THE EPIDEMIOLOGY OF CARDIOVASCULAR MALFORMATIONS

Christopher Wren MBChB, FRCP, FRCPCH
Honorary Senior Lecturer in Paediatric Cardiology

Thesis for Doctor of Philosophy by Published Work

Submitted to Newcastle University

Department of Paediatric Cardiology
Freeman Hospital
Newcastle upon Tyne

January 2008

To my mother, Hazel Wren and my late father, Frederick James Wren,
to whom I owe everything.

ABSTRACT

This thesis is submitted to Newcastle University for the degree of Doctor of Philosophy by Published Work. It includes a series of published papers as well as new unpublished work.

Chapter 1 provides an introduction to epidemiology, particularly in relation to the description and analysis of malformations and birth defects. Chapter 2 gives a brief introduction to the complex topic of cardiovascular malformations, in particular the problems of definitions and terminology and the importance of diagnostic hierarchy of multiple malformations. Chapter 3 describes the paediatric cardiology database and the preliminary studies which produced the first five published papers.

Chapter 4 presents 10 important papers on aspects of the epidemiology of cardiovascular malformations – which together form the main part of this thesis.

Chapter 5 presents a systematic review of published studies of the prevalence of congenital cardiovascular malformations which investigates whether there is any evidence of a real difference between populations. It finds wide variation in the reported prevalence at live birth of all congenital cardiovascular malformations (2-30 per 1000 live births) and of individual malformations and concludes that differences are almost certainly explained by various types of ascertainment bias. Specific malformations predicted to show least susceptibility to ascertainment bias show least variation in reported prevalence. The review makes recommendations for consistent methodology for future reports to allow proper comparison between different populations.

Chapter 6 looks forward to consider the directions in which research might go in the future, looking in particular at outcome research and its use in performance analysis, and at future investigations into the aetiology of malformations.

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PREFACE

Why write a PhD thesis, particularly at my age and at this stage in my career? As a paediatric cardiologist I have found that an interest in cardiovascular malformations led naturally to an interest in epidemiology. Why do cardiovascular malformations occur? Why are there such wide morphological variations? Why are some rare and others common? Do the same variations occur in other populations? The answers are perhaps more likely to come from epidemiology and genetics than from physical study of the anatomy, embryology and morphology of the malformations themselves.

Epidemiology depends fundamentally on population-based data. Working in the North East has given me the opportunity to establish and develop the Northern Regional Paediatric Cardiology Database with great help and support from the Northern Congenital Abnormality Survey, with whom we maintain very close ties. Our data have been used for a series of research papers published over the last 17 years. This thesis gives the opportunity to pull together several of these papers with a common theme as well as to look forward to see in which directions the research might go in the future.

Although I am a graduate of the University of Birmingham, I have been living and working in Newcastle upon Tyne since 1981. I am very grateful to Newcastle University for the opportunity to complete and submit this thesis. I am also grateful for advice, support and encouragement from my supervisor Professor Alastair Burt, Dean of Clinical Medicine.

I also value highly support from Professor Carol Dezateux, professor of paediatric epidemiology and head of the Centre for Paediatric Epidemiology and Biostatistics at the Institute of Child Health in London, and Dr Kate Bull, now Medical Advisor in Family Policy at the Institute of Child Health, who share and have encouraged my interest in the epidemiology of cardiovascular malformations. I continue to work with Carol and Kate and others at the Institute of Child Health on a number of epidemiological studies.

Although this is my own work, this thesis would not have come about without the support encouragement and advice of many friends and colleagues.

ACKNOWLEDGEMENTS

I am indebted to:

- Doctors Mario Abinun, Mario Cleves, Eduardo Chicote, Adeela Hoseine, Annette Klinge, George Kokai, Jan Marek, Eugene Morgan, Anabela Paixáo, Zdenka Reinhardt, Neelmanee Ramphul, Sam Richmond, Jaroslav Stark, Krzysztof Tocewicz, Mauricio Villavincencio, Hideki Uemura, Melanie Vogel, and Qin Yan for help in obtaining or translating original papers or providing additional information for the systematic review in chapter 6.

- Professor John Matthews and Professor David Spiegelhalter FRS OBE for statistical advice for the systematic review in chapter 6.

- My co-authors in papers in chapters 3, 4 and 5 - Majd Abu-Harb, Sean Ainsworth, Martin Barrett, Ginny Birrell, John Burn, Liam Donaldson, Graham Derrick, Alison Emslie, Jill Gregory, Gillian Hawthorne, Edmund Hey, Stewart Hunter, Khuloud Khawaja, Helen Leonard, John Madar, John O'Sullivan, Zdenka Reinhardt, Sam Richmond, Nilofer Sabrine, John Scott, Peta Sharples, Graham Stuart, Kirsty Tanner, Michael Wright and Jonathan Wyllie.

- Mary Bythell, Liam Donaldson, Edmund Hey, Marjorie Renwick, Martin Ward-Platt, Christopher Wright, and all staff at the Regional Maternity Survey Office (home of the Northern Congenital Abnormality Survey and Perinatal Mortality Survey) for collaboration and help with collection and validation of original data.

- Professor Liam Donaldson (then Regional Medical Officer and now Chief Medical Officer) for financial support from the then Northern Regional Health Authority for the original establishment of the Paediatric Cardiology Database and for funding the study published as Wren C, O'Sullivan JJ. Survival with congenital heart disease and need for follow up in adult life. *Heart* 2001;**85**:438-43. No specific funding was sought for any of the other projects in this thesis.

- Denise Hassan, Kati Whiteoak and Valerie Sutherland, the data managers who have run the Paediatric Cardiac Database over the past 17 years.

- Kathryn Pollock and Isobel Bush, my two secretaries, for their hard work and support during this project and for help with typing the drafts of the main chapters and the references.

DOCTORAL STATEMENT

The doctoral statement concerning the work submitted and setting out the proposed basis for the award of the degree of PhD consists of chapters 1, 2, and 6 in this thesis.

DECLARATION OF ORIGINALITY

I declare that this thesis was written by me and has not been submitted or accepted for any other degree. Except where specifically acknowledged, I have collected, analysed and interpreted all the data.

Christopher Wren

CHAPTER 1: AN INTRODUCTION TO EPIDEMIOLOGY

1.1 DEFINITION OF EPIDEMIOLOGY

Epidemiology is the study of the distribution of disease in a population, and of the factors which influence this distribution. A broader definition is that it is the study of the distribution and determinants of health related states or events in specified populations and the application of this study to control of health problems. [Gordis 2004]

1.2 AIMS OF EPIDEMIOLOGICAL RESEARCH

The main aims of epidemiology are:

1. To study the causes of disease and/or risk factors for development of disease.
2. To measure the extent of disease in the population. This is vital for planning health services and the provision of training and facilities for healthcare providers.
3. To study the natural history and prognosis of disease. This is fundamental to assessment of the efficacy of treatment (especially surgery within our context) and the development of effective screening strategies.
4. To assess the effect of prevention, treatment, and the mode of healthcare delivery. Added impetus was given to this by the Bristol Royal Infirmary Inquiry, which recommended in 2001 that “national standards should be developed, as a matter of priority, for all aspects of the care and treatment of children with congenital heart disease. The standards should address diagnosis, surgical and other treatments, and continuing care.” [BRI Inquiry Panel 2001]
5. To provide the foundation for developing public health policy and to make decisions about regulation of environmental problems. Within the context of cardiovascular malformations this relates both to the development of screening programmes and to identification of causative factors (such as the association between maternal rubella infection and persistence of the ductus arteriosus in the offspring, or the association between advanced maternal age, an increased incidence of Down syndrome, and its associated cardiovascular malformations).

1.3 TYPES OF EPIDEMIOLOGICAL STUDY

Various types of study are used in epidemiology, many of them with the aim of identifying aetiological or causal relationships. Only some of these are appropriate for the investigation of congenital malformations.

