.01
Age at entry, mean (SD)	30.4 (18.4)	57.7 (20.9)	31.2 (18.7)	65.8 (19.5)	<0.01
SIMD quintile					
1-most	1520 (74.8)	511 (25.2)	1695 (72.9)	629 (27.1)	0.15
2	1220 (74.0)	428 (26.2)	1254 (69.9)	539 (30.1)	0.01
3	1137 (75.5)	369 (24.5)	1085 (72.8)	406 (27.2)	0.09
4	1084 (76.9)	326 (23.1)	982 (74.1)	344 (25.9)	0.09
5-least	1013 (79.1)	268 (20.9)	937 (75.9)	298 (24.1)	0.05
Comorbidity					
Diabetes	151 (46.0)	177 (54.0)	99 (35.6)	179 (64.4)	0.01
Cancer	58 (28.6)	145 (71.4)	50 (25.3)	148 (74.8)	0.45
AF	403 (51.6)	378 (48.4)	325 (39.3)	502 (60.7)	<0.01
CVD	298 (67.1)	146 (32.9)	315 (64.7)	172 (35.3)	0.61
HTN	312 (69.2)	139 (30.8)	260 (52.5)	235 (47.5)	<0.01
AMI	193 (41.9)	268 (58.1)	115 (26.4)	320 (73.6)	<0.01
Other IHD	514 (56.7)	392 (43.3)	329 (46.1)	384 (53.9)	<0.01
Lesion					
ASD	1436 (81.0)	338 (19.1)	1929 (80.4)	469 (19.6)	0.68
PDA	345 (92.7)	27 (7.3)	582 (95.3)	29 (4.8)	0.10
VSD	784 (70.4)	329 (29.6)	800 (70.7)	331 (29.3)	0.88
Aortic	628 (56.1)	492 (43.9)	389 (38.0)	634 (62.0)	<0.01
Ebstein's	26 (61.9)	16 (38.1)	45 (71.4)	18 (28.6)	0.31
AVSD	211 (78.4)	58 (21.6)	280 (84.6)	51 (15.4)	0.05
TOF	287 (87.8)	40 (12.2)	208 (87.8)	29 (12.2)	1.00
TGA switch	20 (100)	-	15 (100)	-	-
Systemic RV	77 (86.5)	12 (13.5)	38 (86.4)	6 (13.6)	0.98
Complex	518 (80.1)	129 (19.9)	524 (82.1)	114 (17.9)	0.34
Fontan	90 (90.0)	10 (10.0)	61 (91.0)	6 (9.0)	0.82
Valvular	1001 (79.3)	261 (20.7)	597 (66.3)	304 (33.7)	<0.01
Other	621 (74.6)	212 (25.5)	536 (68.5)	247 (31.6)	0.01

Table 6-3 summarizes follow up, crude mortality rates and age at death according to sex and as subdivided by lesion complexity and socioeconomic deprivation.

Overall cumulative follow up was slightly higher for women (85,850 years) than men (82,327 years). This is accounted for by those with simple lesions. For lesions of moderate and great complexity males accumulated more follow up. Crude mortality rate was higher for women (26.1 deaths per 1000 person years) than men (23.4 deaths per 1000 person years). When compared by lesion complexity; simple and complex lesions demonstrate similar mortality rates according to sex, however lesions of moderate complexity have a higher mortality rate for women (37.4 deaths per 1000 person years) than men (25.2 deaths per 1000 person years). Mortality rates for women were slightly higher than for men across all SIMD quintiles.

Mean age at death was higher for women than men (71.5, SD 18.0 and 64.2, SD 19.7 years, $p<0.01$). A statistically significant increased age at death for females was maintained across all lesion complexities and socioeconomic groups (Table 6-3).

Figure 6-4 and Figure 6-5 illustrate the mean age at death for men and women during the first and second half of the data period. The point estimate of mean age at death increased for both sexes and all degrees of lesion complexity from the first to the second half of the data period. For all men, the mean age at death increased from 61.8 (SD 20.2) to 65.2 (SD 19.3) years, $p<0.01$. For men with simple lesions, age increased from 60.7 (SD 17.6) to 65.7 (SD 17.4) years, $p<0.01$. For men with moderately complex lesions there was a non-statistically significant increase from 62.6 (SD 21.4) to 66.5 (SD 19.9), 0.08. The increase in age at death for men with lesions of great complexity was however highly statistically significant (32.8, SD 21.8 years to 47.1, SD 23.5 years, $p=0.01$).

For women, the mean age at death increased from 71.0 (SD 17.3) to 71.8 (SD 18.3) during the first and second half of the data period but this was not statistically significant, $p=0.32$. For women with simple lesions mean age at death increased from 67.3 (SD 14.9) to 70.6 (SD 17.6) years, $p=0.01$. No significant increase was seen for women with moderately complex lesions (74.6,

SD 18.1 to 75.8, SD 17.7 years, p=0.51) or lesions of great complexity (46.6, SD 22.0 to 54.4, SD 20.3, p=0.11) despite demonstrating the greatest absolute increase in point estimate, this is bearing in mind the relatively lower number of women with complex lesions demonstrated in the data set.

Table 6-3: Follow up and age at death according to sex
P value corresponds to the comparison of age at death

	Male				Female				
	N	Follow up (years)	Mortality rate per 1000 years (95%CI)	Mean age at death (SD)	*N*	Follow up (years)	Mortality rate per 1000 years (95% CI)	Mean age at death (SD)	p value
All	7968 (49.2)	82327	23.4 (22.3-24.4)	64.2 (19.7)	8242 (50.9)	85850	26.1 (25.0-27.2)	71.5 (18.0)	<0.01
Lesion complexity									
Simple	3841 (47.3)	39046	18.8 (17.5-20.2)	64.3 (17.6)	4280 (52.7)	46301	17.2 (16.0-18.4)	69.5 (16.9)	<0.01
Moderate	1799 (51.0)	19061	25.2 (23.1-27.6)	65.6 (20.3)	1730 (49.0)	17204	37.4 (34.6-40.4)	75.6 (17.8)	<0.01
Complex	695 (52.5)	7734	14.6 (12.2-17.6)	43.9 (23.8)	629 (47.5)	7146	15.2 (12.7-18.4)	52.5 (20.9)	<0.01
SIMD quintile									
1-most	2031 (46.6)	21549	23.7 (21.7-25.9)	61.5 (19.0)	2324 (53.4)	24515	25.7 (23.7-27.7)	68.8 (18.0)	<0.01
2	1648 (47.9)	16680	25.7 (23.3-28.2)	63.5 (20.2)	1793 (52.1)	18522	29.1 (26.7-31.7)	71.6 (18.2)	<0.01
3	1506 (50.3)	15356	24.0 (21.7-26.6)	64.7 (20.0)	1491 (49.8)	15235	26.6 (24.2-29.4)	71.9 (17.6)	<0.01
4	1410 (51.5)	14089	23.1 (20.8-25.8)	67.2 (19.1)	1326 (48.5)	13952	24.7 (22.2-27.4)	74.1 (16.9)	<0.01
5-least	1281 (50.9)	13512	19.8 (17.6-22.4)	66.6 (19.4)	1235 (49.1)	12722	23.4 (20.9-26.2)	73.9 (18.0)	<0.01

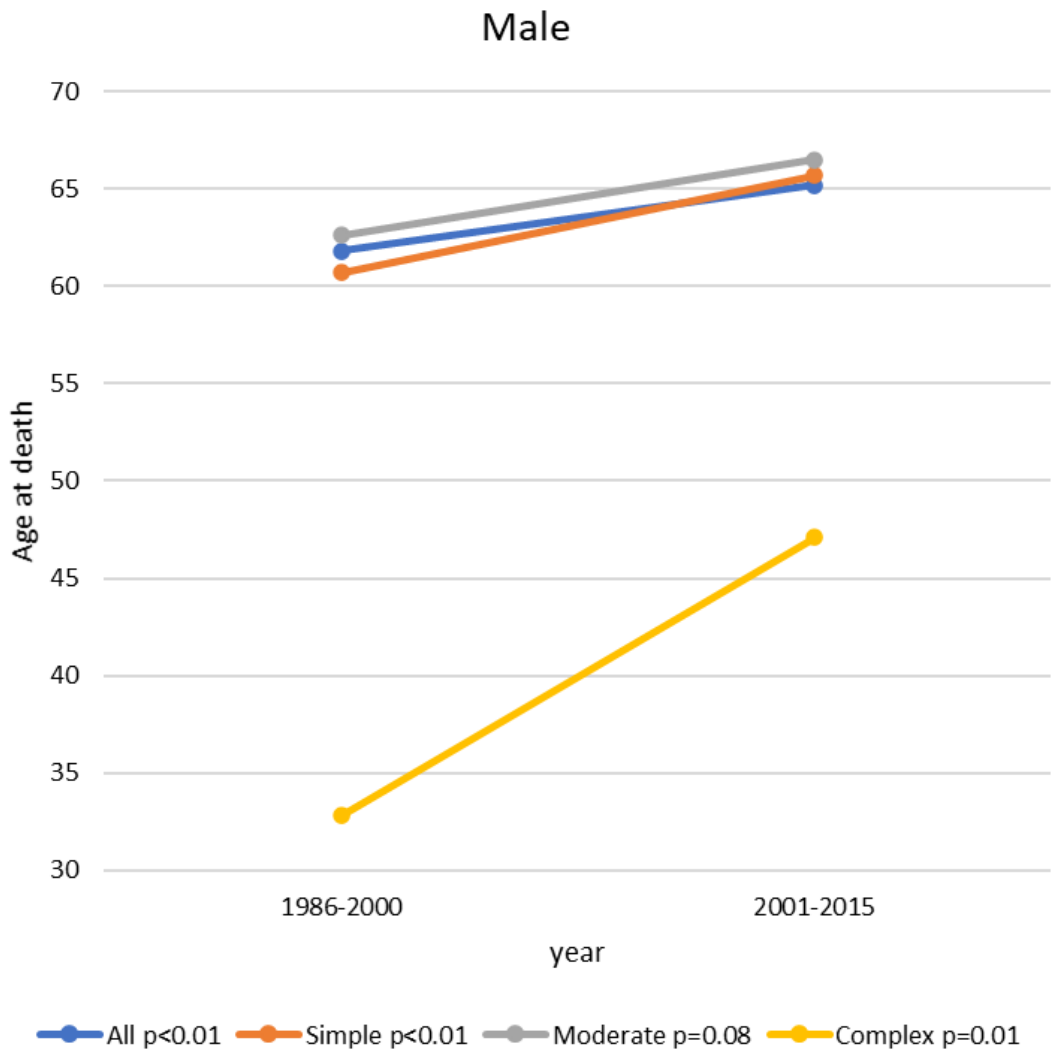


Figure 6-4: Mean age at death during the first and second half of the data period for all men and according to lesion complexity. Significance level for each change provided

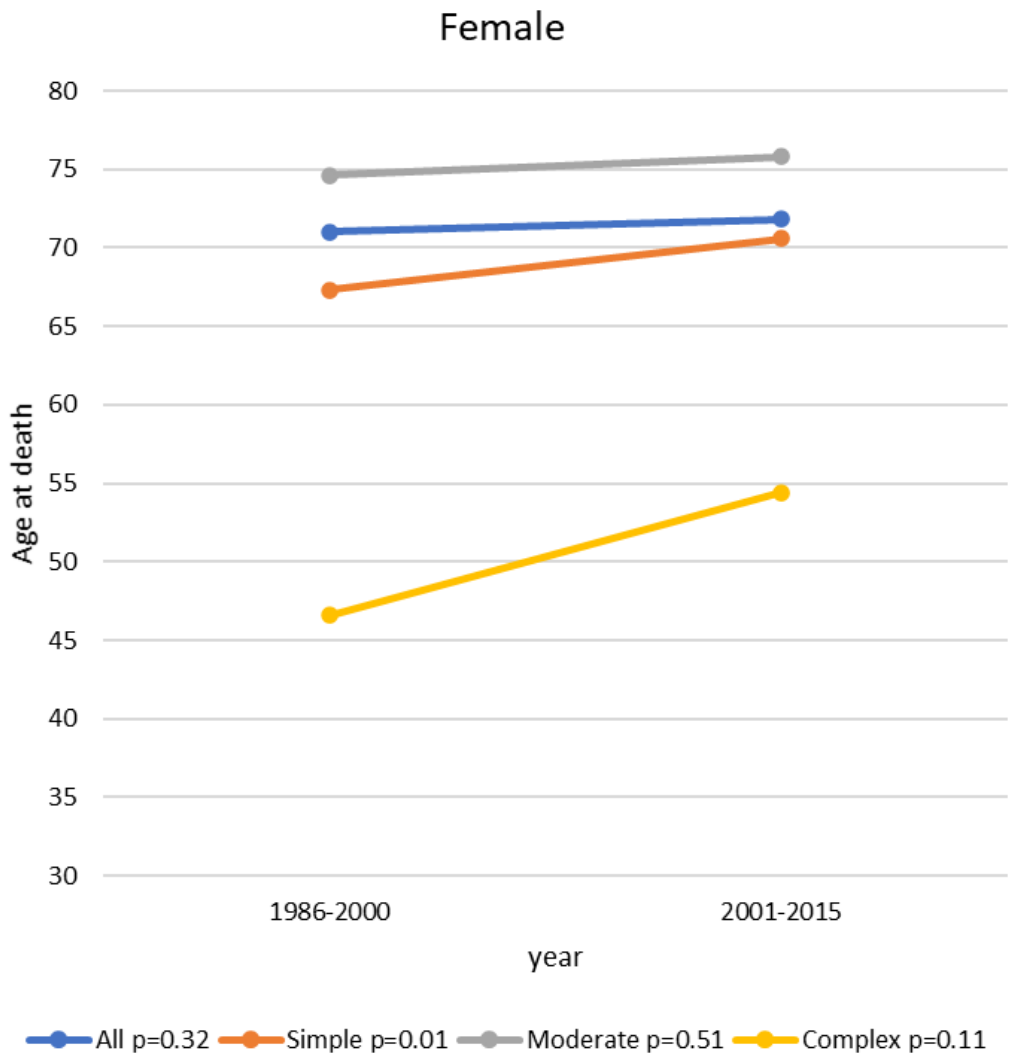


Figure 6-5: Mean age at death during the first and second half of the data period for all women and according to lesion complexity. Significance level for each change provided.

6.2.2.2 Survival according to sex

The Kaplan Meier survival estimates for men and women during the data period are illustrated by Figure 6-6. Unadjusted binary risk of death was significantly lower for men than women when all lesions are included (OR 0.85, 95% CI 0.80 - 0.92 p<0.01). For simple and complex lesions there is no significant difference in risk for all-cause mortality (OR 1.04, 95% CI 0.92 – 1.16, p=0.54 and 0.97, 95% CI 0.72 – 1.30, p=0.83 respectively). For moderately complex lesions there was a highly statistically significant lower risk of death for men compared to women (OR 0.62, 95% CI 0.53-0.71, p<0.01).

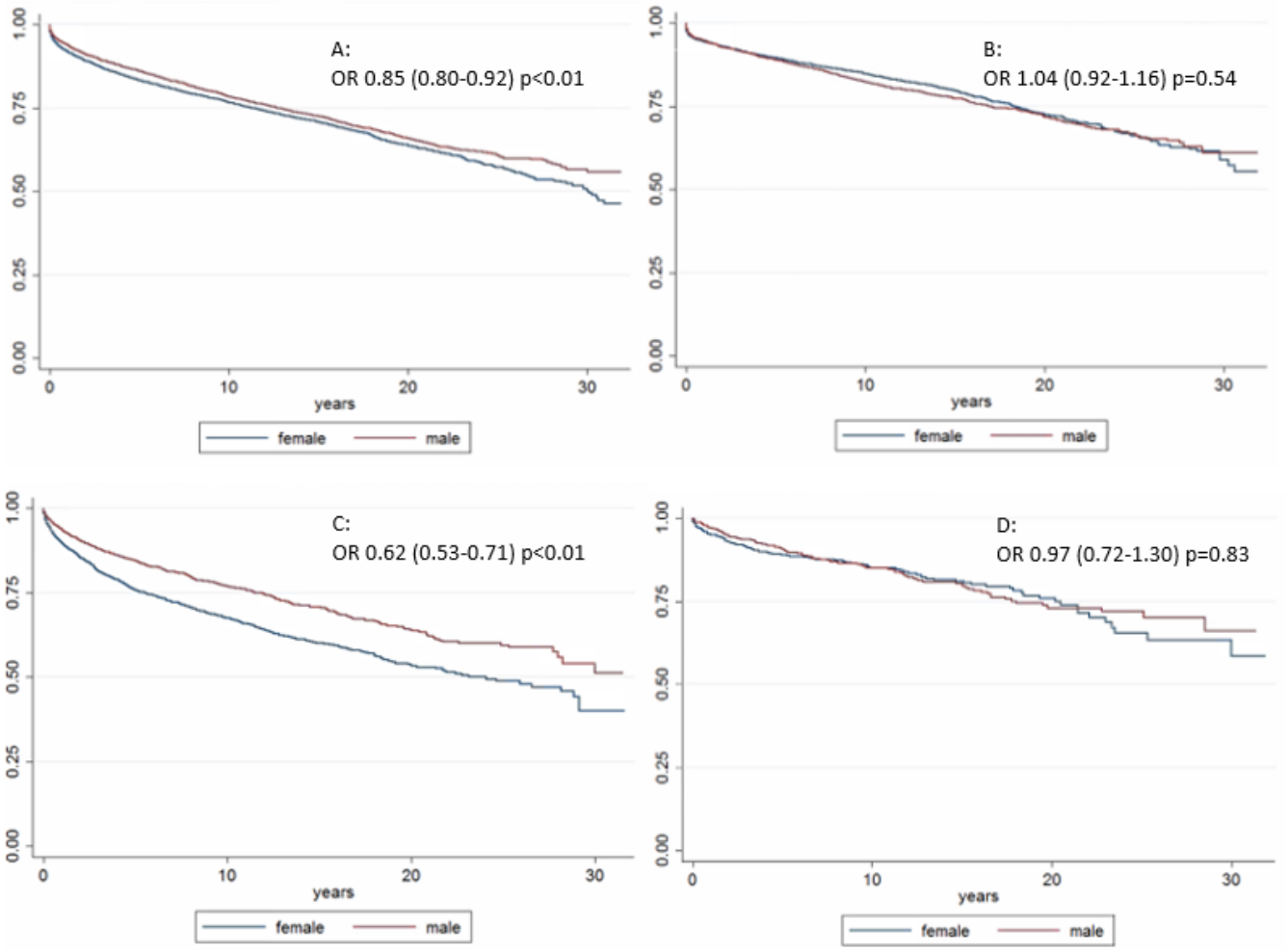


Figure 6-6: Unadjusted Kaplan Meier survival estimates for men and women during the data period
A: All CHD. B: Simple CHD. C: Moderately complex CHD. D: Complex CHD

Figure 6-7 compares the adjusted hazard for all-cause, cardiovascular and non-cardiovascular mortality as conferred by sex. Estimates are adjusted for; age, underlying congenital lesion, comorbidity (diabetes, cancer, atrial fibrillation, acute myocardial infarction, cerebrovascular disease and ischaemic heart disease without acute myocardial infarction and hypertension), year of presentation and socioeconomic grouping (as summarized in Table 6-4).

Male sex confers an increased risk of all-cause mortality (HR 1.12, 95% CI 1.05 – 1.19, p<0.01) and non-CV mortality (HR 1.19, 95% CI 1.08 – 1.30, p<0.01). No significant difference in risk of CV mortality was conferred by sex (male; HR 1.07, 95% CI 0.98 – 1.16, p=0.07).

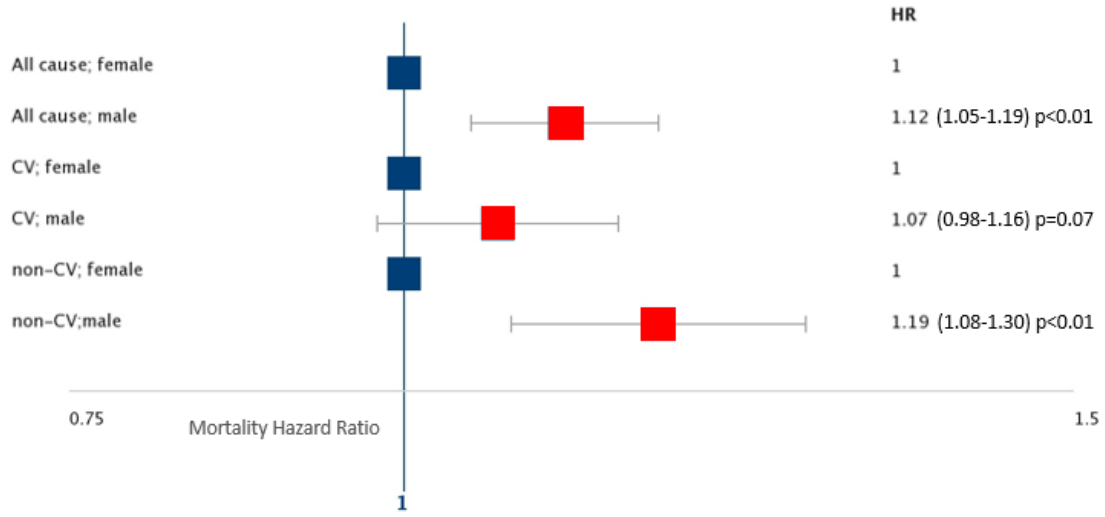


Figure 6-7: Adjusted hazard for all-cause, cardiovascular and non-cardiovascular mortality according to sex

Table 6-4 summarizes the contribution of risk conferred by baseline characteristics, underlying CHD lesion, year of presentation and socioeconomic grouping for all patients, and for men and women. A similar pattern of risk is seen for age and comorbidity for both men and women. Diabetes, cancer, atrial fibrillation and AMI increase the risk of all-cause mortality in both men and women and to a similar degree. Point estimates of risk are higher for men in relation to diabetes, cancer and AF but male and female confidence intervals overlap on all accounts. Point estimate for risk related to AMI is higher for women but again confidence intervals overlap. No significant increase in risk for

all-cause mortality was seen for CVD, HTN or ischaemic heart disease without AMI for men or women.

The risk associated with underlying CHD lesion again follows a similar pattern for men and women. The risk of Fontan circulation appears to be higher for women (HR 3.11, 95% CI 1.34 – 7.01, p=0.01) than men (HR 1.76, 95% CI 0.94 – 3.33, p=0.08) but confidence intervals are wide and overlapping.

Male and female mortality hazard according to socioeconomic group is illustrated in Figure 6-8. A significant reduction in risk is noted for men and women in higher socioeconomic quintiles. The magnitude of risk reduction appears greater for men than women with men in SIMD 5 having a 38% lower instantaneous risk of all-cause mortality and women a 29% lower risk relative to those in SIMD 1 although this difference does not achieve statistical significance.

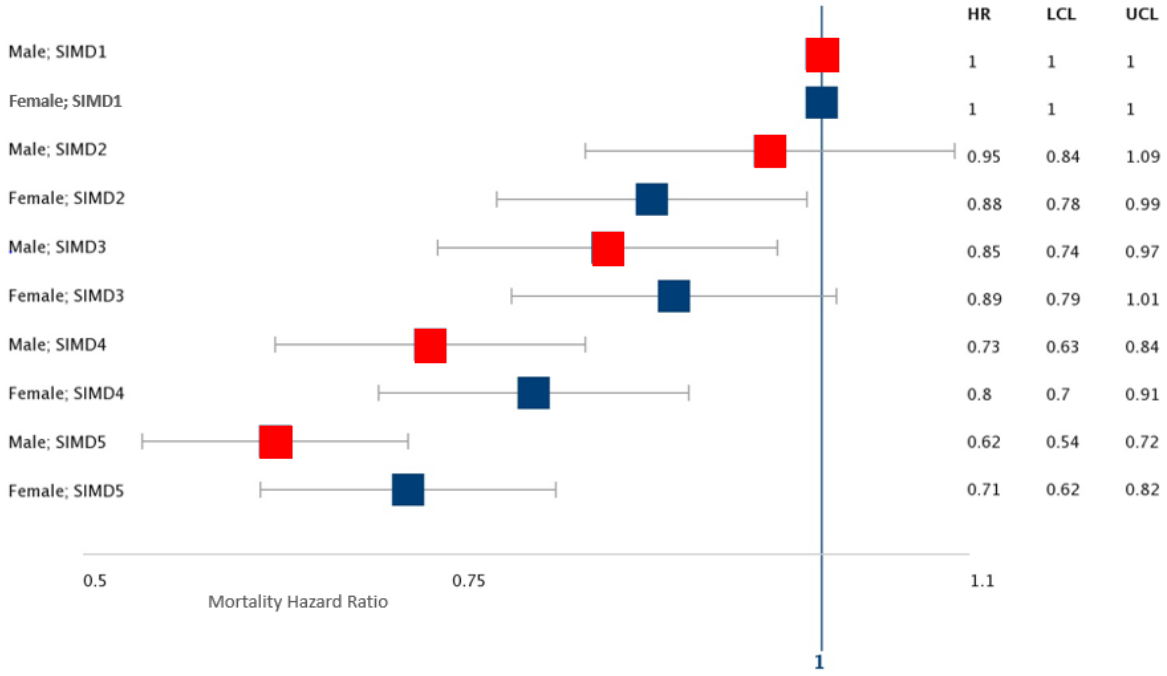


Figure 6-8: Adjusted hazard of all-cause mortality by socioeconomic grouping for men and women

Table 6-4: Adjusted hazard ratios according to baseline characteristics, year of presentation and socioeconomic status for all, men and women

	HR [95% CI] (p value)		
	All	**Male**	**Female**
Age	1.07 [1.06-1.07] (<0.01)	1.06 [1.06-1.07] (<0.01)	1.07 [1.07-1.07] (<0.01)
Year of Presentation			
1986-1990	1	1	1
1991-1995	0.86 [0.78-0.95] (<0.01)	0.88 [0.76-1.01] (0.08)	0.85 [0.74-0.97] (0.02)
1996-2000	0.72 [0.65-0.80] (<0.01)	0.71 [0.61-0.82] (<0.01)	0.74 [0.64-0.86] (<0.01)
2001-2005	0.55 [0.49-0.62] (<0.01)	0.53 [0.44-0.63] (<0.01)	0.57 [0.49-0.67] (<0.01)
2006-2010	0.46 [0.41-0.52] (<0.01)	0.43 [0.36-0.51] (<0.01)	0.49 [0.42-0.58] (<0.01)
2011-2015	0.35 [0.31-0.41] (<0.01)	0.34 [0.28-0.42] (<0.01)	0.36 [0.30-0.44] (<0.01)
Comorbidity			
Diabetes	1.72 [1.54-1.93] (<0.01)	1.78 [1.52-2.09] (<0.01)	1.67 [1.42-1.94] (<0.01)
Cancer	1.81 [1.60-2.04] (<0.01)	1.91 [1.60-2.29] (<0.01)	1.77 [1.49-2.10] (<0.01)
AF	1.24 [1.15-1.35] (<0.01)	1.29 [1.14-1.45] (<0.01)	1.20 [1.08-1.34] (<0.01)
CVD	1.09 [0.97-1.23] (0.14)	1.07 [0.90-1.27] (0.45)	1.11 [0.95-1.31] (0.18)
HTN	0.95 [0.85-1.06] (0.34)	0.93 [0.77-1.11] (0.40)	0.96 [0.83-1.10] (0.54)
AMI	1.39 [1.26-1.53] (<0.01)	1.36 [1.18-1.56] (<0.01)	1.42 [1.25-1.62] (<0.01)
Other IHD	0.94 [0.87-1.02] (0.16)	0.91 [0.80-1.02] (0.10)	0.96 [0.86-1.08] (0.49)
Lesion			
ASD	1	1	1
PDA	0.86 [0.65-1.14] (0.31)	1.19 [0.79-1.78] (0.41)	0.73 [0.50-1.07] (0.11)
VSD	2.01 [1.80-2.24] (<0.01)	1.97 [1.67-2.31] (<0.01)	2.00 [1.71-2.32] (<0.01)
Aortic	1.41 [1.28-1.56] (<0.01)	1.36 [1.17-1.59] (<0.01)	1.38 [1.21-1.58] (<0.01)
Ebstein's	2.46 [1.74-3.47] (<0.01)	2.39 [1.45-3.97] (<0.01)	2.58 [1.60-4.14] (<0.01)
AVSD	1.52 [1.24-1.86] (<0.01)	1.56 [1.17-2.07] (<0.01)	1.42 [1.05-1.90] (0.02)
TOF	1.98 [1.54-2.55] (<0.01)	1.72 [1.23-2.43] (<0.01)	2.20 [1.50-3.23] (<0.01)
Complex	1.77 [1.53-2.05] (<0.01)	1.69 [1.37-2.07] (<0.01)	1.78 [1.44-2.19] (<0.01)
Fontan	2.25 [1.37-3.71] (<0.01)	1.76 [0.94-3.33] (0.08)	3.11 [1.34-7.01] (0.01)
Valvular	1.29 [1.15-1.44] (<0.01)	1.20 [1.01-1.42] (0.03)	1.32 [1.13-1.53] (<0.01)
Other	1.39 [1.15-1.44] (<0.01)	1.18 [0.99-1.40] (0.07)	1.57 [1.34-1.84] (<0.01)
SIMD Quintile			
1 - most deprived	1	1	1
2	0.91 [0.84-0.99] (0.03)	0.95 [0.84-1.09] (0.50)	0.88 [0.78-0.99] (0.03)
3	0.87 [0.80-0.96] (<0.01)	0.85 [0.74-0.97] (0.02)	0.89 [0.79-1.01] (0.08)
4	0.77 [0.70-0.84] (<0.01)	0.73 [0.63-0.84] (<0.01)	0.80 [0.70-0.91] (<0.01)
5 - least deprived	0.67 [0.61-0.75] (<0.01)	0.62 [0.54-0.72] (<0.01)	0.71 [0.62-0.82] (<0.01)

6.2.3 Cause of death according to sex

As in the preceding Chapter, causes of death are grouped into seven categories (as a result of CHD, ischaemic heart disease, peripheral and cerebrovascular disease, other cardiac disease, infection, malignancy, respiratory) as well as 'other' causes. In total 74% of deaths in the male general population and 81% of deaths in the male study population were by one of these seven specific categories, and 68% of deaths in the female general population and 81% of deaths in the female study population fell into these categories. Cause of death according to congenital lesion is summarized for men in Figure 6-9 and for women in Figure 6-10.

Over the duration of the study period 55.6% of female deaths and 53.0% of male deaths were due to cardiovascular causes ($p=0.10$). CV death was more common among men with CHD (53.0%) than the male general population (38.8%), $p<0.01$. This was also true for women (55.6%) compared with the general population (39.5%), $p<0.01$.

Malignancy was the most common cause of death in the general population for men (30.6%) and women (26.9%). In the study population malignancy accounted for significantly fewer deaths in both men (15.3%, $p<0.01$) and women (11.8%, $p<0.01$), being significantly more common in men, $p<0.01$.

Among the study cohort, ischaemic heart disease was the most common cause of death for both men (25.6%) and women (22.8%), being significantly more common for men, $p=0.04$. This was also significantly higher than for the male (14.2%, $p<0.01$) and female (9.6%, $p<0.01$) general population.

For lesions of greater complexity (systemic RV, Fontan, Ebstein's anomaly, TOF and 'complex'), death attributed to CHD predominates for both men and women.

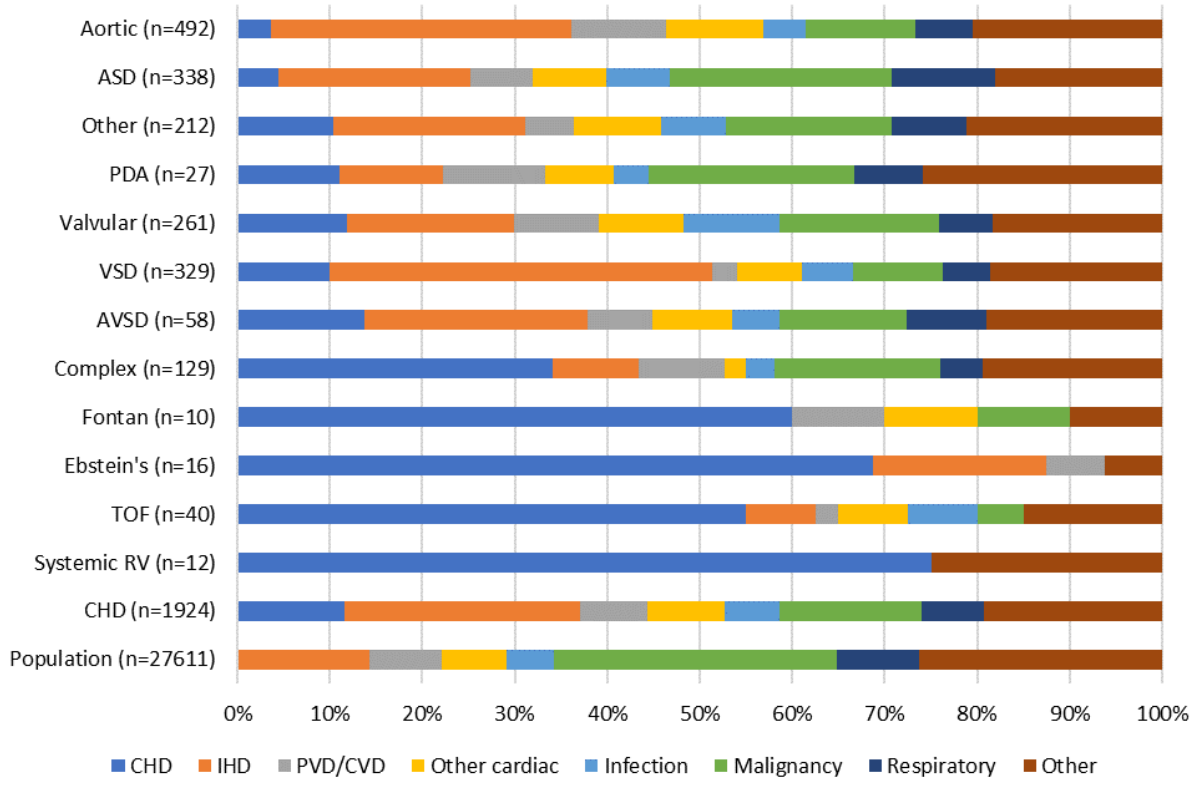


Figure 6-9: Men - cause of death according to underlying congenital lesion as well as for all patients and compared to the general population

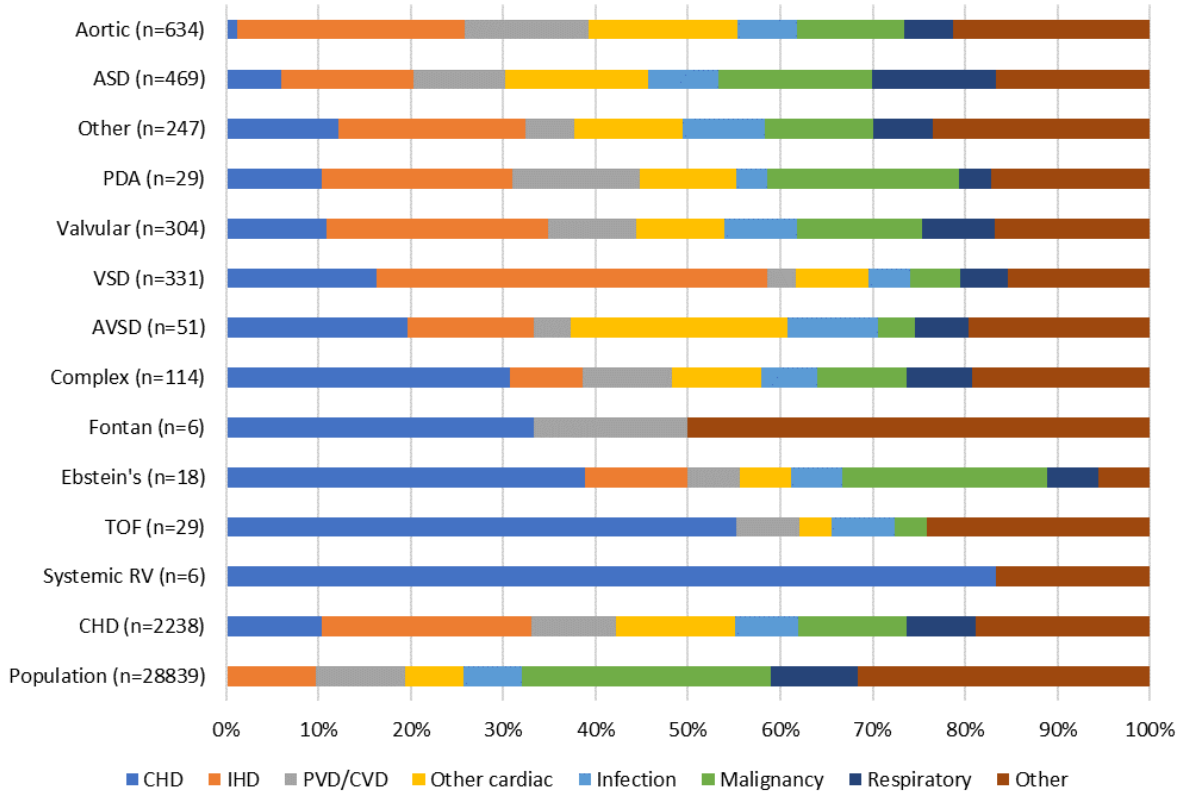
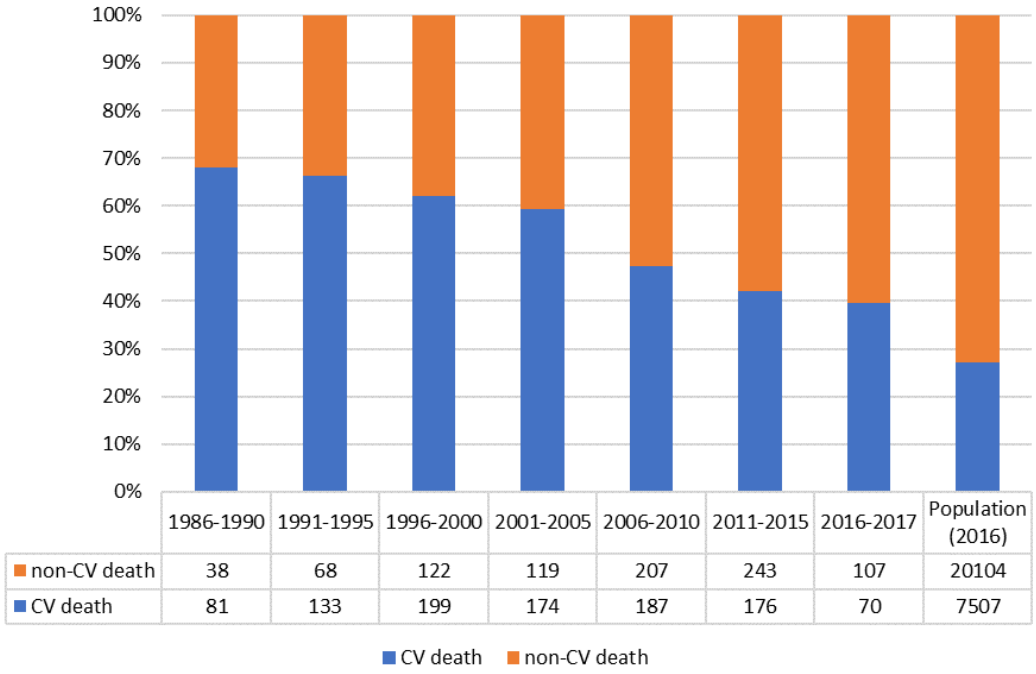


Figure 6-10: Women - cause of death according to underlying congenital lesion as well as for all patients and compared to the general population

6.2.4 Changing causes of death over time, according to sex

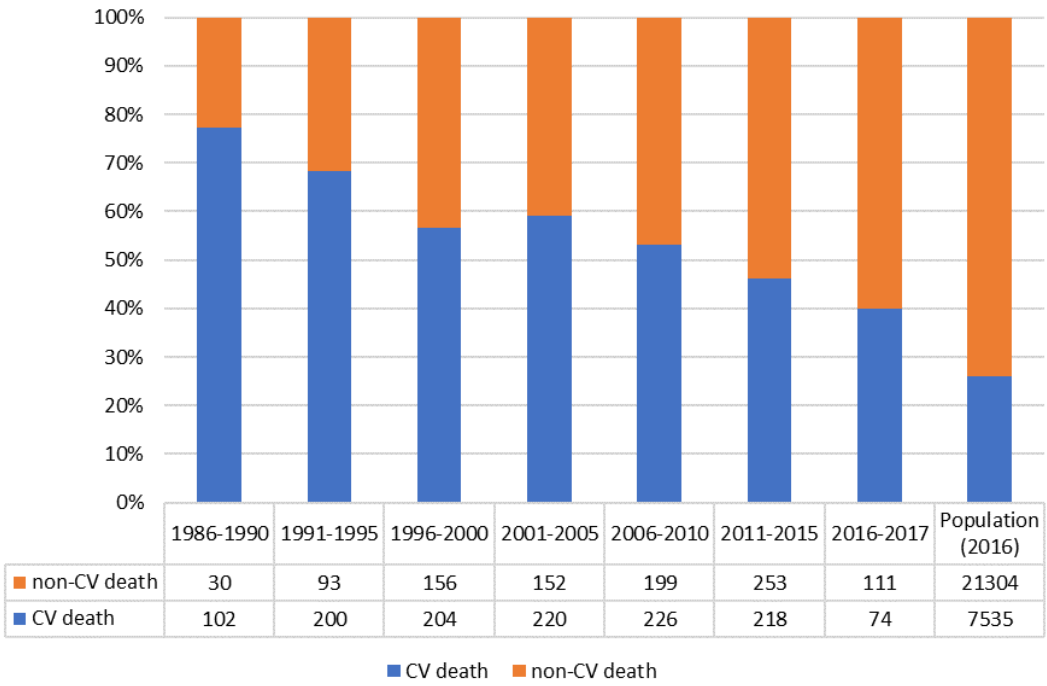
The changing proportion of cardiovascular and non-cardiovascular deaths throughout the data period are summarized in Figure 6-11 for men and Figure 6-12 for women.