Cohort studies

A cohort study is a form of longitudinal study which is used to investigate a suspected association between cause and disease. Fundamentally, the cohort has to be identified before the appearance of the disease under investigation and this type of study cannot normally be used to investigate a group who already have the disease. A good example of a cohort study is the Framingham Heart Study of risk factors for cardiovascular disease in the United States has been under way for more than 50 years.

Cross-sectional studies

A cross-sectional study investigates the relationship between exposure and disease but determines both at the same time. It begins with a defined population and gathers information on both disease and exposure. Four groups are then identified: those who are exposed and have the disease; those who are exposed but do not have the disease; those who are not exposed but have the disease; and those who are not exposed and do not have the disease. This type of study investigates known cases of disease and is also known as a prevalence study. The results of this type of investigation can be displayed in a 2x2 table. A good example of a cross-sectional study is our investigation of cardiovascular malformations in the offspring of mothers with insulin dependent diabetes, discussed in more detail in chapter 4. [Wren 2003]

Case-control studies

A case-control study compares a group of individuals with a disease (cases) with a group of individuals without the disease (controls). They are then examined retrospectively for exposure to a possible cause of the disease. Case control studies are rare in the literature on cardiovascular malformations. They are prone to many biases, particularly selection bias for both cases and controls and recall bias (also known as rumination bias). The best example of a case control study of cardiovascular malformations is the Baltimore-Washington Infant Study 1981-1989. [Ferencz 1993] The aims of this study were to develop descriptive data on infants with cardiovascular malformations and their families compared with non-affected

infants in the same birth cohort; to develop a classification of cardiovascular malformations; to evaluate genetic and environmental factors and relate these to the diagnostic subgroups; and to define methods for future research. The study was an enormous undertaking. It was originally planned to be a three year study with a regional birth cohort of around 300,000 births. To generate adequate statistical power, the study size was increased twice and eventually dealt with a birth population of almost one million births over nine years. The study had many of the problems inherit in case control studies. Whilst it produced many reports, most of these were descriptive and the investigations threw little light on the detailed causes of congenital cardiovascular malformations. Many *associations* between various environmental exposures and individual malformations were identified but these have not led to establishment of *causal* relationships. The Baltimore-Washington Infant Study is one of the reports considered in detail in the systematic review in chapter 5.

Longitudinal observational studies

Longitudinal observational studies are mostly descriptive and do not set out to investigate causes of disease. However, they are important in addressing some of the aims of epidemiology discussed above, such as measuring the extent of disease in the population, studying its natural history and prognosis, predicting the need for resources, and assessing efficacy of prevention, treatment, and screening strategies. Several of the studies in chapter 4 are of this type.

1.4 MEASURES OF DISEASE FREQUENCY

A fundamental requirement of epidemiology is to be able to measure the occurrence or frequency of disease within a population. This can be done using rates or proportions. Rates measure how frequently a disease occurs within a population, whereas proportions measure the fraction of the population affected. Rates and proportions are both used to measure morbidity or mortality.

Incidence

The incidence of disease measures the number of new cases arising over a period of time in a population at risk. One critical element of incidence is that it measures new cases within the population, so the numerator should be free from disease at the start of the study and the denominator should be the population at risk of developing the disease. Incidence studies can measure *risk*, which is the probability of the new development of the disease, and *rate*, which is the average rate of

development of disease over time, also known as incidence density. Because risk and rate cannot be measured instantaneously, data are usually collected over a period of time to produce a cumulative incidence. Although epidemiological reports of cardiovascular malformations do refer to incidence, as will be seen, the term is not directly applicable to this type of investigation.

Prevalence

Prevalence is a measure of the disease burden in a population. This can be measured instantaneously, to produce point prevalence, or over a period of time (such as one year) to produce period prevalence.

There is an obvious inter-relationship between incidence and prevalence. If the number of new cases within a population exceeds the death or cure rate, the prevalence will increase. If prevention, cure and death rates exceed the incidence, the prevalence will decrease. The dramatic improvements in the treatment of cardiovascular malformations have led to a substantial fall in mortality and thus to an increase in prevalence (see chapter 6). Neither incidence nor prevalence in their classical definitions is directly applicable to descriptive studies of congenital malformations. Some cardiovascular malformations have a genetic cause and are effectively present from the moment of conception. Others are probably due to environmental influences which affect the embryo and fetus during gestation. The main development of the heart is complete by the sixth week of pregnancy. The heart is the earliest main organ to be complete because it is essential for the development and growth of the embryo and fetus. Very major cardiovascular malformations are incompatible with life and lead to embryonic or fetal death causing miscarriage or stillbirth. This means that the disease frequency of cardiovascular malformations is unknown. With both new cases (caused by fetal environmental influences) and deaths occurring before ascertainment, neither the classical definition of incidence or prevalence is useful to us in describing the occurrence of cardiovascular malformations.

Most cases of congenital cardiovascular malformation are not immediately apparent at birth but come to notice over time. In one report in chapter 4, we found that 74% of cases are identified in the first year of life, another 18% at age 1-4 years and 8% between 5 and 15 years. [Wren 2001] Even this does not take account of malformations diagnosed in adult life, even though they are present from early

embryonic life. Thus it can be seen that the period of ascertainment will have a significant effect on the measure of disease frequency.

Incidence or prevalence?

Despite all these problems, Julien Hoffman, one of the leading authorities in the field, has argued extensively that the frequency of cardiovascular malformations should be known as the incidence. [Hoffman 2002] [Hoffman & Kaplan 2002] Charlotte Ferencz and Stephen Daniels both favour the use of the term "prevalence at live birth". [Ferencz 1990] [Ferencz 1992] [Daniels 1990] Because many diagnoses are made retrospectively (that is, after birth) the prevalence would appear to increase with time yet this is only due to increasing retrospective diagnosis. Open-ended ascertainment obviously gives the opportunity for further increase in the apparent prevalence at live birth. Ferencz has therefore suggested that ordinarily diagnoses should be made within a year from birth.

Prevalence at live birth

The standard definition of disease frequency used throughout this work will be prevalence at live birth, that is, *the number of cases of cardiovascular malformation within the population present at birth and diagnosed within the first year of life*. Obviously this is not a true measure of disease occurrence or frequency. It does not take account of cardiovascular malformations causing stillbirth or early fetal loss. There is good evidence that the rates of cardiovascular malformations in stillbirths are many times higher than those in live births. [Hoffman 2002] There is also a very different spectrum, with some individual malformations more likely to be associated with or to cause stillbirth. However, ascertainment in such reports is very patchy and no true measure can be obtained. Prevalence at live birth also cannot take account of cases identified antenatally leading to termination of pregnancy and such reports have to be made separately. This means that prevalence at live birth is the best measure we have but can never be a precise measure of total disease frequency. The total amount of disease will be higher because of failure to take account of cases causing death before birth, continued ascertainment in childhood and adult life, and the necessarily restrictive definition of cardiovascular malformation. As will be discussed in chapter two, most epidemiological assessments of cardiovascular malformations exclude abnormalities such as patent ductus arteriosus associated with pre-term birth, isolated bicuspid aortic valve, isolated cardiac arrhythmias etc. These are cardiovascular abnormalities, if not malformations, and they represent work for the cardiologist and surgeon. If they

were taken into account they would increase the apparent “prevalence at live birth” of cardiovascular abnormality to well over 1%. As many children are seen by a paediatric cardiologist because of a suspicion of abnormality which turns out not to be confirmed, the total proportion of live born children seen by a cardiologist is probably nearer 5%. Nevertheless most of the work generated is related to true cardiovascular malformations and prevalence at live birth thus remains a useful epidemiological measure of disease occurrence.