In the earliest data period (1986-1990), 68.1% of men and 77.3% of women died due to cardiovascular causes (p=0.10). By the most contemporary data period (2016-2017), 39.5% of men and 40.0% of women died by cardiovascular causes (p=0.93).



	1986-1990	1991-1995	1996-2000	2001-2005	2006-2010	2011-2015	2016-2017	Population (2016)
non-CV death	38	68	122	119	207	243	107	20104
CV death	81	133	199	174	187	176	70	7507

Figure 6-11: Men - Changing proportion of cardiovascular and non-cardiovascular deaths over time and compared with men in the general population



	1986-1990	1991-1995	1996-2000	2001-2005	2006-2010	2011-2015	2016-2017	Population (2016)
non-CV death	30	93	156	152	199	253	111	21304
CV death	102	200	204	220	226	218	74	7535

Figure 6-12: Women - Changing proportion of cardiovascular and non-cardiovascular deaths over time and compared to women in the general population

The proportion of deaths due to cardiovascular causes fell throughout the data period for men and women with CHD, and for men and women in the general population (Figure 6-13).

From the beginning to the end of the data period, CV deaths in men decreased by 28% amongst those with ACHD compared with 21% for the general population, p<0.01. This constitutes a 0.93% per year decline for those with ACHD compared with 0.70% per year amongst the general population, p=0.38.

A similar pattern was observed for women, where CV deaths amongst those with ACHD decreased by 37% over the total data period, compared with 24% for the general population, p<0.01. This equates to a mean yearly change of 1.23% per year for those with ACHD and 0.80% per year amongst the general population, p=0.89.

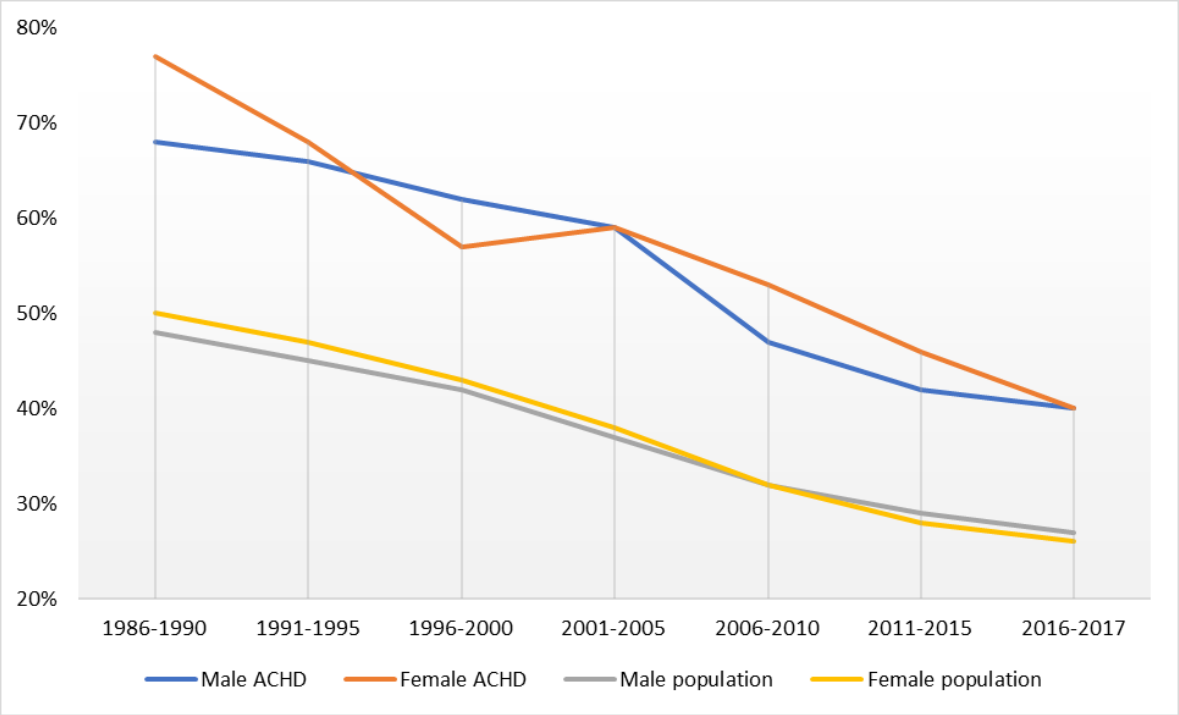


Figure 6-13: Percentage of cardiovascular deaths over time; for men and women with CHD and for the general population

6.3 Discussion

6.3.1 Differences in demographics and baseline characteristics between men and women

A slight albeit statistically significant higher proportion of our data set were women (50.9%) than men (49.2%), p=0.03. It does not however follow that congenital heart disease is more prevalent amongst women. In fact, when indexed to the mean Scottish adult population throughout the study period, 4.02 per 1000 men were included compared with 3.77 per 1000 women. Marelli et al have previously suggested that the higher proportion of women with CHD persists when indexed to population numbers (representing 4.55 and 3.61 per 1000 of the female and male population of Quebec respectively) (9). The likely explanation for the discrepancy in our findings is that Marelli et al include data from primary care and out-patients. As discussed previously, inclusion in our data is reliant on an in patient hospital episode. As such a bias away from milder CHD will be expected and it is in the milder CHD lesions (ASD, PDA, VSD) where women predominate. The female predisposition amongst lesions at the simpler end of the spectrum (Table 6-3) is also the likely reason why women are slightly but significantly older at presentation to our data set.

The sex distribution of each lesion is discussed in the previous Chapter and is according to convention. Only the Fontan group presents a sex distribution distinct from that suggested by my prior literature review. Where we note a slight but significant male predominance, convention is towards an equal sex distribution.

A significantly higher proportion of men than women in our data were found to have diabetes. However, of those with diabetes 54.1% were male and 45.9% female, which is entirely in line with the 54.5% male and 45.5% female UK population estimates (148). In contrast, where AF is more common in men of the general population (149) we found this to be mitigated in those with CHD where no difference was found. This stands to reason as CHD is established to be a major risk factor for AF, such that background variation may almost be negligible (150).

More women than men reside in postcodes conferring higher socioeconomic deprivation. 28.2% of women and 25.5% of men in our data set reside in SIMD 1, representing the quintile of most deprived postcodes in Scotland. By comparison, within the general population an equal proportion of men (19.4%) and women (19.7%) reside in postcodes corresponding to SIMD 1. This inequality is not therefore explained by background population levels and requires further study as to the reasons why.

6.3.2 Differences in mortality and survival between men and women

As illustrated by Table 6-2, more women than men died during the data period. As described above however, women were older and demographics are not evenly distributed between the sexes. In fact, age at death is significantly higher for women than men. This is true for the total cohort and across all complexities of lesions and socioeconomic groups (Table 6-3). Age at death however, increased more for men than women throughout the data period. As different lesions are not expressed uniformly throughout the data period this was also compared according to lesion complexity and remains true for all cohorts (Figure 6-4 & Figure 6-5). In the general population of Scotland, the mean age at death for women in the mid 1980s was 6.2 years greater than for men, reducing to 4.1 years by 2015. In our data set the discrepancy in age at death between men and women, was 8.2 years during the first half and 6.1 years by the second half of the data period. Therefore, the magnitude of difference in life expectancy between men and women is greater in our study than in the general population but the trend of a narrowing gap closely mirrors and is likely explained by population trends (151).

Figure 6-6 illustrates the observed mortality throughout the data period for men and women. This, and the non-adjusted, binary regression for all-cause mortality would suggest that women have reduced survival, particularly for those with lesions of moderate complexity, compared with men. This is entirely mitigated by adjusting for age and when fully adjusted as in Figure 6-7 men clearly and significantly have reduced survival compared with women. Figure 6-7 also illustrates that this excess male mortality is accounted for by non-cardiovascular death. Indeed, when comparing the relative contribution of baseline

characteristics to survival in men and women, as in Table 6-4, acute myocardial infarction confers higher mortality in women than in men, which is also a commonly accepted paradigm amongst the general population (152).

The impact of socioeconomic group on mortality will be explored in detail in the next Chapter. When comparing sex differences on the survival of different socioeconomic groups; not only do women experience higher levels of socioeconomic deprivation but the survival benefit of affluence is seen to a lesser extent for women than for men (Figure 6-8). The interaction of sex and socioeconomic factors has never been studied in the accessible literature regarding ACHD previously and to try to explain this observation would be conjecture. Clearly, further study is required.

The introduction to this Chapter referred to three articles assessing the effect of sex on mortality in congenital heart disease (62,63,73). All three articles controlled estimates of survival for age only. Although the model used in this Chapter is designed to control more intricately for biases in the data set, a sensitivity analysis controlling for age only does not alter the principal finding of statistically significant excess mortality for men when compared with women, as was the finding of Engelfriet & Mulder using European Heart Survey data (62).

6.3.3 Differences in cause of death for men and women

Patterns of cause of death are broadly similar for men and women with CHD. In both cases cardiovascular death predominates overall and is significantly more common than for the comparable group in the general population. Ischaemic heart disease was the most common single cause of death for both men and women and again was more common than in population deaths.

When comparing changes over time, earlier data periods saw a higher proportion of death by cardiovascular causes amongst women than men, falling to similar levels in contemporary analysis. As such, the overall tendency towards homogenisation with population levels of cardiovascular and non-cardiovascular deaths highlighted in the preceding Chapter is disproportionately contributed to by the early decline in CV death noted for women with CHD.

6.4 Conclusions

According to our data, more women than men have CHD. However, after adjusting for the greater adult female population in Scotland, CHD is slightly more prevalent in men than women.

Age at death is higher for women with CHD than men and the life expectancy gap is greater than in the general population. Age at death is increasing over time for men and women with CHD and the gap is closing at a similar rate as in the general population.

Adjusted survival estimates suggest a higher mortality for men compared to women with CHD. This is predominately as a result of increased non-cardiovascular mortality in men.

7 Socioeconomic status and the association with mortality in adults with CHD

7.1 Introduction

The concept of socioeconomic grouping is complex and variable both between and within different societies and cultures. I refer to socioeconomic deprivation although many other terms such as ‘social class’ or ‘socioeconomic group’ are referred to within the vast literature.

On an individual basis, the variables of level of education, occupation, and the closely associated income are the most commonly accepted determinants of socioeconomic deprivation. For the purposes of population level analysis, using a postcode derived measure of socioeconomic deprivation has the obvious advantages of allowing largescale grouping and comparison to allow correlation of measures. The component metrics incorporated into postcode or area determined measures of socioeconomic deprivation are again variable from country to country. In Scotland the most widely accepted and intricate measure of postcode determined socioeconomic deprivation is the SIMD. Recognising the complexity of quantifying socioeconomic deprivation, this measure uses 38 separate indicators to rank 6,505 small areas or ‘datazones’ each with roughly 760 residents of the Scottish population from 1 (most deprived) to 6,505 (least deprived). The 38 indicators are derived from 7 domains:

- Income
- Employment
- Health
- Education
- Skills and training
- Housing
- Crime

This ranking can then be used individually or grouped into equal, relative measures of socioeconomic deprivation within the Scottish population (such as deciles, quintiles or vigintile).

Socioeconomic deprivation is closely linked to health inequality and as such is known to predispose to excess mortality (153) and excess cardiovascular mortality (154). The NHS was founded on 3 guiding principles with the primary aim of negating inequalities in health. That it should; 1 – meet the needs of

everyone, 2 – be free at the point of delivery, and 3 – be based on need and not the ability to pay. In spite of this, evidence would suggest that health inequality continued to widen from the inception of the NHS in 1948 until at least the end of the 20th century (153,155).

Despite the extensive literature and political debate regarding socioeconomic deprivation and health inequality in the UK, this has received very little attention in the research surrounding congenital heart disease. A small number of studies have looked at the relative birth prevalence of congenital heart disease according to socioeconomic deprivation (156,157). However, the socioeconomic effect on outcomes including mortality in adults with congenital heart disease have never been assessed.

7.2 Methods

In addition to the common methodology as set out in section 4, further efforts have been made within this Chapter to ensure the robustness of the categorisation of socioeconomic deprivation.

As touched upon in section 4.3.4, two postcode markers of socioeconomic deprivation have been used at a population level in Scotland. SIMD is now the most commonly encountered and highly nuanced measure. Predating SIMD, the Carstairs-Morris index uses four domains to determine socioeconomic deprivation (Table 4-5). In contrast to the SIMD, none of the determinants of the Carstairs-Morris index are directly derived from health data. As a result, I have included key results in this Chapter as determined both by SIMD and Carstairs-Morris. This was by way of mitigating the potential bias of poorer health outcomes associated with SIMD being attributed to the determinants of SIMD itself. The most up-to-date iteration of Carstairs-Morris derived postcode boundaries of 2011 was used.

7.3 Results

7.3.1 Baseline characteristics according to socioeconomic deprivation

An area grouping of socioeconomic deprivation could be established for 16,045 (99.0%) of the total study population. The baseline characteristics and demographics of individuals resident in each datazone SIMD quintile are summarized in Table 7-1. ACHD was not evenly distributed across the SIMD quintiles ($p<0.01$ for correlation across all quintiles) with significantly more of the cohort residing in areas of highest deprivation (27.1% in SIMD 1) than lowest deprivation (15.7% in SIMD 5), $p<0.01$. This is also true when using the Carstairs-Morris determinant, with 25.0% residing in the most deprived and 17.2% in the least deprived quintiles.

Women with ACHD were more likely to reside in areas of high deprivation than men, with 28.2% of women in the study residing in SIMD 1 compared to 25.5% of men, $p<0.01$.

In total 53.4% of the SIMD 1 study cohort were female, this is compared to 51.8% in the general population.

Individuals from areas of higher socioeconomic deprivation were younger at first entry into the data set than those from areas of low socioeconomic deprivation. Median age at presentation was 29 (IQR 16-55) (mean 36.5 (SD 22.6)) in SIMD 1, compared with 37 (IQR 16-61) (mean 40.8 (SD 23.7)) in SIMD 5, $p<0.01$.

The complexity of underlying CHD lesion was not significantly different according to deprivation (Table 7-1).

Individuals with lower socioeconomic deprivation had a lower prevalence of diabetes (2.7% in SIMD 5 compared with 4.4% in SIMD 1, $p<0.01$) and higher rates of AF (10.8% in SIMD 5 compared with 8.2% in SIMD 1, $p<0.01$). Rates of cancer, AMI and IHD without AMI did not vary according to SIMD quintile. The rate of CVD did not vary significantly across all SIMD quintiles but on direct comparison of

highest and lowest levels of socioeconomic deprivation there was a significantly higher prevalence (6.1% in SIMD 1 and 4.9% in SIMD 5, p=0.03). For HTN, again no significant trend was noted across all SIMD quintiles however on direct comparison prevalence was higher in SIMD 5 (6.4%) than in SIMD 1 (5.1%), p=0.03.

In total 4,118 (25.7%) of those for whom SIMD data was available died during follow up. Despite being younger, the proportion of those who died during follow up was significantly higher amongst those residing in areas of higher socioeconomic deprivation (26.2% in SIMD 1 and 22.5% in SIMD 5, p<0.01).

Table 7-2 compares the survival within each SIMD quintile according to baseline characteristics. This confirms that the lower rate of death in areas of lower socioeconomic deprivation remain true for men (p=0.02) and women (p=0.01). Observed mortality reduces as deprivation decreases for CHD lesions of moderate complexity (p<0.01) but not for lesions of simple (p=0.21) or great (p=0.24) complexity.

With higher deprivation, observed mortality was lower for those with AF (p<0.01), CVD (p=0.02), HTN (p=0.01), and ischaemic heart disease without AMI (p<0.01). But not cancer (p=0.80), diabetes (p=0.23), or AMI (p=0.64).