In order to be able to define the frequency of disease within a population we need to be able to identify both the numerators and denominators. For prevalence at live birth of cardiovascular malformations, denominators should not present too much of a problem if applied to a complete birth cohort with a defined age at ascertainment. However, there are many opportunities for bias, particularly ascertainment bias, and these are discussed at length in chapter 5. Identification of numerators is potentially more difficult. Several possible data sources can be identified. These include birth certificates, death certificates, hospital records, national disease registers, and local surveys or databases. Each has its potential advantages and disadvantages.

Because congenital cardiovascular malformations are relatively uncommon in population terms, we would ideally study a large population to provide sufficient denominators (live births) but we would then run the risk of not being able to identify all numerators (cases of cardiovascular malformation). A study based on a small population is likely to have more complete ascertainment but its findings would be limited because of the small study size. Thus studies based on national registers or birth certificates have consistently been shown to suffer from inadequate ascertainment. [Gillum 1994, Williams & McCrindle 2002, Boyd 2005] Regional or local surveys are likely to have as complete ascertainment as is possible and if linked to a sufficient birth cohort or continued over a period of time, they are likely to provide the ideal compromise between completeness of ascertainment and adequate study size. [Richmond & Atkins 2005] Hospital based information suffers the obvious disadvantage that it is not necessarily linked to a birth cohort and hospital data systems are not sufficiently reliable to be able to identify all cases or all activity. Hospital episodes statistics were used for some of the analyses of cardiac surgical mortality in the Bristol Royal Infirmary Inquiry but their accuracy has been challenged. [Aylin 2004]

1.5 REGISTRIES AND DATABASES

Two types of databases can be identified, disease registries and academic databases. [Williams & McCrindle 2002] A *registry* collects some data on all patients. Resources are applied to collection and entry of data and limit the amount of information which can be collected. As discussed above, used locally they may be the practical ideal. If diagnostic coding is consistent in different centres, multi-institutional registries increase the power. Such devices are particularly useful for analysis of surgical outcome but are of less use in descriptive epidemiology of cardiovascular malformations within whole populations. [Moller 2005, Jacobs 2007] A *research database* collects all of the information for some of patients. Its aim is to investigate a specific sub-group to provide new knowledge. It may also be multi-institutional if sufficient care is taken to harmonise definitions and data collection.

1.6 ETHICAL ASPECTS OF INFORMATION IN DATABASES

In addition to the obvious academic interest in epidemiology, we have a responsibility to our patients and their families to collect valid data on the occurrence and outcome of cardiovascular malformations in order to monitor the effect of diagnostic and screening policies and to monitor the quality and outcome of treatment. Therefore, we have a responsibility to make the data as complete and accurate as is feasible. Disease registries have recently seemed to be under threat from legislative changes brought about by the Data Protection Act 1998 which came into force in March 2000. The protection for population based disease registries probably lies in the anonymisation of data for analysis and output. Health research is unquestionably in the public interest. The Data Protection Act means that consent is required for identifiable patient data. The Information Commissioner has said that "it is a major misconception that the Act always requires the consent of data subjects …" but also says that there is an implied requirement to obtain consent. [Parkes 2004] However, patients are used to the fact that hospital records contain identifiable details and, in fact, could not function without them. Patient confidentiality remains a prime responsibility but so also does valid research, which cannot be based on inadequate or incomplete data sets.

CHAPTER 2: CARDIOVASCULAR MALFORMATIONS

2.1 INTRODUCTION

Cardiovascular malformations account for about 10% of all infant deaths in developed countries and nearly half of all deaths from malformation. [Abu-Harb 1994] [Rosamond 2007] As a group they are the most common type of congenital malformation. [March of Dimes 2007] The cause of an increasing number of malformations is known to be genetic [Pierpont 2007] and a few are environmental in origin [Mone 2004] [Jenkins 2007], but for the majority the cause is unknown. The descriptive epidemiology of cardiovascular malformations has generated much interest over the last 50 years but has not so far provided major clues to the aetiology. There have been many descriptions of disease frequency but comparison between them is hampered by the lack of a common method. Early studies were limited by their inclusion of many unconfirmed clinical diagnoses (before ultrasound was widely available) and some more recent studies, which are institution based, are limited by their inability to define the population from which their patients were derived. Comparisons between studies are also made more difficult by uncertainties over ascertainment and because of the different diagnostic categories and diagnostic hierarchies employed.

2.2 TERMINOLOGY

Congenital heart disease is the group name commonly employed for a wide variety of cardiovascular malformations. They are grouped together for convenience but individually they vary in their aetiology, embryology, morphology, presentation, physiology, management and outcome. There are problems with the use of this term. Firstly, some “congenital” heart disease is not truly congenital if it leads to fetal death or termination of pregnancy, or if it develops after birth, as in persistence of the ductus arteriosus. Secondly, some congenital “heart” disease does not directly affect the heart (for example coarctation of the aorta, persistent ductus arteriosus, aortopulmonary window etc.). Thirdly, some congenital heart “disease” is little more than a curiosity and certainly doesn’t amount to a significant problem (such as isolated bicuspid aortic valve or persistence of the foramen ovale). Throughout this review the term *cardiovascular malformation* is preferred.

2.3 DEFINITIONS, INCLUSIONS AND EXCLUSIONS

Most reports adopt the classic definition first proposed by Mitchell, that is “a gross structural abnormality of the heart or intrathoracic great vessels that is actually or

potentially of functional importance". [Mitchell 1971] This means that minor variations such as isolated systemic venous anomalies (e.g. persistence of the left superior vena cava connecting to the coronary sinus) are almost always excluded. Other very common exclusions are patent ductus arteriosus associated with prematurity, cardiomyopathies, isolated cardiac arrhythmias, cardiac tumours and conditions regarded as physiological variants - such as neonatal pulmonary artery branch stenosis.

The ductus arteriosus is patent at birth and usually closes within hours or days. Persistence of the ductus arteriosus is generally defined as a ductus remaining patent more than six weeks post term. This has an increased prevalence in babies who were born preterm but excludes the situation in which the duct causes problems, and requires treatment, in the preterm baby.

An atrial septal communication, that is a foramen ovale, is a universal finding in fetal life and is a common and normal finding in early postnatal life. It is often not possible to predict whether a neonatal "atrial septal defect" seen on echocardiography will turn out to be a true atrial septal defect, that is one which persists into childhood and may require closure. There is, however, good evidence that the smaller the atrial septal defect detected in infancy, the greater the likelihood of spontaneous closure. [Radzik 1993] Therefore, there is no accepted true definition of an atrial septal defect in infancy. It is also recognised that most atrial septal defects present after infancy. [Wren & O'Sullivan 2001] These factors obviously lead to considerable problems in ascertainment of atrial septal defects in infancy and childhood.

Another common structural abnormality, which is almost always excluded from definitions of congenital heart disease or cardiovascular malformation, is a bicuspid aortic valve without stenosis or regurgitation. The reported prevalence of bicuspid aortic valve ranges from 0.4% to 2.25%. [Ward 2000, Hoffman 2002] Two of the larger reports came up with 0.9% and 1.37%. [Roberts 1970] [Larson & Edwards 1984] However, there is obvious potential for error in trying to predict the prevalence at birth by examining adult autopsies. A recent small but prospective neonatal echocardiographic study found a bicuspid aortic valve in five of 1075 consecutive neonates (0.46%). [Tutar 2005] Because this was a small study the 95% confidence intervals are wide at 0.2-1.2%, i.e. little different from the autopsy studies.

Another condition which is probably common, but is difficult to define, is mitral valve prolapse. [Freed 1999] [Freed 2002] [Warth 1985] It is very rarely diagnosed in infancy. As a minor echocardiographic observation it seems to be relatively common but as a clinical problem it is rare in childhood and most epidemiological studies exclude mitral valve prolapse without regurgitation.