Table 7-1: Comparison of baseline characteristics and demographics according to Scottish index of multiple deprivation (SIMD). SIMD 1 represents the most deprived and SIMD 5 the least

					Lesion Complexity			Comorbidity						
	All (%)	**Dead (%)**	**Female (%)**	**Age mean (SD)**	**Simple (%)**	**Modearate (%)**	**Complex (%)**	**Diabetes (%)**	**Cancer (%)**	**AF (%)**	**CVD (%)**	**HTN (%)**	**AMI (%)**	**Other IHD (%)**
All	16045	4118 (25.7)	8169 (50.9)	39.2 (23.5)	8033 (62.6)	3494 (27.2)	1306 (10.2)	605 (3.8)	401 (2.5)	1593 (9.9)	925 (5.8)	940 (5.9)	885 (5.5)	1613 (10.1)
SIMD 1 (most)	4335 (27.1)	1140 (26.2)	2324 (53.4)	36.5 (22.6)	2202 (63.9)	892 (25.9)	353 (10.2)	193 (4.4)	101 (2.3)	358 (8.2)	266 (6.1)	223 (5.1)	213 (4.9)	384 (8.8)
SIMD 2	3441 (21.5)	967 (28.1)	1793 (52.1)	39.7 (23.9)	1695 (61.5)	794 (28.8)	268 (9.7)	147 (4.3)	84 (2.4)	341 (9.9)	213 (6.2)	204 (5.9)	199 (5.8)	381 (11.1)
SIMD 3	2997 (18.7)	775 (25.9)	1491 (49.8)	40.0 (23.5)	1483 (61.8)	666 (27.8)	251 (10.5)	111 (3.7)	73 (2.4)	314 (10.5)	169 (5.6)	188 (6.3)	164 (5.5)	313 (10.4)
SIMD 4	2736 (17.1)	670 (24.5)	1393 (48.5)	40.5 (23.9)	1353 (62.3)	590 (27.2)	229 (10.5)	85 (3.1)	67 (2.5)	309 (11.3)	155 (5.7)	164 (6.0)	162 (5.9)	296 (10.8)
SIMD 5 (least)	2516 (15.7)	566 (22.5)	1281 (49.1)	40.8 (23.8)	1300 (63.2)	552 (23.8)	205 (10.0)	69 (2.7)	76 (3.0)	271 (10.8)	122 (4.9)	161 (6.4)	147 (5.8)	239 (9.5)
p value	<0.01	<0.01	<0.01	<0.01		0.42		<0.01	0.48	<0.01	0.19	0.15	0.28	0.01

Table 7-2: Survival to the end of the data period according to baseline characteristics for each SIMD quintile

	SIMD 1		SIMD 2		SIMD 3		SIMD 4		SIMD 5		
	Alive (%)	Dead (%)	Alive (%)	Dead (%)	Alive (%)	Dead (%)	Alive (%)	Dead (%)	Alive (%)	Dead (%)	p value
All	3215 (73.8)	1140 (26.2)	2474 (71.9)	967 (28.1)	2222 (74.1)	775 (25.9)	2066 (75.5)	670 (24.5)	1950 (77.5)	566 (22.5)	<0.01
Mean age at entry (SD)	28.3 (17.1)	59.6 (20.1)	30.8 (18.6)	62.4 (20.7)	32.0 (18.9)	62.8 (20.5)	32.5 (19.4)	65.1 (19.2)	33.9 (20.0)	64.5 (20.2)	0.30
Female	1695 (72.9)	629 (27.1)	1254 (69.9)	539 (30.1)	1085 (72.8)	406 (27.2)	982 (74.1)	344 (25.9)	937 (75.9)	298 (24.1)	0.01
Male	1520 (74.8)	511 (25.2)	1220 (74.0)	428 (26.0)	1137 (75.5)	369 (24.5)	1084 (76.9)	326 (23.1)	1013 (79.1)	268 (20.9)	0.02
Lesion complexity											
Simple	1772 (80.5)	430 (19.5)	1353 (79.8)	342 (20.2)	1219 (82.2)	264 (17.8)	1117 (82.6)	236 (17.4)	1064 (81.9)	236 (18.2)	0.21
Moderate	599 (67.2)	293 (32.9)	502 (63.2)	292 (36.8)	451 (67.7)	215 (32.3)	411 (69.7)	179 (30.3)	416 (75.4)	136 (24.6)	<0.01
Complex	294 (83.3)	59 (16.7)	215 (80.2)	53 (19.8)	209 (83.3)	42 (16.7)	191 (83.4)	38 (16.6)	181 (88.3)	24 (11.7)	0.24
Comorbidity											
Diabetes	84 (43.5)	109 (56.5)	55 (37.4)	92 (62.6)	39 (35.1)	72 (64.9)	36 (42.4)	49 (57.7)	35 (50.7)	34 (49.3)	0.23
Cancer	27 (26.7)	74 (73.3)	24 (28.6)	60 (71.4)	21 (28.8)	52 (71.2)	14 (20.9)	53 (79.1)	22 (29.0)	54 (71.1)	0.80
AF	140 (39.1)	218 (60.9)	139 (40.8)	202 (59.2)	150 (47.8)	164 (52.2)	146 (47.3)	163 (52.8)	146 (53.9)	125 (46.1)	<0.01
CVD	177 (66.5)	89 (33.5)	129 (60.6)	84 (39.4)	112 (66.3)	57 (33.7)	97 (62.6)	58 (37.4)	95 (77.9)	27 (22.1)	0.02
HTN	127 (57.0)	96 (43.1)	108 (52.9)	96 (47.1)	114 (60.6)	74 (39.4)	107 (65.2)	57 (34.8)	112 (69.6)	49 (30.4)	0.01
AMI	71 (33.3)	142 (66.7)	65 (32.7)	134 (67.3)	52 (31.7)	112 (68.3)	61 (37.8)	101 (62.4)	56 (38.1)	91 (61.9)	0.64
Other IHD	186 (48.4)	198 (51.6)	170 (44.6)	211 (55.4)	166 (53.0)	147 (47.0)	170 (57.4)	126 (42.6)	148 (61.9)	91 (38.0)	<0.01

7.3.2 Age at death according to socioeconomic deprivation

As stated above, a disproportionate number of the study cohort reside in areas of high socioeconomic deprivation. This translates to a greater duration of cumulative follow up for those residing in the corresponding lower SIMD quintile groups. Table 7-3 summarises follow up, crude mortality rates and age at death as observed for each SIMD quintile. As socioeconomic deprivation decreases, crude mortality rate falls and mean and median age at death is higher. Mean age at death is significantly greater for those resident in SIMD 5 (70.4 +/- 19 years) than SIMD 1 (65.6 +/- 18.8), $p<0.01$. A similarly higher age at death is noted when comparing a Carstairs-Morris quintile of low socioeconomic deprivation (70.3 +/- 19.7 years) with high (65.8 +/- 19.2 years), $p<0.01$.

Table 7-3: Follow up, mortality rate and age at death according to SIMD quintile group. SIMD 1 refers to the most deprived and SIMD 5 the least

	Cummulative follow up (years)	Mortality rate (per 1000 person years)	Age at death, mean (SD)	Age at death, median (IQR)
SIMD 1	46065	24.8 (23.4-26.2)	65.6 (18.8)	70 (55-79)
SIMD 2	35202	27.5 (25.8-29.3)	68.0 (19.5)	74 (58-82)
SIMD 3	30592	25.3 (23.6-27.2)	68.5 (19.2)	74 (59-82)
SIMD 4	28042	23.9 (22.2-25.8)	70.7 (18.3)	76 (63-83)
SIMD 5	26234	21.6 (19.9-23.4)	70.4 (19.0)	75 (61-85)

Mean age at death increased during the data period from 66.9 years to 68.8 years, $p<0.01$. Figure 7-1 illustrates how the mean age at death changed from the first to the second half of the data period. Point estimates for mean age at death increased for all SIMD quintiles. The greatest magnitude of increase was seen for SIMD 5, representing the lowest socioeconomic deprivation, from 67.2 to 72.1 years, $p<0.01$.

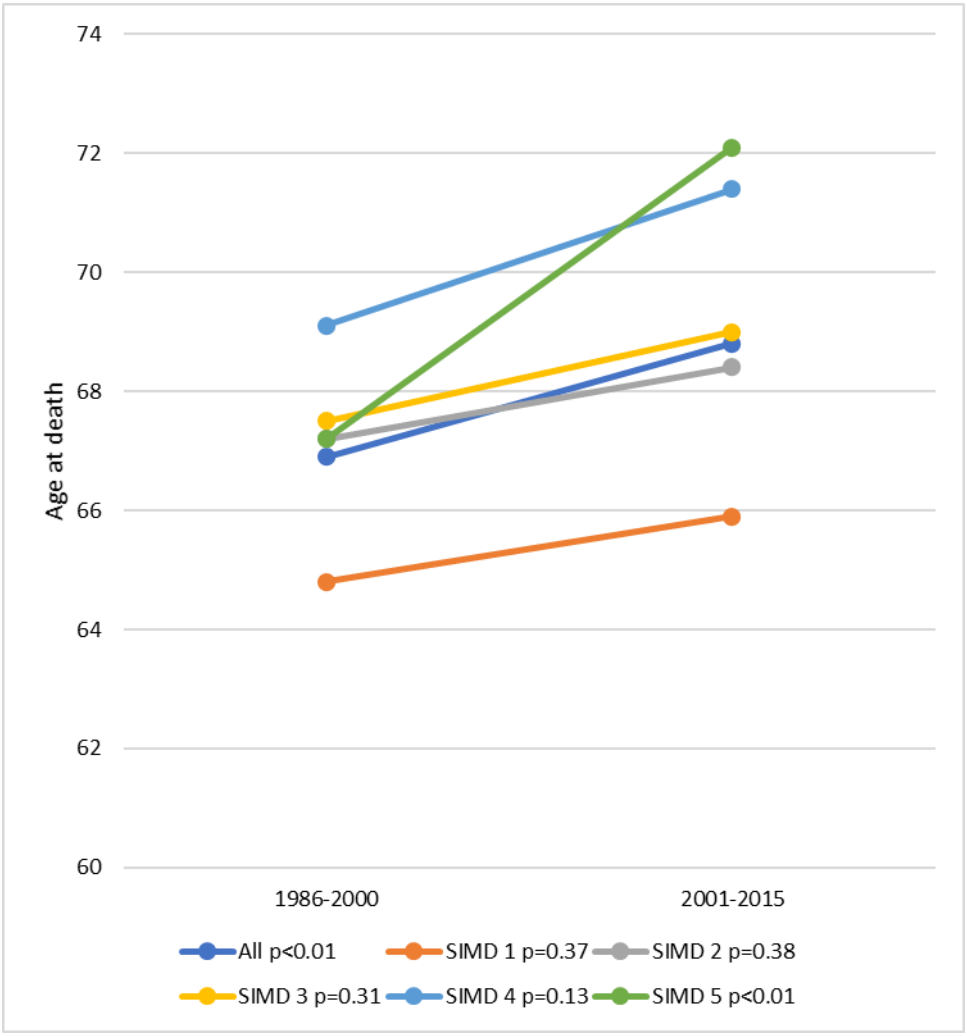


Figure 7-1: Mean age at death for all ACHD and according to Scottish index of multiple deprivation (SIMD) during the first and second half of the data period

7.3.3 Survival according to socioeconomic deprivation

Unadjusted survival estimates for all-cause mortality according to SIMD over the 30 year data period are illustrated in Figure 7-2. Survival was lower for those with higher socioeconomic deprivation (SIMD deciles 1-5) when compared to those with less socioeconomic deprivation (SIMD 6-10) (OR 1.20, 95% CI 1.11-1.29, p<0.01). Figure 7-3 illustrates survival from age 16 for those in the data set.

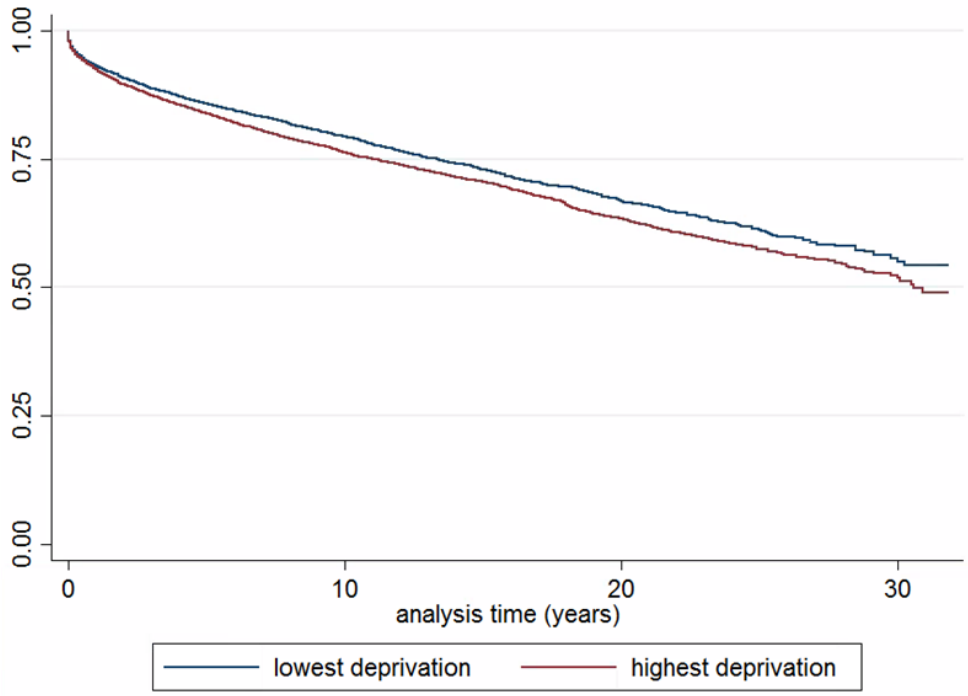


Figure 7-2: Kaplan-Meier estimation of survival as observed during the data period.
'Highest deprivation' refers to SIMD deciles 1-5 and 'lowest deprivation' deciles 6-10

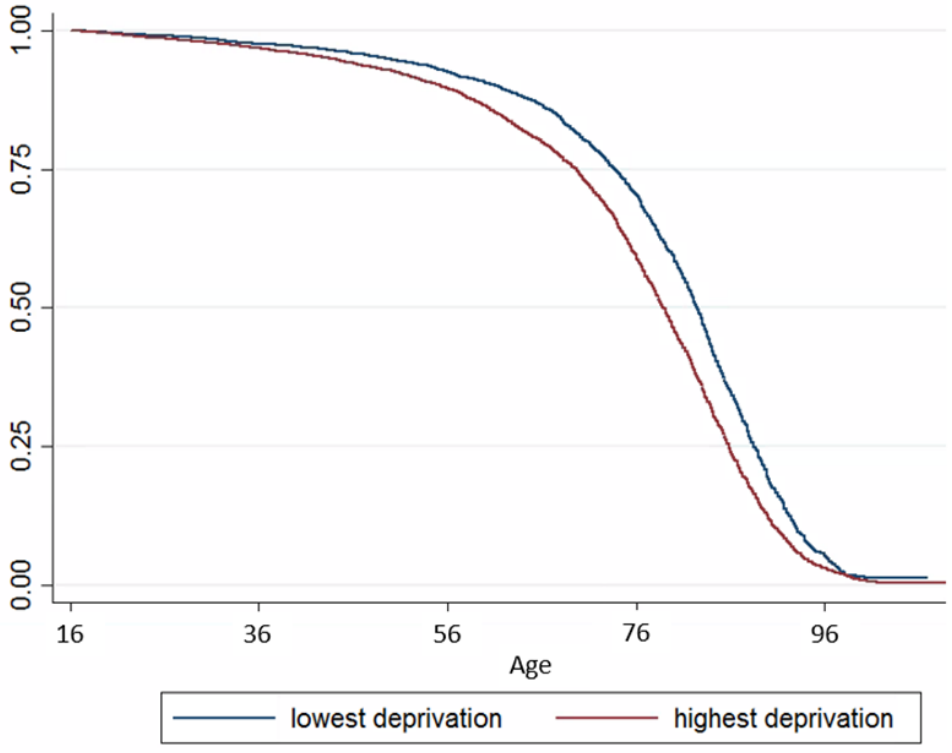


Figure 7-3: Kaplan-Meier estimation of survival from age 16 according to socioeconomic deprivation.
'Highest deprivation' refers to SIMD deciles 1-5 and 'lowest deprivation' deciles 6-10

Figure 7-4 illustrates survival from age 16 for each SIMD quintile. A significant reduction in risk of all cause mortality is observed for each increment of lower socioeconomic deprivation (OR 0.95, 95% CI 0.93-0.97, p<0.01).

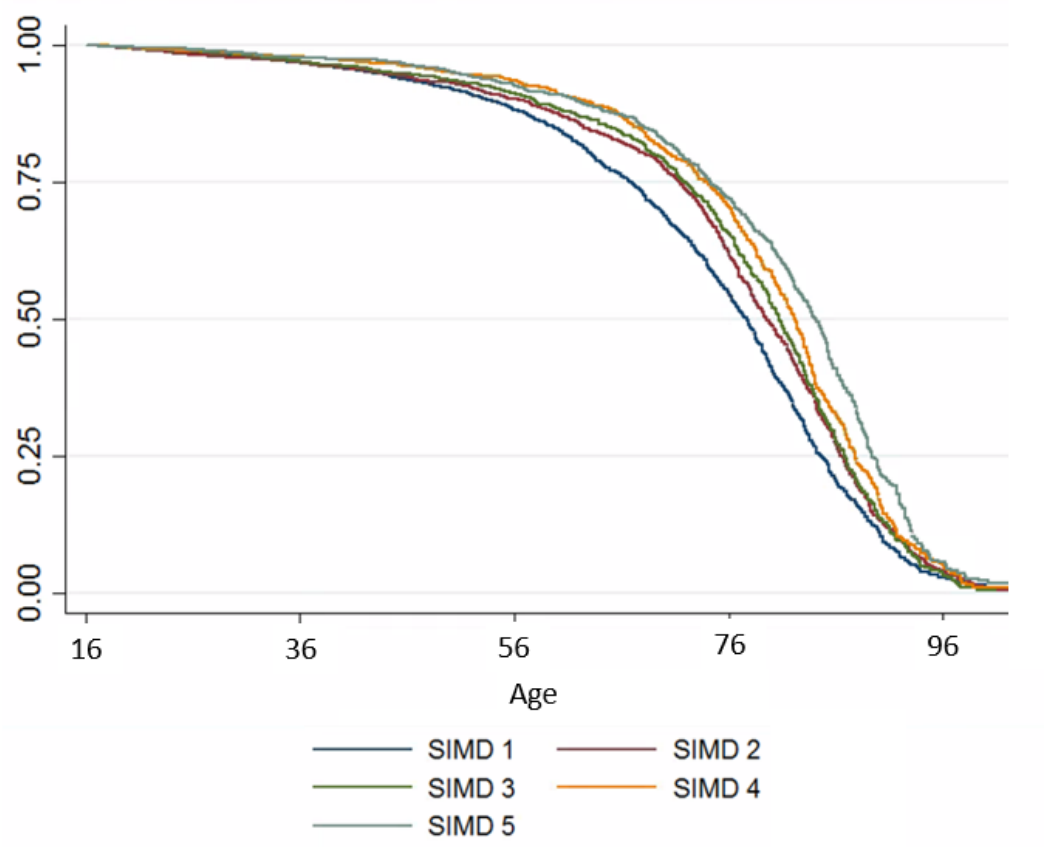


Figure 7-4: Kaplan-Meier estimation of survival from age 16 according to SIMD quintile. SIMD 1 refers to the highest deprivation and SIMD 5 the least

As discussed earlier in this Chapter, baseline characteristics and demographics are not equally distributed according to socioeconomic deprivation. Table 7-4 provides a breakdown of multivariate, adjusted hazards for all cause mortality including SIMD quintile. It also compares the interaction of these variables for those exposed to high levels of socioeconomic deprivation (SIMD decile 1-5) and those exposed to lower levels (SIMD 6-10).

A sustained and statistically significant reduction in hazard for all cause mortality is seen for lower deprivation quintiles. With SIMD1 (most deprivation) as the reference, the adjusted hazard ratio for SIMD 5 is 0.67 (95% CI 0.60-0.74, p<0.01). This represents a 33% reduction in instantaneous risk of all cause

mortality for those exposed to the lowest levels of deprivation compared to the most deprived areas. Figure 7-5 provides graphical illustration of the adjusted hazard for all cause mortality as calculated for each SIMD quintile. A similar pattern is seen when Carstairs-Morris quintile is used in the model in place of SIMD (HR for quintile 2, 0.90, 95% CI 0.82-0.99, p=0.03; HR for quintile 3, 0.89, 95% CI 0.81-0.97, p=0.01; HR for quintile 4, 0.80, 95% CI 0.73-0.88, p<0.01; HR for quintile 5, 0.75, 95% CI 0.68-0.83, p<0.01).

Adjusted HRs for cardiovascular mortality also reduced significantly as deprivation decreases (HR for SIMD 5, 0.71, 95% CI 0.62-0.82, p<0.01). The greatest reduction in hazard was seen for non-cardiovascular mortality (HR for SIMD 5, 0.62, 95% CI 0.53-0.72, p<0.01).

According to Table 7-4 a similar pattern of hazard is conferred by baseline characteristics for those in low and those in high SIMD groups. However, the increased hazard associated with male sex amongst those with higher socioeconomic deprivation (HR 1.21, 95% CI 1.11-1.31, p<0.01) is not seen for those with lower socioeconomic deprivation (HR 1.03, 95% CI 0.93-1.14, p=0.60). Additionally, those with IHD without AMI have a lower risk of all cause mortality in areas of low socioeconomic deprivation (HR 0.82, 95% CI 0.71-0.94, p<0.01) but not high socioeconomic deprivation (HR 1.01, 95% CI 0.91-1.12, p=0.88).

Again, a similar risk of all cause mortality attached to underlying congenital lesion is seen in those with higher and those with lower socioeconomic deprivation. One exception appears to be the Fontan cohort, for whom the risk of all cause mortality (when compared to the reference lesion ASD) is greater amongst those experiencing high (HR 2.80, 95% CI 1.61-4.90, p<0.01) than those experiencing low (HR 1.21, 95% CI 0.39-3.80, p=0.74) socioeconomic deprivation.

Table 7-4: Multivariate hazard ratios for all-cause mortality comparing highest (SIMD deciles 1-5) and lowest (SIMD deciles 6-10) levels of socioeconomic deprivation

	HR [95% CI] (p value)		
	All	**Highest deprivation**	**Lowest deprivation**
Female	1	1	1
Male	1.13 [1.06-1.21] (<0.01)	1.21 [1.11-1.31] (<0.01)	1.03 [0.93-1.14] (0.60)
Age	1.07 [1.06-1.07] (<0.01)	1.07 [1.06-1.07] (<0.01)	1.07 [1.06-1.07] (<0.01)
SIMD Quintile			
1 - most deprived	1	NA	NA
2	0.92 [0.84-1.00] (0.05)	NA	NA
3	0.87 [0.80-0.96] (<0.01)	NA	NA
4	0.77 [0.70-0.85] (<0.01)	NA	NA
5 - least deprived	0.67 [0.60-0.74] (<0.01)	NA	NA
Year of Presentation			
1986-1990	1	1	1
1991-1995	0.87 [0.79-0.96] (<0.01)	0.81 [0.71-0.91] (<0.01)	0.98 [0.84-1.15] (0.83)
1996-2000	0.72 [0.65-0.80] (<0.01)	0.70 [0.61-0.80] (<0.01)	0.75 [0.63-0.89] (<0.01)
2001-2005	0.54 [0.48-0.60] (<0.01)	0.55 [0.47-0.63] (<0.01)	0.54 [0.44-0.65] (<0.01)
2006-2010	0.45 [0.40-0.51] (<0.01)	0.46 [0.39-0.53] (<0.01)	0.45 [0.37-0.55] (<0.01)
2011-2015	0.34 [0.30-0.39] (<0.01)	0.34 [0.28-0.41] (<0.01)	0.33 [0.27-0.42] (<0.01)
Comorbidity			
Diabetes	1.68 [1.50-1.88] (<0.01)	1.52 [1.33-1.75] (<0.01)	2.13 [1.75-2.60] (<0.01)
Cancer	1.78 [1.57-2.01] (<0.01)	1.74 [1.48-2.06] (<0.01)	1.84 [1.53-2.21] (<0.01)
AF	1.25 [1.15-1.35] (<0.01)	1.21 [1.10-1.35] (<0.01)	1.28 [1.13-1.46] (<0.01)
CVD	1.10 [0.98-1.23] (0.12)	1.14 [0.99-1.32] (0.07)	1.04 [0.85-1.27] (0.71)
HTN	0.96 [0.86-1.08] (0.51)	1.02 [0.89-1.17] (0.81)	0.88 [0.73-1.05] (0.15)
AMI	1.38 [1.25-1.51] (<0.01)	1.48 [1.30-1.67] (<0.01)	1.29 [1.11-1.49] (<0.01)
Other IHD	0.93 [0.86-1.01] (0.09)	1.01 [0.91-1.12] (0.88)	0.82 [0.71-0.94] (<0.01)
Lesion			
ASD	1	1	1
PDA	0.88 [0.66-1.56] (0.35)	0.87 [1.11-1.31] (0.42)	0.91 [0.57-1.48] (0.71)
VSD	1.94 [1.74-2.16] (<0.01)	1.87 [1.62-2.15] (<0.01)	2.08 [1.75-2.48] (<0.01)
Aortic	1.38 [1.25-1.53] (<0.01)	1.42 [1.25-1.61] (<0.01)	1.34 [1.15-1.58] (<0.01)
Ebstein's	2.43 [1.72-3.44] (<0.01)	2.48 [1.54-3.97] (<0.01)	2.46 [1.48-4.08] (<0.01)
AVSD	1.50 [1.23-1.84] (<0.01)	1.48 [1.14-1.92] (<0.01)	1.59 [1.15-2.20] (0.01)
TOF	1.94 [1.50-2.50] (<0.01)	1.81 [1.33-2.47] (<0.01)	2.27 [1.46-3.54] (<0.01)
Complex	1.74 [1.50-2.01] (<0.01)	1.82 [1.51-2.19] (<0.01)	1.66 [1.32-2.10] (<0.01)
Fontan	2.18 [1.33-3.60] (<0.01)	2.80 [1.61-4.90] (<0.01)	1.21 [0.39-3.80] (0.74)
Valvular	1.24 [1.11-1.39] (<0.01)	1.26 [1.10-1.46] (<0.01)	1.24 [1.04-1.49] (0.02)
Other	1.37 [1.21-1.54] (<0.01)	1.41 [1.21-1.64] (<0.01)	1.32 [1.09-1.60] (<0.01)

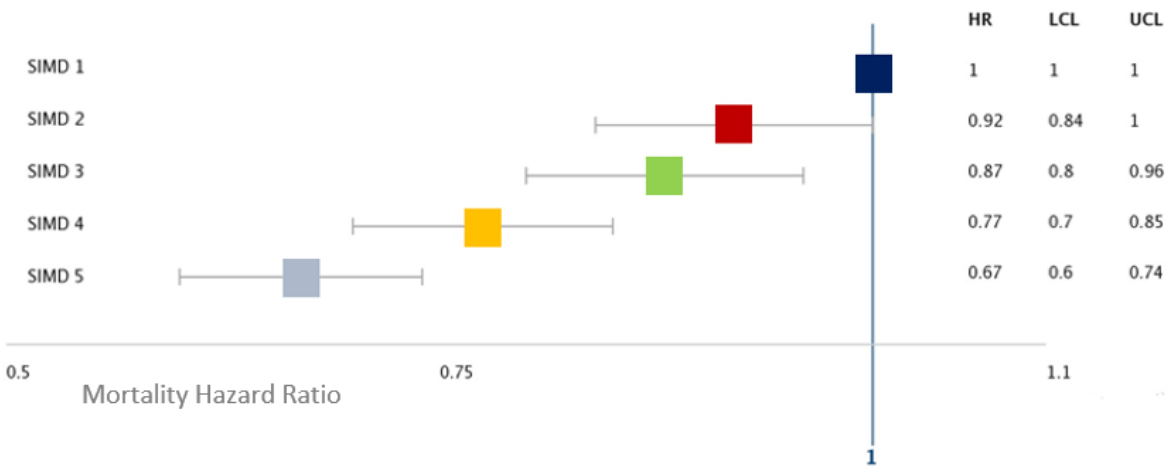


Figure 7-5: Forrest plot comparing adjusted hazard ratios for all-cause mortality according to Scottish index of multiple deprivation (SIMD) quintile.
SIMD 1 refers to the highest levels of deprivation and SIMD 5 the lowest

7.3.4 Cause of death according to socioeconomic deprivation

Cause of death for each congenital lesion is summarised for those with lower deprivation in Figure 7-6 and higher deprivation in Figure 7-7. Data regarding the general population (of all socioeconomic groups) is provided for comparison.

For the total CHD cohort, IHD was the most frequent cause of death irrespective of high (24.7%) or low (22.8%) level socioeconomic deprivation. In both groups, malignancy was the next most frequent specific cause of death (13.5% for higher and 13.4% for lower deprivation). In fact, there was no significant difference in the proportional distribution of cause of death according to high and low level socioeconomic deprivation, p=0.10. This is also true when comparing cause of death for high and low level socioeconomic deprivation for each of the CHD lesion groups (ASD p=0.79, PDA p=0.69, VSD p=0.43, aortic lesions p=0.39, Ebstein's anomaly p=0.20, AVSD p=0.07, TOF p=0.40, systemic RV p=0.48, Fontan p=0.87, complex lesions p=1.00, valvular lesions p=0.61, other lesions p=0.84).

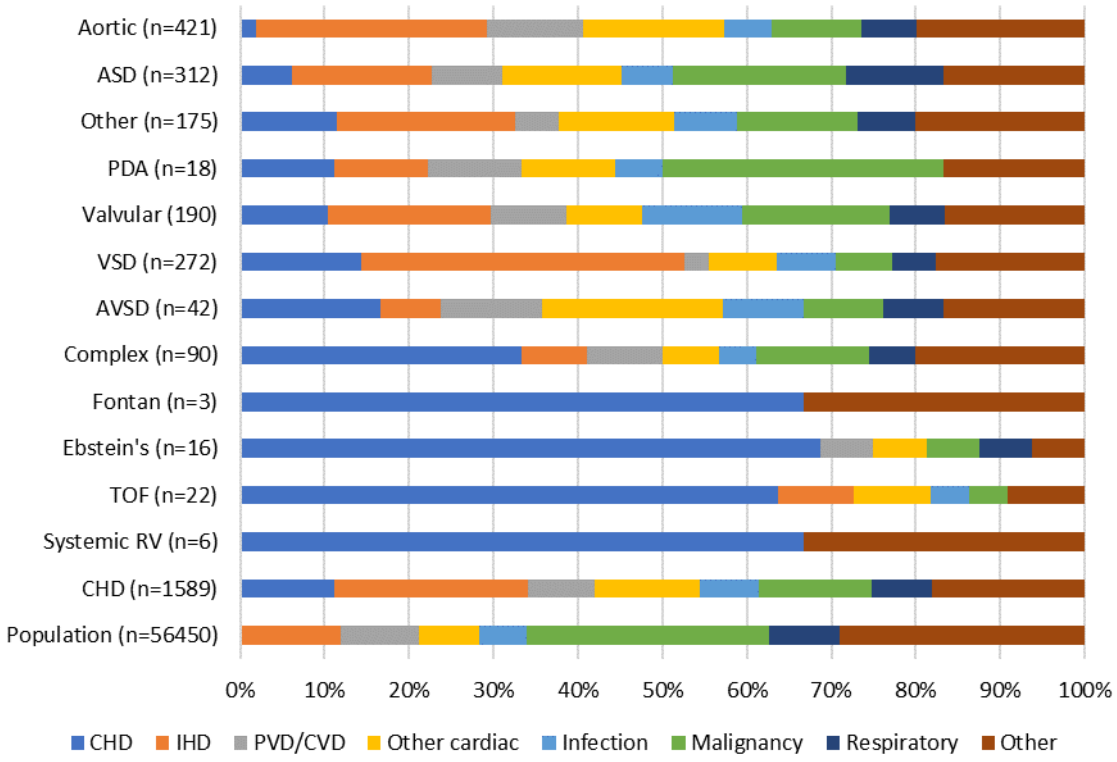


Figure 7-6: Proportional distribution of cause of death for each congenital lesion and compared to the general population- Lower deprivation (SIMD deciles 6-10).

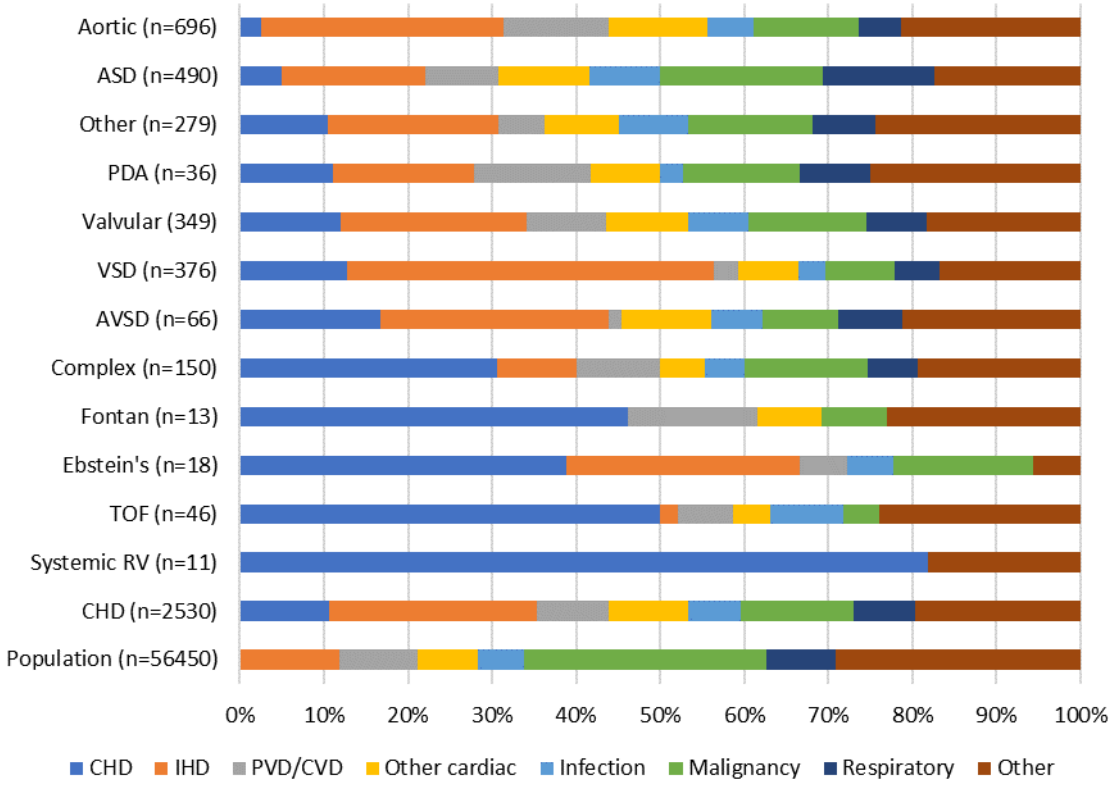


Figure 7-7: Proportional distribution of cause of death for each congenital lesion and compared to the general population – Higher deprivation (SIMD deciles 1-5).

Over the total data period, death due to cardiovascular causes predominates for those exposed to higher levels of socioeconomic deprivation (53.8%) and those exposed to lower levels (55.2%), with no significant difference between the two groups (p=0.38).

Cause of death according to SIMD quintile, irrespective of underlying lesion is summarised in Figure 7-8.

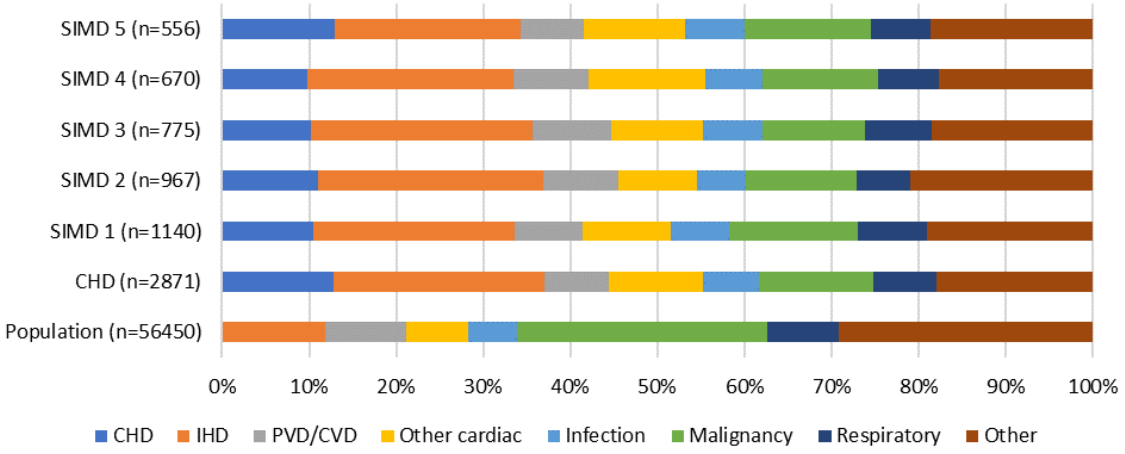


Figure 7-8: cause of death according to Scottish index of multiple deprivation (SIMD) quintile and compared to the general population

Figure 7-9 illustrates the changing proportion of CV to non-CV deaths throughout the data period for those with lower levels of socioeconomic deprivation (SIMD deciles 6-10), and Figure 7-10 those with higher level (SIMD 1-5). In both cases, data from the general population (of all SIMD groups) is provided for comparison.

The proportion of cardiovascular deaths fell throughout the data period for both lower (from 74.4% to 39.7%) and higher (from 72.0% to 39.9%) socioeconomic deprivation groups. The proportion of cardiovascular to non-cardiovascular deaths did not vary significantly between the higher and lower socioeconomic groups at any time cohort other that 2001-2005 where a higher proportion of cardiovascular deaths were seen in the lower socioeconomic deprivation group (65.1% compared with 56.4%, p=0.03). Over the course of the data period CV deaths fell by 1.16% per year amongst those with lower socioeconomic

deprivation and by 1.07% per year amongst those with higher level socioeconomic deprivation (p=0.84).

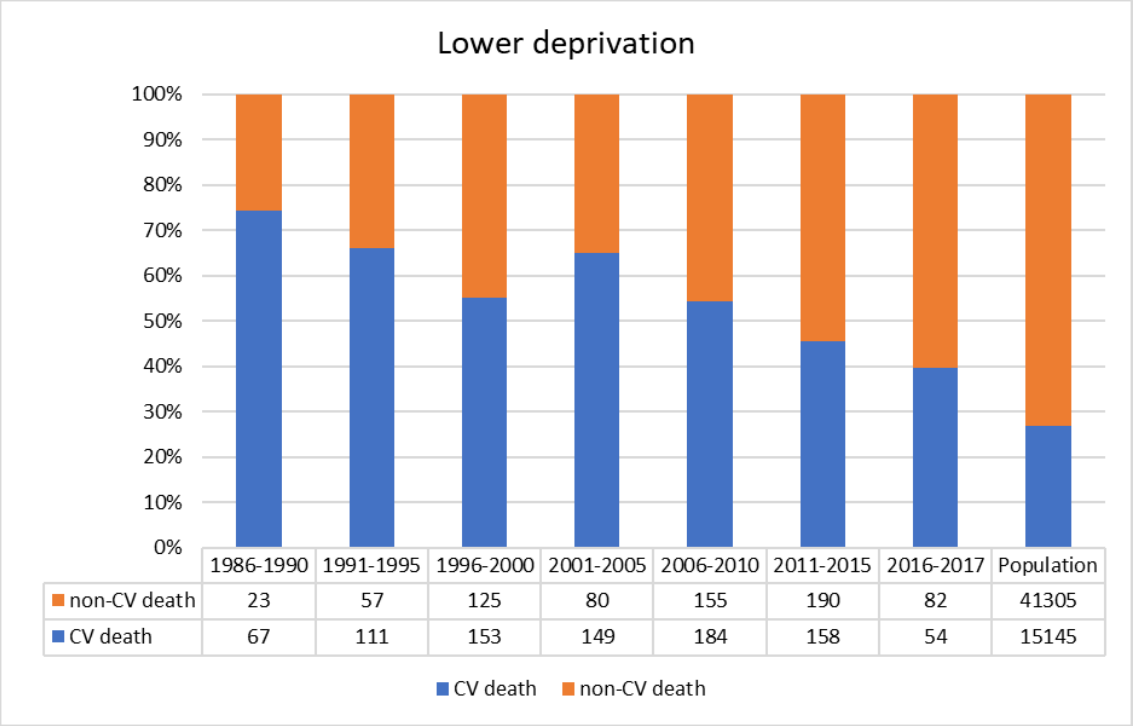


Figure 7-9: Proportional distribution of cardiovascular and non-cardiovascular deaths over time and compared to the general population in 2016 Lower deprivation (SIMD deciles 6-10).