Many congenital cardiovascular malformations are easy to define and one would expect clinical ascertainment to be complete. Two conditions which are exceptions to this but are very common are mild pulmonary valve stenosis and mild aortic valve stenosis. The diagnosis of stenosis implies that the Doppler velocity measured by echocardiography is higher than normal. Very few reports of the prevalence of cardiovascular malformations define the “upper limit” of normal and thus define mild aortic valve stenosis. Exceptions are Kitchiner [1993a] [1993b] where aortic stenosis is a Doppler velocity >2 m/s and Ooshima [1995] who uses >1.6 m/s (a low upper limit which will obviously lead to more diagnoses). The diagnosis of mild pulmonary valve stenosis is also based on the finding of increased flow velocity through the valve on Doppler echocardiography. Again the “upper limit” of normal is rarely defined and also varies with age. Exceptions are Ooshima [1995] (>1.2 m/s), Gielen [1999] (>1.6 m/s) and Chehab [2004] (>2 m/s). The frequent lack of a definition, and lack of consistency when there is one, means that there is likely to be considerable variation between studies and this will lead to ascertainment bias.

In some reports double outlet right ventricle is a relatively common diagnosis whereas in others it does not occur at all. Double outlet right ventricle defines one part of a malformation, which is of importance when contemplating surgical repair [Jacobs 1997], but it does not have a constant definition [Kleinert 1997] [Samanek 1999] and does not define an anatomically or physiologically distinct group of malformations [Kleinert 1997]. It includes diagnoses that will otherwise be described as transposition of the great arteries, tetralogy of Fallot, ventricular septal defect etc. There are other instances of methods of classification leading to apparent inconsistencies in birth prevalence of cardiovascular malformations. In many North American reports, pulmonary atresia with ventricular septal defect is considered as a variation of tetralogy of Fallot and is coded as tetralogy of Fallot. This accounts for the apparent lack of cases of pulmonary atresia with ventricular septal defect in many US reports. [Ferencz 1993]

2.4 DESCRIPTION OF COMPLEX MALFORMATIONS

There is a roughly inverse relationship between the prevalence and the complexity of severity of cardiovascular malformations. The most common are minor and do not require treatment. Many of those that are rare are complex and severe. Most cardiovascular malformations are easily described by a single term such as ventricular septal defect or coarctation of the aorta. Some common abnormalities, such as tetralogy of Fallot are in fact made up of more than one morphological abnormality but occur together so frequently that the pattern is universally recognised. On the other hand, individual malformations occur much more commonly in association with others than by chance and these need to be described separately. Some malformations are complex and cannot be described by a single term or combination of terms. [Kurosawa 2006] In this case sequential analysis is employed to describe the total cardiac morphology and connections beginning at the venous end of the heart and progressing to the great arteries. [Anderson 2002] Such analysis was developed in the 1980s and can theoretically cope with a malformation of any degree of complexity although it is unnecessary for the large majority.

2.5 DIAGNOSTIC CODING

The descriptive epidemiology of cardiovascular malformations relies on precise and accurate structural diagnosis. Diagnostic coding is becoming increasingly harmonised internationally, both for diagnosis and for description of surgery. [Franklin 2006] The “European” codes have evolved in the past few years and are now accepted and employed internationally. In parallel, European and American coding has evolved to provide a universally accepted description and classification of surgery for cardiovascular malformations. [Jacobs 2005] Only when this is achieved can we confidently combine and compare data from difference centres, different registries and different countries.

Because cardiovascular malformations are many and varied they are often grouped and classified, although in several different ways. Simple groupings relate to the presentation or outcome, such as division into cyanotic and non-cyanotic defects. Individual malformations are sometimes grouped together to allow better analysis where the numbers of individual malformations might be relatively small. Reports have thus grouped “complex”, “significant”, and “minor” malformations [Abu-Harb 1995] or “severe”, “moderate”, and “mild” defects [Hoffman 2002]. Other accounts deal with malformations which either do, or do not, require surgery, or group

together abnormalities which are morphologically varied but suitable for a common type of palliative surgery. [Jacobs 2006]

In accounts of the descriptive epidemiology of cardiovascular malformations, individual diagnoses are usually presented in tabular form. They might be listed in order of prevalence, in which case ventricular septal defect is always the first mentioned. Other classifications are by anatomical severity (worst to least), functional importance [Knowles 2005] or by presumed embryological aetiology. Several methods have been proposed to group anatomical diagnoses into speculative aetiological groups. They include a "mechanistic classification" [Ferencz 1993] and a "potential morphogenetic classification" [Jackson 1996]. There are similarities but also inconsistencies between these classifications and they group together malformations that may be unrelated embryologically, aetiologically, or physiologically. In other reports malformations of the same part of the heart are often grouped together (such as "conotruncal" abnormalities). [Adams 1989] However, there is no real logic to this as malformations of the same part of the heart would not necessarily have the same cause or embryology and certainly do not present in the same way and are treated differently.

2.6 DIAGNOSTIC HIERARCHY

Classification of cases with multiple cardiovascular malformations is a difficult problem and almost all reports have allocated all cases a single diagnosis based on the malformation which is judged to be most important. This means that the number of cases of various diagnoses can be added to equal the total number of patients in the series. If cases with more than one diagnosis have to be given one label, some type of hierarchy is required to decide in which category they fit best. Unfortunately, there is no consensus on how this can best be achieved. Many reports, particularly older ones, ignore the problem altogether and don't define how multiple diagnoses were dealt with.

The main hierarchies which have been employed can be described as anatomical, physiological, embryological, and functional. Many reports have adopted either the classification proposed in the New England Regional Infant Cardiac Programme which defined a hierarchy based mainly on anatomical severity [Fyler 1980] or that in the Baltimore-Washington Infant Study in which priority was given to "the malformation components with the earliest embryonic disturbance" [Ferencz 1993]. In practice these two approaches, which both use a broadly "anatomical" hierarchy,

are fairly similar. Reports which are institution-based and which cannot define the denominator population, usually adopt a “physiological” hierarchy, taking as the most significant that abnormality which requires the earliest intervention or which causes the greatest haemodynamic disturbance.

A good example of the problem is the common association between ventricular septal defect and coarctation of the aorta. Both are common abnormalities but they frequently occur together in the same patient. A common clinical situation is a neonate presenting at a week of life with sudden onset of heart failure caused by the presence of a coarctation. Further assessment reveals the presence of a ventricular septal defect which may be large, and therefore will require later separate surgery, or may be small and functionally unimportant. With a physiological hierarchy, the baby would be coded as having a coarctation and the ventricular septal defect would be ignored. With an anatomical hierarchy the baby with coarctation with a large ventricular septal defect would be coded as having a ventricular septal defect. In contrast the baby with coarctation associated with a small ventricular septal defect would be coded as having coarctation of the aorta. There are several other common clinical situations which present similar problems. The lack of a consensus on hierarchical classification means there will continue to be considerable variation in reported prevalence because of this type of selection or ascertainment bias.

Some reports get round the problem by coding multiple malformations separately as “miscellaneous” or “complex”. [Garne 2004] [Forrester 2004] Others employ double counting which obviously means the total of individual malformations is higher than the number of individuals in the report and doesn’t really make much sense. [Abushaban 2003] [Cleves 2003] In other descriptions of hierarchies reported, cases are coded according to the malformation which is “most important” [Howie 1970], “most grave” [Czeizel 1972], “most severe” [O'Brien 1972], “predominant” [Cloarec 1999] [Chehab 2004], “leading” [Andersen 1994], or are “arbitrary” [Meberg 2005].

The only report which tried to assess the inherent variation caused by different hierarchical classification is discussed in more detail in chapter 4. [Wren 2000] It showed that the use of a one dimensional anatomical classification would lead to under ascertainment of coarctation of the aorta by 39%, of pulmonary atresia by 27%, and of interruption of the aortic arch by 100% when compared with a physiological classification.

2.7 AETIOLOGY OF CARDIOVASCULAR MALFORMATIONS

As discussed in chapter 1, one of the main aims of the descriptive epidemiology of cardiovascular malformations is to try to elucidate the aetiology. At present the cause of around 75% of cases is unknown. Somewhere around 15-20% are caused by chromosal or other genetic or syndromic abnormalities. [Pierpont 2007] Perhaps around 5% are related to fetal environmental effects – mostly factors such as maternal illness (e.g. diabetes mellitus, phenylketonuria), maternal drug ingestion (eg anticonvulsants), or maternal infection (e.g. rubella). [Jenkins 2007] There have been isolated reports of associations with factors such as contaminations such as drinking water but these often do not stand up to scrutiny. [Goldberg 1990] [Watson 2006] The Baltimore-Washington Infant Study was a case control study, the optimal design for investigating the influence of environmental factors. [Ferencz 1993] It found an increased number of specific malformations related to maternal occupational or environmental exposure to factors such as degreasing solvents, pesticides or lead soldering. Obviously this only reports associations, which may not be causal. Statistical analysis in this situation is also difficult and complex. The use of 95% confidence intervals may not be appropriate in the examination of very many individual malformations and very many environmental exposures as, by chance, the findings would be outside the 95% confidence intervals in one case in twenty. The Baltimore-Washington Infant Study failed to find any association with maternal exposure to anticonvulsants, phenytoin, codeine, and ampicillin where other previous smaller reports had done so. [Ferencz 1993]

2.8 CONCLUSIONS

Congenital cardiovascular malformation is a term used to describe a wide variety of malformations of the heart and great vessels. The cause of most is unknown and they differ in aetiology, embryology, clinical presentation and management. Cardiovascular malformations occur in association much more frequently than by chance. There is no consensus on how to decide the relative hierarchy of multiple malformations in the same patient – a subject of great importance to descriptive epidemiology studies. Most studies fail to define the common malformations, leading to the potential for ascertainment bias.

CHAPTER 3: THE NORTHERN REGIONAL PAEDIATRIC CARDIAC DATABASE: EARLY EPIDEMIOLOGICAL RESEARCH STUDIES

3.1 INTRODUCTION

Good epidemiological research is based on good data. A registry database is a structured collection of information containing some data for all the patients of interest. [Williams & McCrindle 2002] This means that, as a minimum, every patient can be identified. Depending on the project in hand, it may be necessary to obtain some more detailed information retrospectively.

3.2 EPIDEMIOLOGICAL DATABASES IN THE NORTHERN REGION

The Northern Health Region has an unrivalled record in collecting and analysing information in two widely renowned registries based at the Northern Regional Maternity Survey Office (RMSO). The Northern Regional Perinatal Mortality Survey (PMS) was established in 1980 to collect information on all registered perinatal deaths in babies born to mothers resident within the region. It was a collaborative enterprise based in every health district and maternity unit in the region and collected information from obstetricians, paediatricians, midwives, as well as pathologists and other specialists. In a report on the first two years' data collection, published in 1984, it was already the largest perinatal mortality survey in England and Wales. [Northern Regional Health Authority Co-ordinating Group 1984]. The PMS is now well established and was recently able to report trends over 19 years from 1982-2000. [Bell 2004]

A closely associated registry, the Northern Congenital Abnormality Survey (NorCAS), previously known as the Fetal Abnormality Survey (FAS), was established in 1984 as a pilot project. [Northern Regional Survey Steering Group 1992] It has collected data prospectively since 1985. It uses multiple sources of ascertainment including obstetric ultrasonographers, obstetricians, neonatologists, clinical geneticists, cytogeneticists, perinatal pathologists, paediatric cardiologists, paediatric surgeons and general paediatricians. Details of any antenatal or postnatal investigations are reported to the survey office. Data are collected on malformations in any baby born to a mother resident in the region, wherever birth occurs and regardless of whether the abnormality was first diagnosed in utero, at birth, or during the first year of life.

The original establishment of this survey was approved by the ethics committees of all districts involved. Data are held by NorCAS in compliance with the data protection act 1998 and the survey has appropriate exemption under Section 60 of the Health and Social Care Act 2001. [Parkes 2004] A recent comparison of data from four local surveys, including NorCAS, with national data found that ascertainment by local surveys was considerably more complete and that NorCAS had the most complete ascertainment of postnatally diagnosed anomalies currently available. [Boyd 2005] The survey has been validated from the start by cross checking the information available from District Health Authority SD56 Returns to the Office of Population Censuses and Surveys (OPCS) [now the Office of National Statistics (ONS)]. Notifications to NorCAS consistently outnumber those submitted to OPCS. A recent report was able to summarise trends in accuracy of prenatal diagnosis compared with postnatal findings over sixteen years. [Richmond & Atkins 2005].

As one would expect, the administrative structure of both surveys improved over time. Access to data for both is controlled by steering groups. In the late 1980s Liam Donaldson, the Regional Medical Officer (later Professor Sir Liam Donaldson, Chief Medical Officer), took over chairmanship of the NorCAS steering group. It was apparent at that time that the survey contained very few data on cardiovascular malformations, despite the fact that these are the most common type of congenital malformation. In 1990 Professor Donaldson funded the appointment of a research fellow to establish the regional paediatric cardiology database. Although this is based in Freeman Hospital, it has always worked very closely with the RMSO, with bidirectional cross validation. Cardiology data were ascertained retrospectively for babies born in 1985-1989 and have been ascertained prospectively since 1990. A research fellow did the initial case finding and coding but in more recent years there has been a full time data manager funded by the Children Heart Unit's Fund.

Original case finding used multiple sources of ascertainment from original files. These included hospital case notes for all ward admissions and all ward and outpatient attenders. Data were also obtained from theatre books, which documented every operation performed, and ward and intensive care admission books. Data were also checked in all original NorCAS files. During this process it became apparent that NorCAS and PMS had recorded a number of deaths from babies with cardiovascular malformations who had never been known to the

paediatric cardiology service. These data were analysed in more detail to produce the second report from the paediatric cardiology database (see below).

3.3 EARLY PUBLISHED REPORTS

3.3.1 Stuart AG, Wren C, Sharples PM, Hunter S, Hey EN. Hypoplastic left heart syndrome: more potential transplant recipients than suitable donors. *Lancet* 1991;337:957-9. The first published report based on regional data was an investigation into the possibility of finding donors for primary neonatal cardiac transplantation for treatment of hypoplastic left heart. At the time there was a wide-ranging debate on the use of neonatal donors for infant heart transplantation. The dominant indication for transplantation was hypoplastic left heart, which at that time was an almost universally fatal condition. Primary heart transplantation seemed to offer some hope and had been proven to be feasible in North American centres, most notably that based at Loma Linda. [Bailey 1993] Because regional data were available, this first report ascertained all live births and terminations of pregnancy with hypoplastic left heart in the eight years 1983-1990 (figure 3.1). The first antenatal diagnosis was made in 1987 and there were a few terminations of pregnancy in the last four years. 41 babies were live born in eight years, 31 of whom would have been suitable for transplantation. In a modelling exercise, these were matched against potential donors from the same population. Two groups were examined. The first theoretical donor pool was live born babies with anencephaly with a birth weight >2 kg. Of 228 cases of anencephaly in eight years, three could potentially have been sources of donor hearts (figure 3.2) (There are obvious major ethical concerns about the use of anecephalic donors, which were widely debated at the time. [Landwirth] Such a practice is now not acceptable. [Pasquerella]) In the USA and Canada most infant cardiac donors at that time had died of trauma, birth asphyxia or sudden infant death syndrome. We also analysed eight years' data on fatal head injury in infants and small children. There were 30 such cases, one of which might potentially have been suitable to be a donor (figure 3.3) Thus there were four potential donors in eight years for a potential 31 recipients. Data from a further three years (1986-1989) were examined for a potentially wider donor pool including late deaths from sudden infant death and birth asphyxia. Of 426 cases of post-neonatal sudden infant death syndrome there were only two potential donors and there were no late deaths from birth asphyxia in this time.