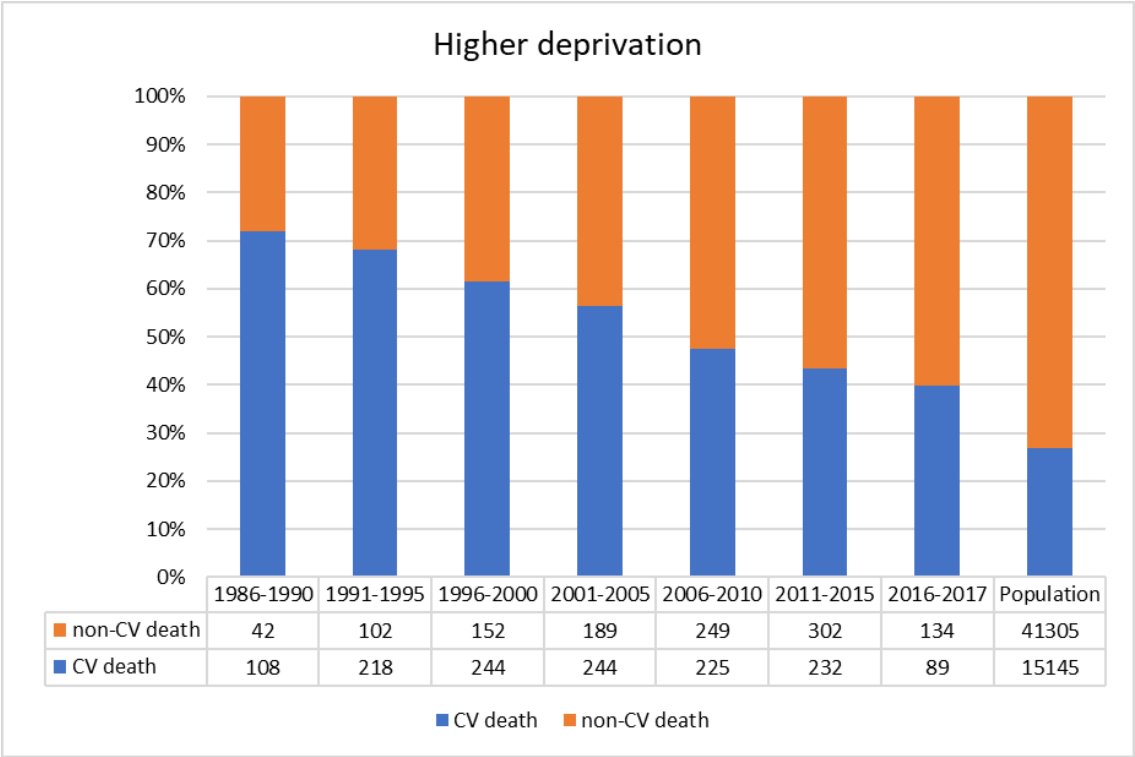


Figure 7-10: Proportional distribution of cardiovascular and non-cardiovascular deaths over time and compared with the general population in 2016 Higher deprivation (SIMD deciles 1-5).

7.4 Discussion

A limited number of studies have previously demonstrated an increased birth incidence of congenital heart disease amongst those from areas of high socioeconomic deprivation (158,159). It has been postulated in these prior studies that there may be an environmental causative aetiology related to socioeconomic deprivation. Alternatively, Sheridan et al. suggest that consanguinity is a major contributing factor to non-chromosomal congenital anomaly (although not specific to heart disease) (160) and Knowles et al suggest higher levels of consanguinity in areas of higher socioeconomic deprivation as one possible explanation (133). Although UK based, these studies are predominantly composed of patient cohorts from southern England and proposed explanations are not necessarily reproducible in the Scottish population.

Our finding that high level socioeconomic deprivation persists in adulthood provides a further potential explanation. Although few congenital heart defects express Mendelian patterns of inheritance, it is well established that incidence is increased in the offspring of those effected (161). It may therefore be the case that higher levels of socioeconomic deprivation are as a result of reduced availability or attainment in education, as has previously been described by Oster *et al* (162), or employment, as described by Kamphuis *et al*. (46), amongst those with CHD. Socioeconomic deprivation ensues and resultant birth incidence amongst these individuals is naturally higher than the population average.

Despite the founding and driving principles which manifest equal access to healthcare in the NHS, health inequalities in the UK are well documented and this has been shown to include excess mortality for cardiovascular disease in general (154). Our findings confirm excess mortality amongst adults with congenital heart disease who experience higher socioeconomic deprivation. Our Kaplan-Meier estimation of survival according to socioeconomic deprivation suggest a significant effect, and this is augmented by the adjusted models, particularly by accounting for the younger age in the higher socioeconomic deprivation groups. This excess in mortality is not exclusive to those experiencing the very highest levels of deprivation but appear to be on a continuum as socioeconomic deprivation increases. What is not clear from these analyses is whether mortality in ACHD is disproportionately influenced by

socioeconomic deprivation as compared to the general population. Unfortunately, NRS do not stratify mortality data, including mortality rates, by SIMD. This would permit calculation of standardised MRs. Another option in future analyses would be to utilise a population matched cohort, which would provide a substrate by which to compare adjusted hazard ratios according to SIMD for those with ACHD and those without.

Tackling the question as to why CHD patients experience higher levels of socioeconomic deprivation is complex. Despite improved early identification and management of CHD, the majority of moderately and greatly complex CHD requires surgical intervention in childhood. This has an educational implication for school age children who may need to take significant time away for health reasons. This is backed up by previous evidence suggesting that basic secondary school and higher educational attainment is significantly reduced in long term survivors of CHD (163). Education is both a direct facet of socioeconomic deprivation (being factored into many composite measures, including SIMD) and has obvious implications for future income which is the single biggest determinant. A similar pattern is seen with employment: Individuals with CHD show less job participation than the general public and those with complex CHD less than those with simple (46). As most recognised metrics of socioeconomic deprivation are postcode derived (including SIMD), for epidemiological purposes the socioeconomic status of children and young adults will often be defined by that of their parents as long as they share a household. The demands of looking after a dependant with congenital heart disease are often major and it has been shown that significant childhood illness (albeit not specific to CHD) does significantly impact parental earning potential (164). And even out with shared house occupancy, parental socioeconomic status is an established determinant in the child's 'socioeconomic potential' (165).

In Scotland, care for adults with CHD is delivered via a 'hub and spoke' structure. What this means in real terms is that most patients will receive at least some of their care in the single referral centre at the Golden Jubilee National hospital in Clydebank, and for those with more complex disease this may be the majority or all of their care. For those individuals who reside remote to this site, a significant financial burden may result, both in relation to

travelling costs and time out of employment, which despite the efforts of the clinical and management teams cannot be completely negated.

Although the age at death has increased over time for all levels of socioeconomic deprivation, worryingly the greatest increase in age at death is seen for those experiencing least socioeconomic deprivation, raising the possibility that the effect of socioeconomic deprivation is increasing. It may be argued that the younger age at death in areas of higher socioeconomic deprivation could be explained by the phenomenon where individuals born with the most severe forms of CHD survive childhood to die early in adulthood where they previously would not have survived to inclusion in cohorts such as this. This would appear unlikely as lesion severity was seen to be evenly distributed throughout the strata of socioeconomic deprivation.

Women with CHD are exposed to greater levels of socioeconomic deprivation than men with CHD (see sections 6.2.1 and 6.3.1). This is not the case in the general population. The reasons for this are not clear and likely to be complex. The prospect that women may suffer a disproportionate financial burden due to perceived or actual disability is concerning. One theory centres around pregnancy and fertility. It is regularly proposed that the gender pay gap within the general population may be at least in part explained by maternity and the impact that this has on employment (166). In CHD, maternity and fertility are affected. Pregnancies are frequently more complex and spontaneous miscarriage rates are higher (167). It is logical, albeit conjecture, that this may magnify any proposed effect that maternity imposes on earning capacity, the most heavily weighted of the socioeconomic deprivation domains.

In terms of comorbidity, diabetes was more common when socioeconomic deprivation was high. Although HTN, AMI and other forms of IHD were not more common in areas of high socioeconomic deprivation these established risk factors for mortality are directly correlated to increasing age and since individuals from areas of high socioeconomic deprivation were significantly younger, this apparent equivalence in comorbidity may actually suggest a relative excess where socioeconomic deprivation is high. Interestingly, on multivariate regression, ischaemic heart disease without AMI appears protective against all cause mortality when socioeconomic deprivation is low but not high.

This may represent more aggressive risk factor modification within this cohort, reflecting better access to health services and therapies.

Although socioeconomic deprivation is associated with excess all cause and cardiovascular mortality, the greatest excess is seen with non-cardiovascular mortality. Indeed, the proportion of CV deaths is comparable between high and low deprivation groups and changes over time are mirrored. This may suggest that the increased mortality associated with socioeconomic deprivation is significantly or even completely driven by background population effect, albeit with disproportionate deprivation amongst CHD patients.

7.5 Conclusions

Adults with CHD experience higher socioeconomic deprivation than the general population. Women with ACHD experience higher socioeconomic deprivation than men.

Deprivation is associated with excess mortality amongst individuals with CHD.

Comparative studies are needed to establish to what degree the association between mortality and socioeconomic deprivation is governed by population effect and to what degree it is specific to CHD. Irrespective of the cause, the disproportionate deprivation suffered by CHD patients must be addressed. This is a complex issue, but as clinicians we can start by remaining mindful to the socioeconomic and financial implications of our decisions and recommendations. Individualising care to minimise time away from education and employment and permitting local care where possible or requested may go some way to minimising the burden for our patients. From an institutional and organisational perspective, the findings presented here should be borne in mind when advocating for the needs of our patient population.

8 Survival and circumstances of death according to lesion complexity

8.1 Introduction

The diverse range which constitutes the spectrum of congenital heart disease proves one of its greatest barriers to study. This has been touched on in earlier Chapters but merits further discussion here. The number of individual ICD codes which correspond to congenital lesions ranges into the hundreds and even within each code significant variability may exist. This thesis has already described the unequivocal increase in prevalence of ACHD over time but in spite of this, most individual congenital heart lesions/diagnoses remain uncommon or frankly rare. This poses a problem when one wishes to consider outcomes, as a well-defined patient population of sufficient size to allow generalisation is rarely forthcoming. This predicament is not limited to ACHD as an academic pursuit, and in fact it is from clinical practice that the most commonly rendered solution has been established. The 2001 'Task force' for the changing profile of congenital heart disease acknowledged and attempted to redress the problem of health service allocation where disease classification had previously proven unhelpful (42). The resultant system of classifying all ACHD as one of three categories pertaining to simple, moderate, or great complexity, provides a much-simplified reference aid with the intended purpose of informing health services at a provision level as to the anticipated requirement for referral centres and ACHD specialists. It is worth emphasising that this classification system was devised to predict need for specialist services and pertains to complexity of care needs and inference of outcomes such as mortality was never proposed.

Irrespective of the intended utility of the 'Bethesda' classification of ACHD it has become common place in the literature that cohorts be stratified by this system or a modification of this system (118,121,147,168). In general a positive correlation between lesion complexity and excess mortality has been reported (44,121). However, there has been some ambiguity as to the relative implications on mortality conferred by lesion complexity when compared to the general population. This has been most notable amongst those with 'simple' lesion which have been variably reported to confer similar survival prospects to the general population (88,169) and significantly higher mortality (118,170,171). The changing survival prospects over time have never been directly factored into this debate.

8.2 Results

8.2.1 Baseline characteristics and demographics according to lesion complexity

Classification of lesion complexity could be achieved for 12,974 (78.9%) of the total study population. Simple CHD was most common, representing 62.6% with complex CHD least common with 10.2%.

A comparison of the baseline characteristics according to lesion complexity is shown in Table 8-1. Significant heterogeneity across the complexity groups is observed for all baseline characteristics other than SIMD quintile group. Women are more common amongst those with simple CHD (proportion women 52.7%), and men amongst complex CHD (proportion women 47.5%), p<0.01. Age at entry to the data set was younger amongst those with complex CHD (mean 25.9, SD 17.8, median 16, IQR 16-28.5) compared to simple (mean 37.3, SD 21.5, median 33, IQR 16-35) or moderate (mean 39.8, SD 26, median 29, IQR 16-65). Comorbidity was more common in simple and moderate CHD than was seen for complex CHD. This was true for all recorded comorbid diagnoses. There was no significant difference in baseline socioeconomic grouping across complexity of CHD (p=0.42).

Table 8-1: Study population characteristics according to lesion complexity

	All (%)	Simple (%)	Moderate (%)	Complex (%)	p value
All	12974	8121 (62.6)	3529 (27.2)	1324 (10.2)	<0.01
Female	6639 (51.2)	4280 (52.7)	1730 (49.0)	629 (47.5)	<0.01
Age at entry, mean (SD)	36.8 (22.9)	37.3 (21.5)	39.8 (26.1)	25.9 (17.8)	<0.01
Comorbidity					
Diabetes	423 (3.3)	265 (3.3)	139 (3.9)	19 (1.4)	<0.01
Cancer	276 (2.13)	151 (1.9)	109 (3.1)	16 (1.2)	<0.01
AF	1250 (9.6)	728 (8.9)	434 (12.3)	88 (6.7)	<0.01
CVD	763 (5.9)	613 (7.6)	132 (3.7)	18 (1.4)	<0.01
HTN	696 (5.4)	381 (4.7)	283 (8.0)	32 (2.4)	<0.01
AMI	589 (4.5)	409 (5.0)	171 (4.9)	9 (0.7)	<0.01
Other IHD	997 (7.3)	596 (7.3)	365 (10.3)	36 (2.7)	<0.01
SIMD quintile	12833				
1 - most deprived	3447 (26.9)	2202 (27.4)	892 (25.5)	353 (27.0)	
2	2757 (21.5)	1695 (21.1)	794 (22.7)	268 (20.5)	
3	2400 (18.7)	1483 (18.5)	666 (19.1)	251 (19.2)	0.417
4	2172 (16.9)	1353 (16.8)	590 (16.9)	229 (17.5)	
5 - least deprived	2057 (16.0)	1300 (16.2)	552 (15.8)	205 (15.7)	

Individuals with moderate lesions were more frequently observed to die during follow up (1124 of 3529, 31.9%) than simple (1529 of 8121, 18.8%) or complex (218 of 1324, 16.5%) CHD, p<0.01. Table 8-2 illustrates the demographics and baseline characteristics for those who survived and those who died during follow up for simple, moderate and complex CHD. Those who died during follow up were older at entry to the data set for each lesion complexity. Individuals with complex CHD who died during follow up were younger at entry to the data set than those with simple or moderate CHD who died, p<0.01.

The proportion of men and women who died during follow up were comparable among those with simple lesions (18.6% and 19.1% respectively, p=0.12) and complex lesions (16.3% and 16.7% respectively, p=0.59). For moderate lesions, more women died than men (37.2% and 31.9%, p<0.01). For all socioeconomic groupings the proportion of those who died during follow up was greater amongst those with moderate lesions than simple or complex, p<0.01. A greater proportion of those with moderately complex CHD who have comorbidity died during follow up that those with simple or complex CHD. This was significant for all recorded comorbidity other than cancer (p=0.21).

Table 8-2: Demographics of those with simple, moderate, and complex lesions for those who survived and those who died during follow up. The p value compares the proportion of those who died

	Simple		Moderate		Complex		
	Alive (%)	Dead (%)	Alive (%)	Dead (%)	Alive (%)	Dead (%)	p value
All	6592 (81.2)	1529 (18.8)	2405 (68.2)	1124 (31.9)	1106 (83.5)	218 (16.5)	<0.01
Mean age at entry (SD)	31.8 (18.3)	60.9 (18.2)	27.6 (18.1)	65.8 (21.3)	22.9 (14.6)	41.3 (23.5)	<0.01
Female	3485 (81.4)	795 (18.6)	1087 (62.8)	643 (37.2)	524 (83.3)	105 (16.7)	<0.01
Male	3107 (80.9)	734 (19.1)	1318 (73.3)	481 (31.9)	582 (83.7)	113 (16.3)	<0.01
SIMD							
1	1772 (80.5)	430 (19.5)	599 (67.2)	293 (32.9)	294 (83.3)	59 (16.7)	<0.01
2	1353 (79.8)	342 (20.2)	502 (63.2)	292 (36.8)	215 (80.2)	53 (19.8)	<0.01
3	1219 (82.2)	264 (17.8)	451 (67.7)	215 (32.3)	209 (83.3)	42 (16.7)	<0.01
4	1117 (82.6)	236 (17.4)	411 (69.7)	179 (30.3)	191 (83.4)	38 (16.6)	<0.01
5	1064 (81.9)	236 (18.2)	416 (75.4)	136 (24.6)	181 (88.3)	24 (11.7)	<0.01
Comorbidity							
Diabetes	131 (49.3)	134 (50.6)	38 (27.3)	101 (72.7)	7 (36.8)	12 (63.2)	<0.01
Cancer	50 (33.1)	101 (66.9)	26 (23.9)	83 (76.2)	6 (29.7)	10 (62.5)	0.21
AF	413 (56.7)	315 (43.3)	126 (29.0)	308 (71.0)	55 (62.5)	33 (37.5)	<0.01
CVD	503 (82.1)	110 (17.9)	42 (31.8)	90 (68.2)	10 (55.6)	8 (44.4)	<0.01
HTN	269 (70.6)	112 (29.4)	122 (43.1)	161 (56.9)	19 (59.4)	13 (40.6)	<0.01
AMI	112 (27.4)	297 (72.6)	40 (23.4)	131 (76.6)	6 (66.7)	3 (33.3)	0.02
Other IHD	367 (61.6)	229 (38.4)	114 (31.2)	251 (68.8)	21 (58.3)	15 (41.7)	<0.01

8.2.2 Follow up and age at death

A cumulative follow up of 136,247 years was achieved amongst those for whom complexity could be determined. Those with simple lesions accumulated the greatest follow up (85,347 years) followed by moderate (36,265 years) then complex (14,635 years) CHD. The observed, crude mortality rate was greatest for those with moderate complexity (31.0 deaths per 1000 person years, 95% CI 29.2-32.9) followed by simple (17.9 deaths per 1000 person years, 95% CI 17.0-18.8) then complex CHD (14.9 deaths per 1000 person years, 95% CI 13.0-17). Table 8-3 summarises follow up, crude mortality rate and age at death according to complexity of CHD.

Table 8-3: Comparison of follow up, crude mortality rate and age at death for each lesion complexity

	N	Follow up (years)	Mortality rate per 1000 years (95%CI)	Mean age at death (SD)
All	12974	136247	21.1 (20.3-21.9)	67.3 (19.6)
Lesion complexity				
Simple	8121	85347	17.9 (17.0-18.8)	67.0 (17.4)
Moderate	3529	36265	31.0 (29.2-32.9)	71.3 (19.6)
Complex	1324	14635	14.9 (13.0-17.0)	48.1 (22.8)
				p<0.01

Mean age at death was lower for those with complex CHD (48.1 years, SD 22.8, median 45.5, IQR 28-69) than simple (67.0 years, SD 17.4, median 71, IQR 57-80), or moderate (71.3 years, SD 19.6, median 77, IQR 63-85), p<0.01, with the higher age at death amongst moderate compared to simple lesions also being significant, p<0.01. Figure 8-1 compares the mean age at death during the first and second half of the data period for each lesion complexity. A significant increase in mean age at death was observed for all degrees of complexity from the first to the second half of the data period (simple; 64.3 and 68.2 years, p<0.01, moderate; 68.9 and 71.9 years, p=0.03, complex;.39.7 and 50.5 years, p<0.01).

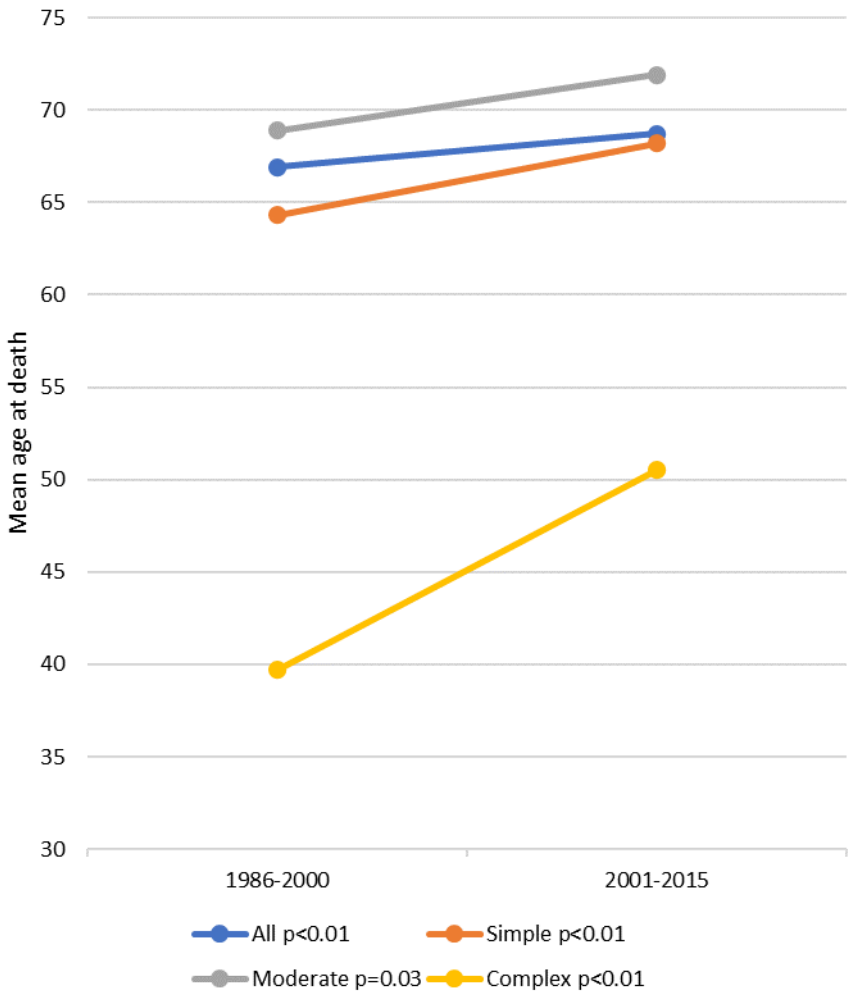


Figure 8-1: Mean age at death for all patients and according to lesion severity, comparing the first and second half of the data period Significance level for each change provided.