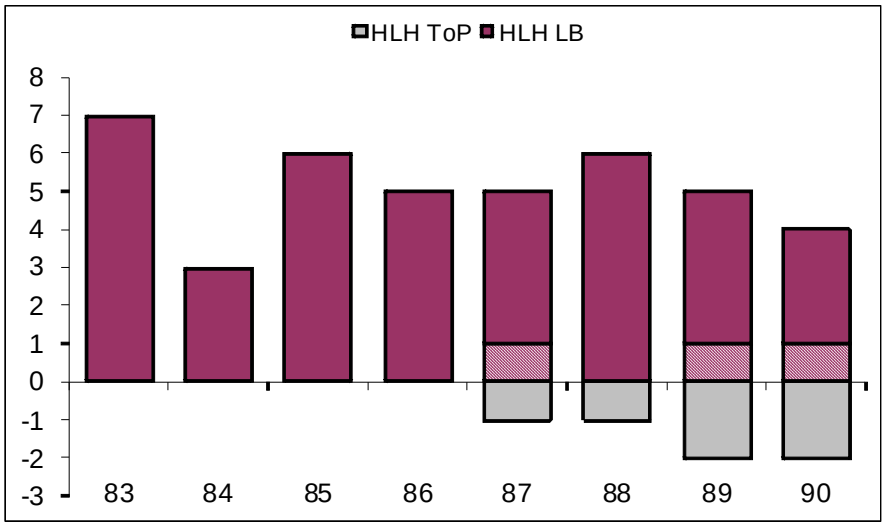

Figure 3.1. Cases of hypoplastic left heart recorded in eight years 1983-90. Maroon = live born (LB) postnatal diagnosis; hatched = live born prenatal diagnosis; grey = prenatal diagnosis and termination of pregnancy (ToP).

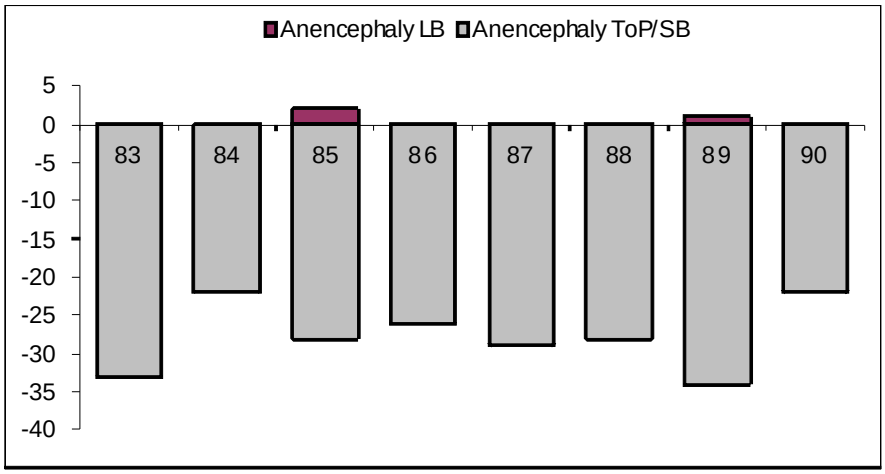

Figure 3.2. Cases of anencephaly recorded in eight years 1983-90. Maroon = live born with birth weight >2kg; grey = prenatal diagnosis and termination of pregnancy or birth weight <2kg.

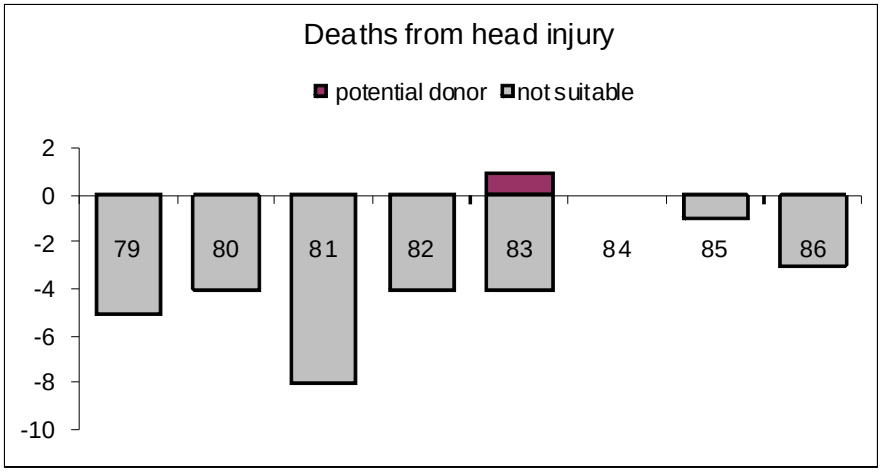

Figure 3.3. Cases of fatal head injury recorded in eight years 1979-86. Maroon = potential donor; grey = not suitable as donor (see text).

Given the fact that there was at the time a maximum two week window from diagnosis to transplantation and that ABO compatibility between donor and recipient was required, it was obvious that primary neonatal cardiac transplantation within the UK was not a feasible option. *Google Scholar* lists 18 citations for this paper at the end of 2006.

3.3.2 Abu-Harb M, Hey E, Wren C. Death in infancy from unrecognised congenital heart disease. *Arch Dis Child* 1994;71:3-7. During the initial data collection to make good the deficit in ascertainment of cardiovascular malformations, it became apparent that the PMS and NorCAS contained many cases of deaths from or with cardiovascular malformations which were not recognised in life. Detailed analysis of these cases led to our first report based on data on all malformations collected consecutively from January 1985. Data were collected retrospectively on all births in 1985-1990. We found that 56 of 1074 cases of cardiovascular malformation were identified only after death. Because of the initially retrospective data collection, the live birth prevalence of cardiovascular malformations was relatively low at 4.7 per 1000 live births. This was due to under-ascertainment of minor cardiovascular malformations. Thus the finding that 5% of all cases were diagnosed only after death is probably an overestimate. Nevertheless, the finding that 30% of deaths from or with a cardiovascular malformation were unknown in life (2.8% of all infant deaths) would not have been affected by ascertainment. About half of these infants who died had severe non-cardiovascular malformations, which either led to early death or discouraged other investigations because they were intrinsically fatal problems such as trisomy 13 or trisomy 18. This report highlighted the difficulty in clinical diagnosis of potentially fatal heart disease and led to our interest in subsequent reports discussed in chapters 4 and 5. The paper has been very widely quoted - *Google Scholar* lists 65 citations at the end of 2006. A more recent analysis of the timing and mode of presentation of potentially life-threatening cardiovascular malformation in the 20 years 1985-2004 shows that post-mortem diagnosis is now rare (see section 4.11).

3.3.3 Abu-Harb M, Wyllie J, Hey E, Richmond S, Wren C. Presentation of obstructive left heart malformations in infancy. *Arch Dis Child* 1994;71:F179-F183. Because the previous paper had identified certain malformations which had the potential to cause early death but were suitable for treatment, these cases were analysed further in a subsequent study. The leading diagnoses were various types of left heart obstruction, notably hypoplastic left heart, aortic stenosis, coarctation of

the aorta and interruption of the aortic arch. The paper was a retrospective analysis of the mode and timing of presentation of these four diagnoses in 120 consecutive infants born in 1987-1991. The slightly later timeframe was used because of under-ascertainment of minor cardiovascular malformations in the early part of the survey, although this had no effect on the numerator in this investigation. Our analysis showed that 10% of all cases became symptomatic or died within the first 24 hours of life. Only 34 of 108 babies had an abnormal neonatal examination and only 14 of these were diagnosed before discharge. Thus 94 babies were sent home with no diagnosis and 58 of these (62%) became symptomatic or died before six weeks of age, the time of the next scheduled examination. A six week check was performed in 36 babies and this led to another 16 diagnoses. Of the remaining 20 babies 18 were late clinical diagnoses and two with aortic stenosis were diagnosed only after death. Figure 3.4 shows the age at onset of symptoms of heart failure (as opposed to age at diagnosis).

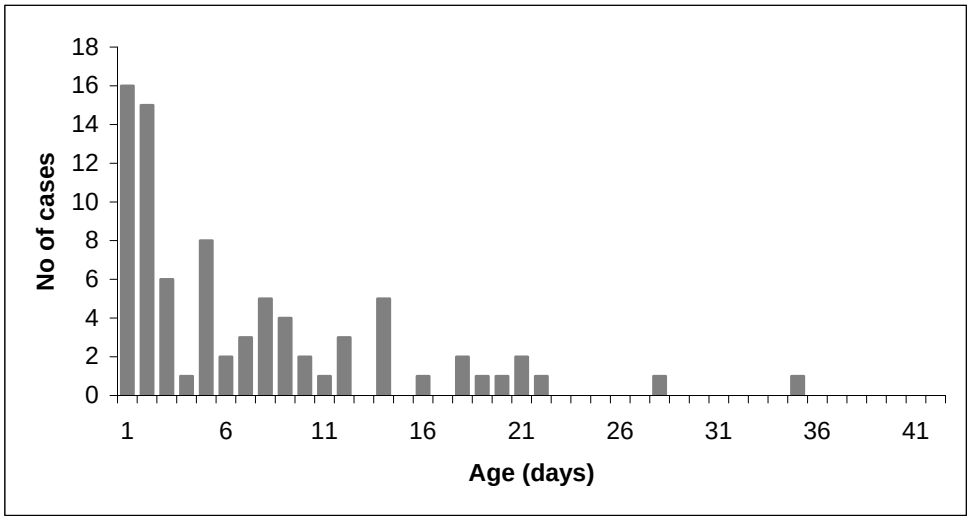

Figure 3.4. Age in days at the onset of symptoms of heart failure in 81 infants. As can be seen, 78/81 (96%) developed symptoms by the age of three weeks.

These four diagnoses remain difficult to detect and they are still the most likely to be found after discharge from hospital, as discussed in chapter 5. This paper was widely cited (Google Scholar lists 32 citations at the end of 2006) and influenced the subsequent research strategy especially the group of three papers (Ainsworth et al, Gregory et al, and Wren 1999 et al) discussed in detail in chapter 4. The paper also had a significant influence on epidemiological research on the topic of screening for neonatal heart disease and has been used to help define national screening policy.

3.3.4 Abu-Harb M, Wyllie J, Hey E, Richmond S, Wren C. Antenatal diagnosis of congenital heart disease and Down's syndrome: the potential effect on the practice of paediatric cardiology. ***Br Heart J*** **1995;71:192-8.** The third paper based on data in the paediatric cardiology database was published in 1995. This used data on the prevalence at live birth of cardiovascular malformations and Down syndrome in a modelling exercise to predict the influence of antenatal diagnosis and termination of pregnancy on the practice of paediatric cardiology. At the time it was being predicted that cardiovascular malformations would follow the model of neural tube defects, with the large majority being diagnosed antenatally and a policy of termination of pregnancy leading to a large reduction in live births. [Murphy 1996] [Northern Regional Survey Steering Group 1992] In this study all live born cardiovascular malformations were classified as being either "detectable" or "not detectable", based on the likelihood of recognition in a routine examination by an obstetric sonographer (as opposed to an expert fetal echocardiographer). All diagnoses were also classified as being complex, significant, or minor. Complex malformations were those with an absent or hypoplastic ventricle or valve. Significant malformations had four valves and chambers but required surgical repair. Minor malformations (mostly small ventricular septal defects and mild valve stenosis) were those that did not require intervention.

The usefulness of this dual classification of detectability and severity of cardiovascular malformations was validated by the relationship between classification and outcome shown below.

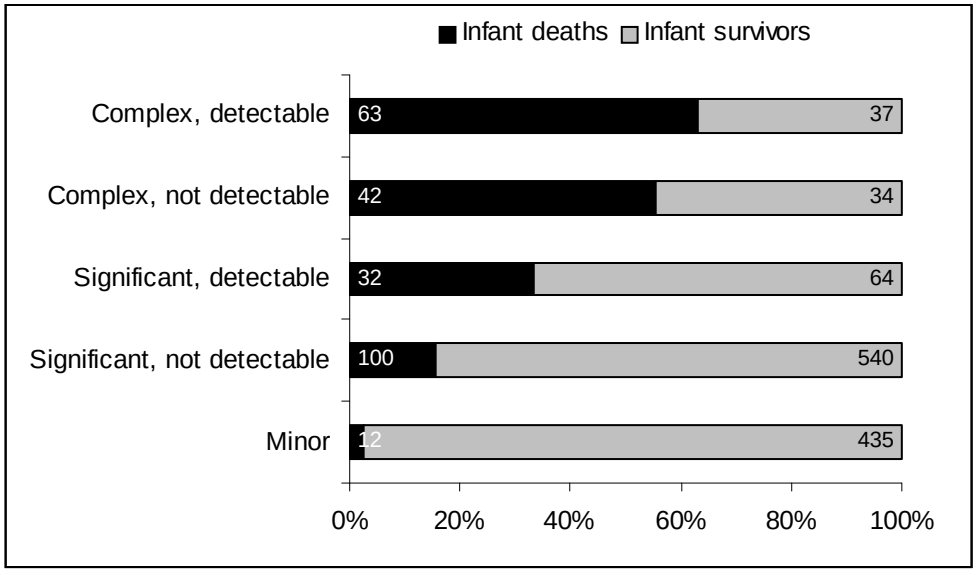

Figure 3.5. Outcome for live born cardiovascular malformations based on severity of the malformation and potential for antenatal diagnosis (see text).

The effect of antenatal diagnosis on outcome obviously depends on the product of the potential detectability, the achieved detection rate and the termination rate as shown in figure 3.6 (taken from the paper) below.