8.2.3 Survival according to lesion complexity

Multivariate, adjusted hazard ratios for all-cause mortality conferred by baseline characteristics for each degree of CHD complexity are summarized in Table 8-4.

Male sex did not confer a risk of mortality for moderate or complex CHD (p=0.07 and 0.58 respectively) but did confer an increased mortality risk for simple lesions (HR 1.41, 95% CI 1.27-1.57, p<0.01). Survival was better amongst those in socioeconomic groups with lowest deprivation across all degrees of lesion complexity. Amongst those with simple lesions, a consistent reduction in hazard was noted for each increment of SIMD. Amongst those with moderate and complex lesions the interaction was more complex.

Survival improved over time for all degrees of lesion complexity. Amongst those with simple and moderately complex lesions, survival according to year of presentation improved in a linear manner. For complex lesions survival improved greatly from the earliest to the second time period (HR 0.63, 95% CI 0.42-0.96, p=0.03) with only a small change in point estimates from then on.

A similar pattern of survival was conferred by comorbidity across all lesion complexity cohorts, although AMI did not predict mortality in those with complex lesions (HR 0.53, 95% CI 0.16-1.70, p=0.29) but did in simple (HR 1.87, 95% CI 1.61-2.16, p<0.01) and moderately complex (HR 1.33, 95% CI 1.10-1.61, p<0.01) CHD.

Table 8-4: Hazard of all-cause mortality according to baseline characteristics for simple, moderate, and complex lesions

	HR [95% CI] (p value)		
	Simple	Moderate	Complex
Female	1	1	1
Male	1.41 [1.27-1.57] (<0.01)	1.12 [0.99-1.27] (0.07)	1.08 [0.82-1.42] (0.58)
Age	1.08 [1.07-1.08] (<0.01)	1.07 [1.06-1.07] (<0.01)	1.06 [1.05-1.07] (<0.01)
SIMD Quintile			
1 - most deprived	1	1	1
2	0.83 [0.72-0.96] (0.01)	0.95 [0.81-1.12] (0.56)	1.10 [0.75-1.62] (0.61)
3	0.80 [0.68-0.93] (<0.01)	1.00 [0.83-1.19] (0.97)	0.74 [0.49-1.11] (0.14)
4	0.69 [0.59-0.81] (<0.01)	0.75 [0.62-0.91] (<0.01)	0.83 [0.54-1.27] (0.39)
5 - least deprived	0.69 [0.58-0.81] (<0.01)	0.58 [0.47-0.72] (<0.01)	0.52 [0.32-0.86] (0.01)
Year of Presentation			
1986-1990	1	1	1
1991-1995	0.89 [0.76-1.05] (0.16)	0.85 [0.64-1.13] (0.28)	0.63 [0.42-0.96] (0.03)
1996-2000	0.67 [0.55-0.82] (<0.01)	0.65 [0.50-0.84] (<0.01)	0.62 [0.39-0.98] (0.04)
2001-2005	0.46 [0.39-0.55] (<0.01)	0.51 [0.39-0.68] (<0.01)	0.70 [0.39-1.28] (0.25)
2006-2010	0.36 [0.30-0.44] (<0.01)	0.54 [0.40-0.73] (<0.01)	0.41 [0.23-0.71] (<0.01)
2011-2015	0.28 [0.23-0.35] (<0.01)	0.34 [0.24-0.49] (<0.01)	0.53 [0.29-0.97] (0.04)
Comorbidity			
Diabetes	1.61 [1.34-1.94] (<0.01)	1.60 [1.29-1.98] (<0.01)	1.91 [0.99-3.71] (0.05)
Cancer	2.06 [1.67-2.53] (<0.01)	1.31 [1.04-1.65] (0.02)	1.82 [0.88-3.78] (0.11)
AF	1.15 [1.00-1.32] (0.04)	1.26 [1.10-1.44] (<0.01)	0.92 [0.60-1.43] (0.72)
CVD	0.85 [0.69-1.04] (0.11)	1.15 [0.92-1.43] (0.21)	1.90 [0.90-4.05] (0.09)
HTN	0.94 [0.77-1.15] (0.77)	1.04 [0.87-1.23] (0.69)	0.96 [0.51-1.81] (0.89)
AMI	1.87 [1.61-2.16] (<0.01)	1.33 [1.10-1.61] (<0.01)	0.53 [0.16-1.70] (0.29)
Other IHD	0.79 [0.68-0.92] (<0.01)	1.07 [0.92-1.24] (0.38)	0.84 [0.48-1.49] (0.56)

Figure 8-2 compares survival from all cause, cardiovascular and non-cardiovascular mortality for simple, moderate and complex CHD. Survival estimates are adjusted for all measured baseline characteristics as summarised

in Table 8-4. Increased hazard for all cause, CV and non-CV mortality was noted for moderate and complex CHD when compared to simple (although this does not achieve statistical significance for non-CV mortality amongst those with moderately complex CHD). Point estimates suggest that CV mortality is most strongly associated with increasing lesion complexity.

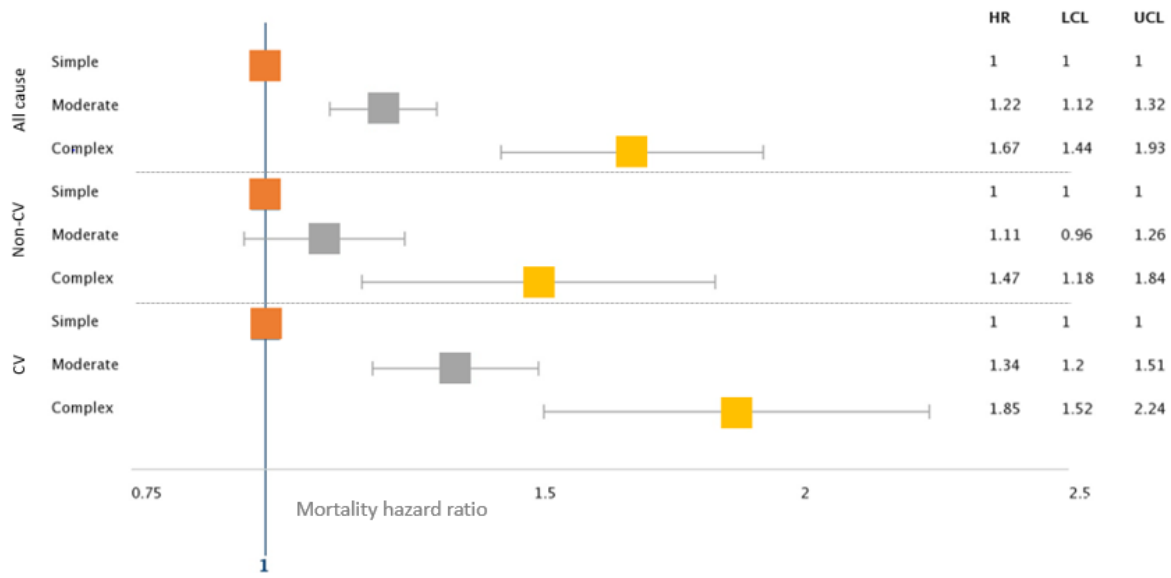


Figure 8-2: Adjusted hazard ratios for all cause, cardiovascular, and non-cardiovascular mortality comparing simple, moderate and complex lesions

8.2.4 Cause of death according to lesion complexity

Cause of death according to CHD complexity and compared to the full CHD cohort and the general population is shown in Figure 8-3. Compared to the general population more deaths are due to cardiovascular causes (CHD, IHD, PVD/CVD and other cardiac) and fewer are attributable to malignancy in the study cohort. According to lesion complexity, a similar proportion of deaths are by cardiovascular causes. However, for those with complex CHD this is predominantly accounted for by deaths attributed directly to CHD and for those with simple and moderately complex CHD by ischaemic heart disease.

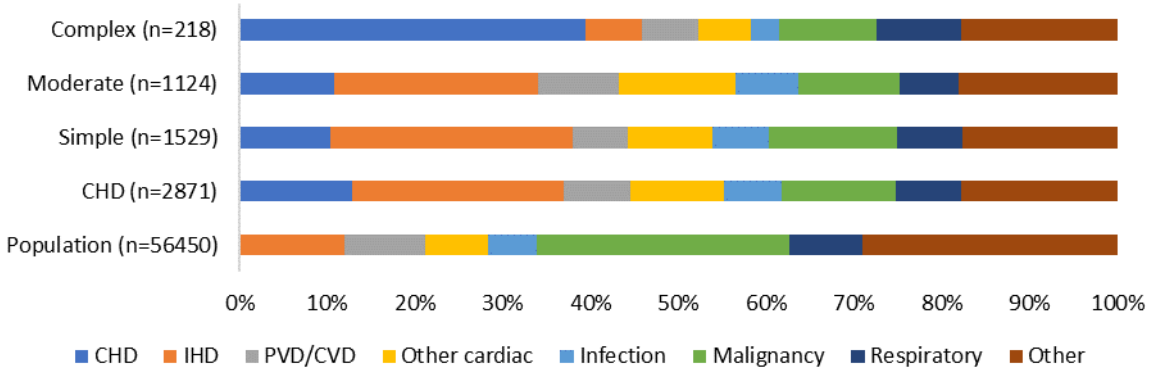


Figure 8-3: Cause of death according to lesion complexity and compared to the entire study cohort and the general population

The changing proportion of cardiovascular and non-cardiovascular deaths over time, according to lesion complexity are shown in Figure 8-4. Across all cohorts of lesion complexity, the proportion of cardiovascular deaths decreases and trends towards that of the general population. During the most contemporary time cohort a similar proportion of deaths were by CV causes for simple (43.1%), moderate (42.5%) and complex (42.3%) CHD. For simple and moderately complex lesions the proportion of cardiovascular deaths begins to decrease from the beginning of the data period and continues in gradual manner. For complex CHD the proportion of cardiovascular deaths is not seen to decrease until halfway through the data period but then declines rapidly from 2005 onwards. The trend of proportions of cardiovascular deaths are compared in Figure 8-5.

From the earliest to current time period, the proportion of CV deaths fell amongst those with simple lesions by a total of 28.25% equating to 1.23% per year. This is compared to a 22.7% amongst the general population over the total time period ($p<0.01$) and 0.73% per year, $p=0.09$. For moderately complex lesions, CV deaths fell by 51.6% over the total data period ($p<0.01$), corresponding to a 1.66% reduction per year, $p<0.01$ (as compared to population change). For lesions of great complexity, CV deaths decreased by a total of 30.42% over the data period ($p=0.04$), corresponding to 0.98% per year, $p=0.74$ (as compared to population change).

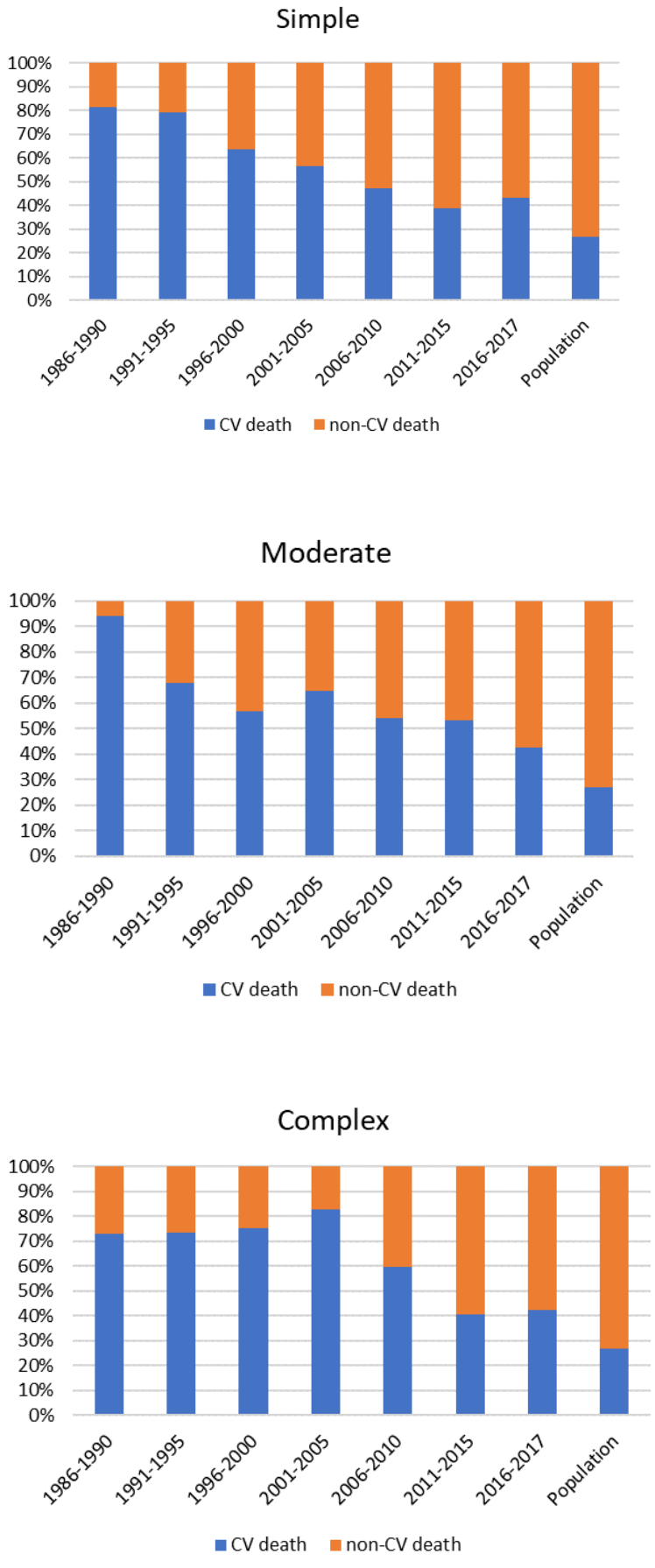


Figure 8-4: the proportion of cardiovascular and non-cardiovascular deaths over time according to ACHD complexity and compared to that of the general population in 2015

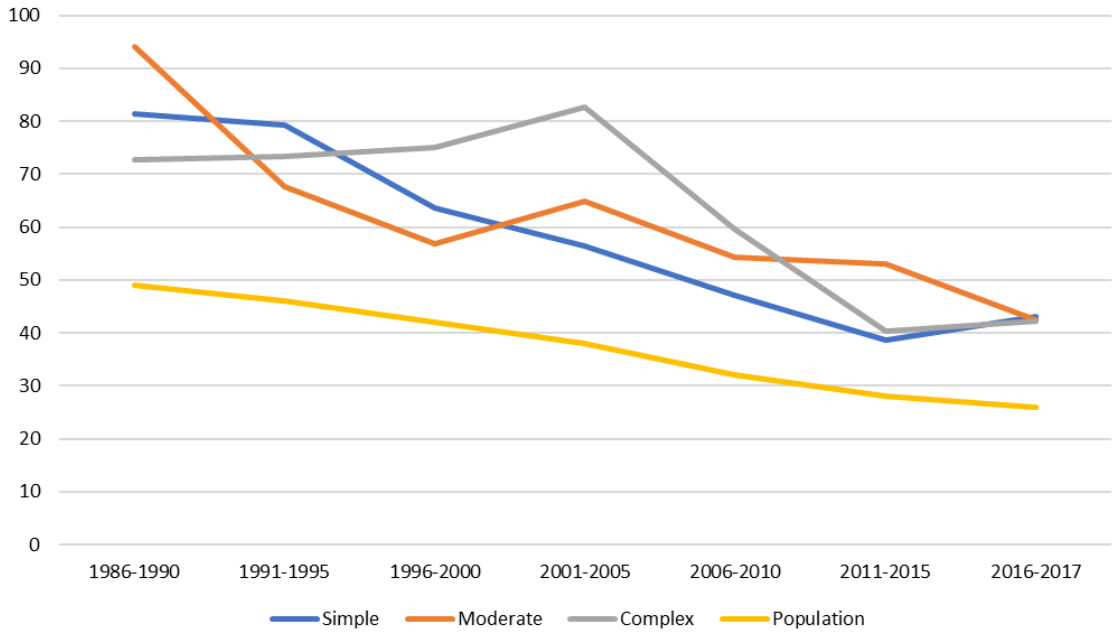


Figure 8-5: The changing proportion of cardiovascular deaths over time, comparing simple, moderate and complex lesions as well as the general population.

8.3 Discussion

The concept of categorising CHD lesions by degree of complexity was intended to aid with the planning and provision of specialised health care. Despite this, it has become common place for stratification by lesion complexity to be used when comparing outcomes, particularly mortality, within the published literature.

Women predominate amongst the group with simple lesions as expected, in line with the abundance of shunt lesions which are established to occur more frequently in women (55). Similarly, the male predisposition of complex lesions is explained by the inclusion of conotruncal lesions which occur more commonly in men (62). The relatively low crude mortality rate associated with complex when compared to simple and moderate lesions is most readily explained by the younger age at inclusion amongst those with complex lesions. This follows logic as these individuals are more likely to have presented to the data via intervention in the paediatric sector and followed hence forth. Indeed, age at death is significantly lower for those with complex CHD when compared with simple and moderate. This should be considered in the context of the relative sparsity of complex CHD in the adult population, particularly at the inception of our data period. In the 1980s, childhood death remained common amongst those with the most complex CHD (56) and as a result, follow up and management protocols and guidelines for these individuals in the adult sector were less well defined than today.

Age at death was seen to increase for all categorise of lesion complexity but this was most marked for lesions of great complexity. From the first to the second half of the data period mean age at death increased by 3.9 years and 3.0 years for simple and moderate lesions respectively. This may well be explained simply by population effects as the mean life expectancy in Scotland covering the same time periods increased by 3.2 years (123). In comparison, the mean age at death for complex CHD increased by 10.8 years and although this does not truly equate to life expectancy it is likely to represent the more significant stepwise changes in the management of complex CHD such as the transition towards arterial as opposed to atrial switch operations in the late 1980s and early 1990s. This increase in age at death for complex CHD was somewhat unexpected as one may

presume a temporal shift towards mortality in early adulthood for some patients, reflecting improving survival in the paediatric sector. As a result, the temporal increase in age at death may be actually even greater than quoted for the majority of the greatly complex cohort.

Multivariate survival analysis confirms the increased mortality burden associated with moderate compared to simple CHD and complex compared to moderate or simple CHD. Interestingly, for moderate CHD this increased hazard is governed by the increased risk of cardiovascular mortality whereas with complex CHD a significantly increased hazard persists for both cardiovascular and non-cardiovascular mortality. This may well reflect the evolving knowledge of the multisystem impact of many of the complex congenital heart lesions. Fontan and univentricular circulations in particular are increasingly implicated in both acute and chronic pathology in the hepatic, renal and gastrointestinal systems (172–175). Additionally, complex CHD confers a risk of immunosuppression and infection (176), and of course maternal mortality is well described (177).

The interaction, or more accurately, lack of interaction between SIMD and CHD complexity on survival is worth mentioning. Table 8-4 illustrates that the magnitude of improved survival amongst those exposed to lowest levels of deprivation remains essentially constant across all lesion complexities. Socioeconomic deprivation has most closely been linked to mortality associated with acquired lifestyle risk factors such as tobacco smoking, diet and exercise (178). One may expect that this would disproportionately influence the survival of those with more simple CHD who tend to live longer and acquire more risk factors. Our finding that SIMD risk persists even in complex disease may reflect either the improved survival of complex patients, allowing for more influence of acquired risk; or that risk factors such as smoking, diet and exercise may be of additional importance among younger patients with more complex CHD, owing to more fragile physiological conditions. A third possibility, that those of lower socioeconomic grouping may have lesser availability to healthcare resources must also be considered. Similarly, health priorities may be different depending on socioeconomic status leading to lesser engagement in follow up or treatments. In fact Ellis *et al* (179) have previously demonstrated in a Scottish population wide cohort, albeit in primary care, that SIMD groups of higher

socioeconomic deprivation are more likely to repeatedly not attend appointments. Taking this finding into context with the cause of death data presented in Figure 8-3 it would seem that the acquired risk factors and resource availability influence rather than dictate mortality amongst those with complex CHD as a clear tendency towards death directly attributed to CHD is noted in comparison to simple and moderate CHD. This is most notably seen at the expense of deaths attributable to IHD which is of course classically associated with acquired risk factors and socioeconomic deprivation (180,181). It is also noteworthy that deaths by CV causes are higher amongst all degrees of lesion complexity when compared to the general population (Figure 8-3 and Figure 8-5). Although perhaps surprising, particularly for those with simple lesions, this is a finding echoed in previous studies, although the absolute risk imposed and underlying causes of death remain disputed and are recognised as an area for further study (37,182).

8.4 Conclusions

Age at death is significantly lower amongst those with complex compared to those with simple and moderate CHD. Age at death was seen to increase throughout the data period but this was most notable for complex CHD.

Cardiovascular mortality was greater amongst those with moderate compared to simple CHD and both cardiovascular and non-cardiovascular mortality was greater for those with complex CHD. Despite the most common primary cause of death amongst those with complex CHD being directly attributed to the underlying lesion, socioeconomic deprivation remains an important risk factor suggesting increased vulnerability to acquired risk factors and the possibility of inequalities in health service availability.

9 Final Discussion

9.1 Summary of findings

The aim of these studies was to delineate survival and mortality amongst adult survivors with congenital heart disease in Scotland. This has been outlined in terms of temporal trends as well as influencing factors such as sex, socioeconomic deprivation and disease complexity, both as observed and when adjusted for a range of clinical and demographic variables. Amongst this cohort survival was found to improve over time, for both sexes, across all lesions and degrees of ACHD complexity.

By using the SMR to identify records, we have accrued the largest patient cohort and cumulative follow up of Scottish ACHD amongst the available literature. Despite the pre-requisite of an in patient episode, crude prevalence estimations are similar to previously published literature, suggesting a significant capture rate of the total Scottish ACHD population.

The ACHD population of Scotland are a heterogenous group. At a population level, there are significant sex differences in ACHD. Simple lesions are more common in women and complex lesions in men. Women with ACHD are exposed to higher socioeconomic deprivation than men. Adjusted mortality is poorer for men than women particularly as a result of death due to non-cardiovascular causes. There is significant co-morbidity in adults with CHD particularly in older age groups. Coupled with improved temporal survival, this suggests an increasingly complex and multi-morbid patient cohort.

High level socioeconomic deprivation corresponds to reduced survival. This remains true when adjusted for sex, age, year of presentation, underlying lesion and co-morbidity. It is also true across all degrees of lesion complexity. Adults with CHD experience higher socioeconomic deprivation than the general population.

Increasing lesion complexity corresponds to higher adjusted mortality. Age at death increased throughout the study period for all degrees of complexity but this is most marked amongst lesions of great complexity.

9.2 Changes over time

In some respects, caring for individuals with congenital heart disease has become a victim of its own success. Perhaps the greatest challenge in the contemporary practice of ACHD cardiology will be adapting to cater for the increasing patient cohort driven by improved patient survival. At least this has been the rhetoric amongst literature from mainland Europe and North America in recent years (8,9,75). My study confirms a similarly improved survival amongst the Scottish ACHD population since the mid 1980s with an instantaneous risk of all-cause mortality estimated at 65% less for those with index presentations between 2011-2015 than those who presented in 1986-1990. Although this may appear simply to agree with the existing literature, my analyses are additive on several fronts. Prior studies, although sometimes large scale, tend to utilise single centre cohorts, recruited registries, or regional private health care remuneration databases. Non-selective population analyses based on point of care coding have not previously been used to describe temporal survival. This study design should reduce omission bias and is not vulnerable to interviewer bias. Although some attempt has been made to adjust analyses in prior published literature (33) this has been limited to sex, age and congenital lesion. Factors such as the presence of comorbidity and relative socioeconomic deprivation have not previously been factored. We have shown that temporal survival improves over time, independent of theses variables.

A further strength of these analyses has been the ability to include, by way of record linkage, cause of death data. As a result, and unique to the current literature we have demonstrated a significant and sustained trend away from cardiovascular and towards non-cardiovascular death. Of course, some of the ‘non-cardiovascular death’ may well be influenced by cardiovascular factors. For instance, Fontan operations have in recent years been identified as a major risk factor the development of hepatocellular carcinoma and so death as a result would be non-cardiovascular but the underlying ACHD remains a major determinant of this (172,183,184). The changing pattern remains important however as it is only now that adult survivors of Fontan operations are living longer, that this late complication has been discovered. Similar examples of non-cardiovascular death governed by the underlying ACHD could be argued in cases

of infective endocarditis or even with malignancies following high cumulative medical radiation exposure (185).

The shift from cardiovascular to non-cardiovascular death is noted for men and women, for those exposed to both high- and low-level socioeconomic deprivation, and for simple, moderate and complex ACHD. This finding adds significant detail to the idea of improved survival in ACHD. Without this knowledge, population level analysis showing significant improvements in survival could simply correspond to individually small changes in most or all individuals with CHD but impacting each individual little. Understanding that the mode of death has changed on a population level would challenge this argument and suggests more wholesale changes in the prognosis of this patient cohort.

9.3 Using mortality data to inform clinical practice

Despite the growing ACHD patient cohort, relative to other cardiology subspecialties, exposure to ACHD remains low. As a result training and experience in ACHD has been recognised as insufficient to meet current and prospective demands (186). Clearly the shortage of ACHD specialist consultants must be addressed. Perhaps more important than ensuring adequate staffing of centralised, specialist centres with advanced ACHD cardiologists, will be ensuring a more disseminated level of expertise via cardiologist with an interest in ACHD and generalists with an understanding. This is crucial as it is local Emergency Departments that will experience growing demand in treating ACHD emergencies and also managing non cardiological emergencies in patients with ACHD. Ensuring an adequate network of ACHD knowledge is available at all times to acute services in Scotland will be essential to support the needs of this growing patient cohort. This body of work has been presented to the National Services Division of the NHS and forms part of a consensus drive to the expansion of the SACCS remit. This includes; a growing consultant body; an expanding regional out-reach service; and plans for an out-of-hours on-call ACHD rota for the first time in Scotland. Further work is planned on a collaborative basis to inform service provision further.

Of course, the ACHD cohort is not simply growing, it is changing. The shift from cardiovascular to non-cardiovascular mortality is perhaps the best indicator of

this. It is telling that in some centres the term GUCH or ‘grown-up congenital heart disease’ remains. Adult congenital heart disease is deliberately favoured by the author as it better serves our patients as adults in their own right and not simply grown-up children. Although seemingly pedantic this is an important distinction which reminds us that practice has moved on. More individuals with ACHD than ever will be starting families, contributing to the work force, choosing to smoke tobacco, drink alcohol and be exposed to myriad other lifestyle factors common to adult medicine. In the most contemporary cohort in my analyses, 60% of all deaths and 57.7% of deaths in those with complex ACHD were due to non-cardiovascular causes. It is clear that a holistic approach to patient management is required for improvements to continue. It is no longer appropriate to simply optimise therapy related to ventricular function, assess rhythm control and consider haemodynamics upon specialist review. Following my analyses, a significant change in the proportion of my face-to-face clinic time is concentrated on the ‘bigger picture’ of risk factor modification, counselling and patient education.

Adults with CHD often have well established relationships with ACHD specialists as follow up is frequently lifelong. There is a risk that this can usurp the individual’s engagement with local services and general practitioners; why bother making a GP appointment when you are due to see the congenital team the following week? Being responsive to signs and symptoms other than those traditionally gleaned from the cardiology clinic visit is paramount. Malignancy was responsible for many of the non-cardiovascular deaths in this cohort. It goes without saying that red flags such as unexplained weight loss, change in bowel habit and chronic, unexplained cough should never be ignored, however systematic measures should be in place to ensure these findings are acted upon, particularly when the review is in a national centre, physically and systematically remote from the individuals usual health board, and therefore not necessarily subject to the usual mechanisms for local referral for tests and follow up.

According to my analyses, differences in ACHD amongst men and women are subtle and some differences seemingly non-modifiable such as the distribution of lesions by sex. Women were noted to present later in life more frequently than

men. This appears to be due to the increased prevalence of simple lesions, predominantly shunt lesions, which may be hidden until incidentally found subject to comorbidity or due to symptom onset later in life. Increased sensitivity of foetal ultrasound in recent years may improve the pick-up of some of these lesions, reducing this disparity (187). Also, with the increasing prevalence of CHD in the adult sector one would hope that the incidental pick-up rate during non-cardiovascular imaging such as non-cardiac CT or MRI may improve as experience grows in this arena. Clearly education and awareness to this end should be driven from within the ACHD community where possible.

More women than men with CHD reside in postcode areas corresponding to high level socioeconomic deprivation. The converse is also true, with fewer women than men residing in affluent areas. In fact, socioeconomic deprivation was higher for the total ACHD population than for the general population of Scotland and this deprivation was associated with premature mortality. This is true for CHD of simple, moderate and great complexity. To the best of my knowledge, no study has previously analysed socioeconomic deprivation amongst an adult cohort with CHD.

Clearly there will be important variation by which socioeconomic deprivation will influence outcomes in CHD on a global scale. One would assume that the UK would compare rather favourably in this regard as the NHS is frequently considered amongst the most, if not the most, equitable health care system in the world (188). Of course, equity in availability of services does not necessarily result in equity in uptake of services. Although free at point of contact it is feasible that financial and non-financial barriers may still influence service uptake. In Scotland, ACHD care is centralised with the Golden Jubilee National Hospital with additional local or regional clinics in each health board. Although measures are in place to reasonably remunerate patients for travel and accommodation to the national centre for follow up and intervention, if nothing else this provides an extra consideration for the patient. This then needs to be taken into context with the greater complexity of health priorities amongst more socioeconomically challenging communities. Whether or not there is equity of service uptake across socioeconomic groups remains conjecture pending further study, however acceptability to the patient has previously been outlined as a

key principle or ‘pillar’ of quality in health care (189). Ensuring equity of uptake must therefore revolve around assuring acceptability to the patient. This must involve a fine balance; review must be adequate but not unnecessarily frequent; patients must be seen by an appropriately skilled specialist but remain local when at all possible; and time out of work and education must be factored into decision making, with the patient’s input being of paramount importance.

Even if equity in uptake of services could be guaranteed irrespective of socioeconomic group, this does not guarantee equity in survival. The relationship between cardiovascular risk and socioeconomic deprivation is complex. Although there is an association with higher risk factor profile (smoking, obesity, sedentary lifestyle) (190) and the co-morbidities conferred (hypertension, hypercholersterolaemia, type 2 diabetes, ischaemic heart disease) (191), socioeconomic deprivation has been shown to increase ischaemic heart disease and heart failure risk even when independent of these variables (192,193). Although I was unable to adjust for clinical variables such as smoking and obesity, my results would suggest a similar association with mortality in ACHD as it persists even when adjusted for HTN, previous MI, and T2DM. This should not undermine the importance of risk factor modification amongst this group of patients, particularly given the increasing age at death in contemporary cohorts, but it does merit further study as to the role of socioeconomic deprivation as an independent risk factor for mortality in ACHD.

Background factors remain important in determining the risk of mortality associated with socioeconomic deprivation in the ACHD patient and in recent years a further driver of inequality has been well-publicised. Since the introduction of austerity measures following the 2008 global financial crisis, survival improvements have slowed in Scotland (194). This finding was replicated in other developed countries where austerity measures were implemented but not those where they were not. This slowing of survival improvements was established to be driven by an actual increase in mortality rates for those residing in SIMD quintiles of greater socioeconomic deprivation. Clearly, in addition to clinical measures being required to narrow the gap in outcomes governed by socioeconomic deprivation amongst adults with CHD, a more

general fiscal and political review will be required to reduce the background effects of widening socioeconomic disparity.

Although survival improved for all degrees of complexity of ACHD throughout my analyses, observed age at death increased most substantially for those with complex CHD. This was accompanied by a shift from cardiovascular towards non-cardiovascular mortality, which by the end of the data period mirrored the shift seen for lesions of simple and moderate complexity. Of course, adjusted survival remained poorer for those with complex CHD than moderate or simple and interestingly this was true for cardiovascular and non-cardiovascular mortality. Arrhythmic, heart failure related, and sudden cardiac deaths have long been the dominant mode of mortality for those with complex CHD, so it is the higher hazard of non-cardiovascular mortality which appears more unusual. In recent years more has been learned about the long-term implications of grossly abnormal cardiovascular physiology imposed by lesions of great complexity or the surgical interventions they mandate. This has been most robustly established for Fontan and univentricular physiology with hepatic, gastrointestinal and immunological implications discussed in the previous chapter. Moving forward it must be essential to ensure all latest developments in this regard are incorporated into clinical routine. As an example, it should now be commonplace for individuals without a sub-pulmonary ventricle to have close monitoring of liver function and interval screening for hepatocellular carcinoma.

These non-cardiovascular manifestations of complex CHD will inevitably lead to complex interdisciplinary networks with non-cardiology specialists, ideally with an interest and additional training in ACHD. A case for joint clinics with ACHD cardiologists could also be made. This is all the more complex due to the structure of congenital services in Scotland being centred around a single, national centre fed by multiple health boards.

9.4 Limitations of the studies

These studies are not without some limitations. Whilst the population-based, non-selective nature of the data collection is of benefit in several ways, including large study numbers and limiting recruitment and observer biases, it has its drawbacks. The ICD and OPCS coding systems were changed and

significantly improved during the data period. Necessarily, patient inclusion was not consistent throughout the data period. This was most noticeable for certain complex CHD lesions which were reliant on the new OPCS procedure codes to be defined (TGA with arterial switch and Fontan's for example). As a result, no individuals with these diagnoses were identified in the early data period and were instead contained within the less specific lesion categories (complex CHD), thus limiting their study. What Is more, as only adults older than 16 were included, there is a lead-in time of 16 years from the updated OPCS system until follow up times begin for these lesions. As this ISD database matures, provided that the OPCS system requires no major overhaul, this will cease to be an issue and its usefulness will be even greater particularly when sufficient to allow for longitudinal analysis of an entire 'natural' life span of a cohort.

Although the accuracy of coding for inclusion in the ISD database is externally validated on an annual basis and maintains high standards, this has not been independently validated for congenital heart disease ICD or OPCS codes. It is feasible that this esoteric area of coding may not be truly reflected by the reassuring figures for the ISD database as a whole.

As the data set was solely derived from coded data with full anonymisation it was not possible to be certain of the complete procedural history for an individual. If an ICD code pertaining to ASD was encountered but no code corresponding to closure was found this does not necessarily mean they have not had this done. They may have had a procedure predating the database or the appropriate coding system or they may have had the procedure out with Scotland. For this reason, procedural status could not be factored into survival analyses or lesion complexity approximation.

Accurately representing survival of this data set graphically was challenging as individuals were included either at the point of their 16th birthday, having been identified in the paediatric sector, or later in life due to an in patient episode during the data period. As ACHD is by definition present from birth, survival is equal to age. However, this mandates survival curves to be extended leftwards (to age 16 in my analyses) for those entering the data set at a later stage in life. This imposes a survivor bias as an equivalent individual may have died prior to, or without generating an in patient episode over the same time period. This is

not necessarily an inaccuracy but limits the usefulness of observed survivor data such as Kaplan Meier graphs as they overestimate survival. They have thus been included for a visual comparator of the observed data only. There is also a vulnerability at the 'right' of the survival curves as individuals will either be known to die or not known to die, where they will undergo administrative censoring. There may be some individuals who emigrate or die out-with Scotland who will not be recognised and will therefore contribute to the right of the survival curve until the administrative censorship date. This would falsely improve the observed survival in question. The effect of this may be expected to be small overall but could have a significant effect on smaller groups (such as with less common lesions e.g. Fontan or Ebstein's anomaly) where excess mortality free follow up may introduce a significant error.

9.5 Recommended further work

The benefits of this large volume, unselected study methodology cannot be overstated given otherwise sparsity of similar data in ACHD, but there are limitations as stated above. To counter the drawbacks of incomplete interventional history, lack of investigation outcomes when defining lesions and their complexity, and incomplete censoring or mortality recording due to emigration etc. the implementation and collaborative use of a national ACHD database could be extremely powerful. This may allow observational analyses and outcome predictors to be applied to interventions and therapies whilst also robustly validating diagnostic coding.

Even separate to the implementation of a national ACHD database or registry, which would undoubtedly incur significant financial and personnel outlay, independent validation of ISD data with specific regard to ACHD coding would be desirable. This would be unlikely to incur a significant financial cost but would be at the discretion of ISD as it would require unblinding of a proportion of this robustly anonymised data.

The utility of the Scottish Morbidity Record and subsequent linkage to other national databases has been described throughout this thesis. The records utilised in these studies could be further utilised to describe predictors of mortality. For example, co-morbidity has been included as a control variable in

these analyses to adjust survival models. Further work could expand on this to estimate survival according to co-morbidity. For example, does AF predict mortality for all CHD or only shunt lesions?

Recently a further database, the Prescribing Information System (PIS), has become available for linkage. This would allow all community prescribed medications for a data set to be identified and tracked longitudinally. This service has been provided since 2009 (195) and it has now been represented in the medical literature, including an observational study by Mueller et al. (196) regarding the comparative safety and efficacy of different direct oral anticoagulant (DOAC) medications amongst the Scottish AF population. This is a simple example of a very useful application PIS could provide in the ACHD population where DOAC efficacy and safety is far from established. Although pharmacoepidemiology in this population has myriad uses, given the extreme difficulty over the years of compiling randomised trials in ACHD patients, observational studies of outcomes relating to pharmacotherapy at a population level holds much promise.

Although efforts have been made throughout my analyses to provide a population comparator to the study population when possible, this has been via the utility of freely available population statistics. Ideally certain analyses and even basic graphical illustration of survival would be better served using a matched population cohort. Again, this would be at the discretion of ISD and the Public Benefit Privacy Panel upon application.

9.6 Conclusions

The conclusions from the results reported in this thesis can be summarised as follows:

The SMR is an effective tool for identifying and linking records of adults with CHD in Scotland.

Individuals with ACHD in Scotland are a heterogenous group. Deaths are observed in all age groups and co-morbidity is frequently encountered.

Adults with ACHD experience disproportionate socioeconomic deprivation when compared to the general population.

Women with ACHD experience more socioeconomic deprivation than men with ACHD.

Higher socioeconomic deprivation is associated with increased mortality, even when adjusted for underlying congenital lesion, age, and multiple co-morbidities including IHD, HTN and diabetes.

Individuals presenting to the data set in more recent years experienced better survival irrespective of underlying lesion, disease complexity, sex or socioeconomic group.

At the beginning of the study, the majority of deaths were due to cardiovascular causes. This is no longer the case, with non-cardiovascular mortality more prevalent.

Men with CHD experience higher mortality than women, and this is predominantly due to non-cardiovascular causes.

The transition from cardiovascular to non-cardiovascular mortality over time is noted for all degrees of ACHD complexity.

Mortality is higher for ACHD of greater complexity.

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