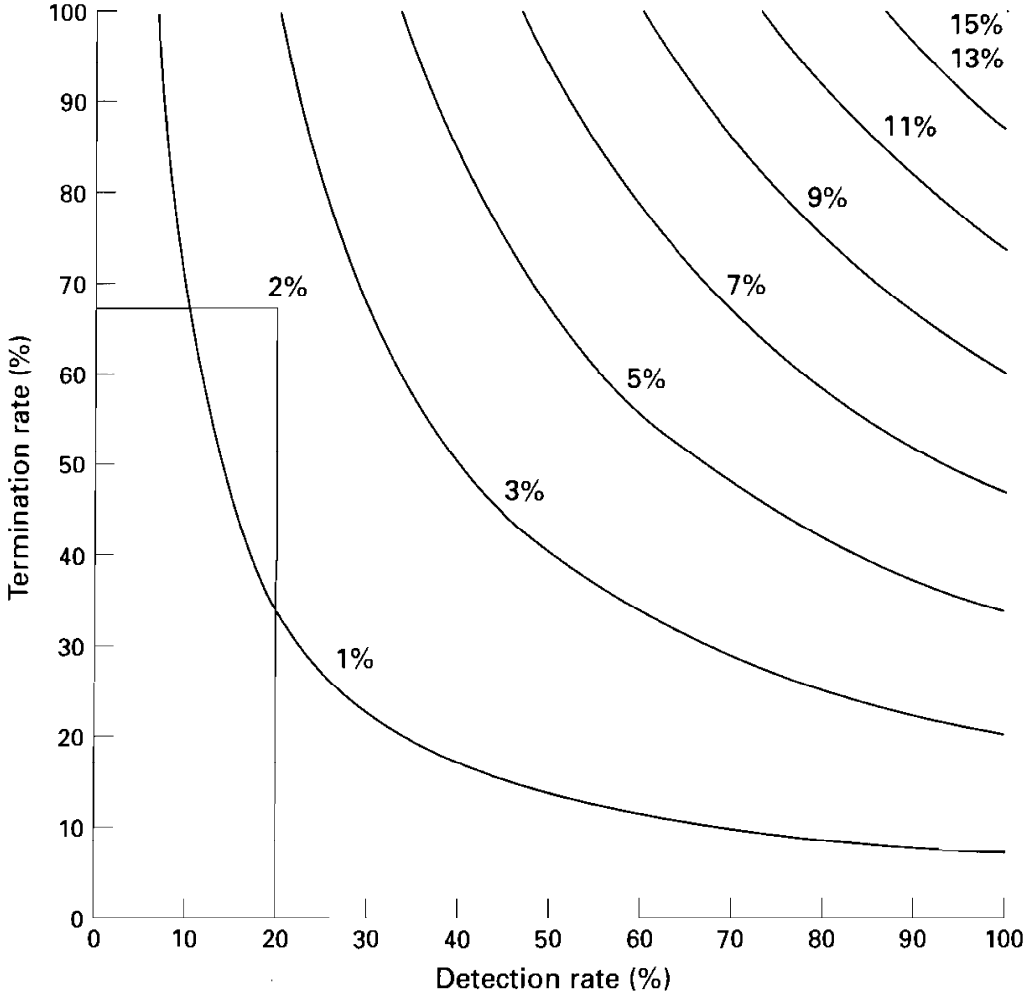

Figure 3.6. Cumulative effect of detection rate and termination rate on the prevalence at live birth of congenital heart disease. 15% of all cases were "detectable" so a detection rate of 100%plus a termination rate of 100% would reduce live born congenital heart disease by 15%. Assuming 20% of "detectable" and two thirds of detested cases are terminated, the reduction in live born congenital heart disease would be 2%. The effect of any detection rate with any termination rate ccan be calculated from this graph.

Analysis of surgical activity showed that 78% of operations were done in patients with antenatally undetectable malformations. Our data on the prevalence and spectrum of malformations enabled prediction of the impact of antenatal diagnosis.

Further analysis showed that a 20% detection rate and 67% termination rate would lead to a 2% reduction in live born cardiovascular malformations, a 5% reduction in infant mortality from cardiovascular malformations and a 3% reduction in paediatric cardiac surgical activity. A similar analysis of live born Down syndrome assumed 75% uptake of triple screening, 60% detection and 100% termination of detected affected pregnancies. This would lead to a 45% reduction in Down syndrome, a 3.5% reduction in cardiovascular malformations, and a 2.6% reduction in cardiac surgery. These levels were used as they were widely quoted by "modelling" studies in that era, although we thought at the time and said in the paper that these were unlikely to be achieved. It is interesting to look back ten years later. The number of cardiovascular malformations continues to rise (see papers in chapter 4). The numbers of paediatric cardiac surgical operations is increasing as a result of improvements in outcome leading to more and more survivors requiring further surgery. Live born Down syndrome is also increasing as the population effect of increasing maternal age is outpacing the effect of antenatal diagnosis and termination of pregnancy (see below: Irving et al, paper submitted for publication). Google Scholar lists 14 citations for this paper at the end of 2006.

3.3.5 Wyllie JP, Madar RJ, Wright M, Burn J, Wren C. Strategies for antenatal detection of Down's syndrome. *Arch Dis Child* 1997;76:F26-F30. This paper explored further the theme of trends in live birth of Down syndrome. It used data on all Down syndrome pregnancies in the region in 1985-1991. Ascertainment used all available sources including the fetal medicine, genetics, paediatric cardiology and NorCAS databases. 412 affected pregnancies were identified and those in mothers under 35 and 35 and over were analysed separately. A theoretical population with no termination of pregnancy was produced by allocating all cases ending in termination of pregnancy to have been live born or stillborn according to the proportions observed in non-terminated pregnancies and according to maternal age. In the observed population there were 18% terminations, 6% stillbirths, and 76% live births. In the theoretical population there were 93% live births and 7% stillbirths (figure 3.7).

Further analysis of the data showed that age-related amniocentesis with a predicted 50% uptake and 100% termination (both high estimates and unlikely to be achieved) would lead to a 16% termination rate and 78% live births. A similar analysis of maternal serum screening assumed 81% uptake, 70% detection, 79% amniocentesis, and 90% termination (all the highest published figures at the time but

again unlikely to be achieved). The predicted effect overall would be termination in 0.81 x 0.70 x 0.79 x 0.90, i.e. in 38% of cases, with 58% being live born. The combined effect of age-related amniocentesis, maternal serum screening, and fetal echocardiography was predicted to result in 40% termination and 56% live births in Down syndrome.

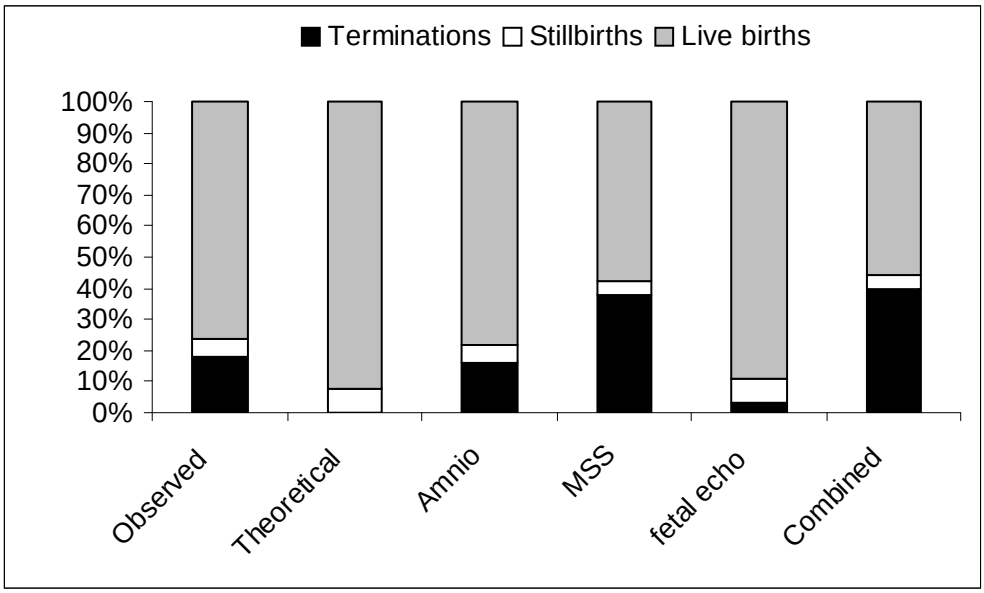

Figure 3.7. The predicted effects of different screening strategies on the outcome of pregnancies with Down syndrome. (Amnio = amniocentesis; MSS = maternal serum screening; echo = echocardiography; combined = amnio + MSS)

Table 3.1, taken from the paper, shows the predicted effects per 100,000 pregnancies and per year in the UK.

Table 3.1 Projected numbers of live born babies with Down syndrome for various screening strategies.

	Per 100000 pregnancies	*UK per year*
Total Down's pregnancies	144	1080
Live births/observed population	111	833
Live births/amniocentesis > 35 years	115	863
Live births/maternal serum screening	85	638
Live births/maternal serum screening + fetal echocardiography	81	608

This report attracted criticism despite the modelling using the highest reported detection, amniocentesis, and termination rates. [Sharland 1997] In fact, as noted above, the prevalence at live birth of Down syndrome continues to rise. In the Northern Region in 2000-2004 amniocentesis and chorionic villus biopsy have

reached a plateau at around 35 per 1000 registered births (3.5%), maternal serum screening at around 35% of registered births, and termination of pregnancies at around 0.9 per 1000 registered births. As can be seen from figure 3.8, the prevalence at live birth of Down syndrome continues to rise with significant implications for those planning long term medical and other care for people with Down syndrome.

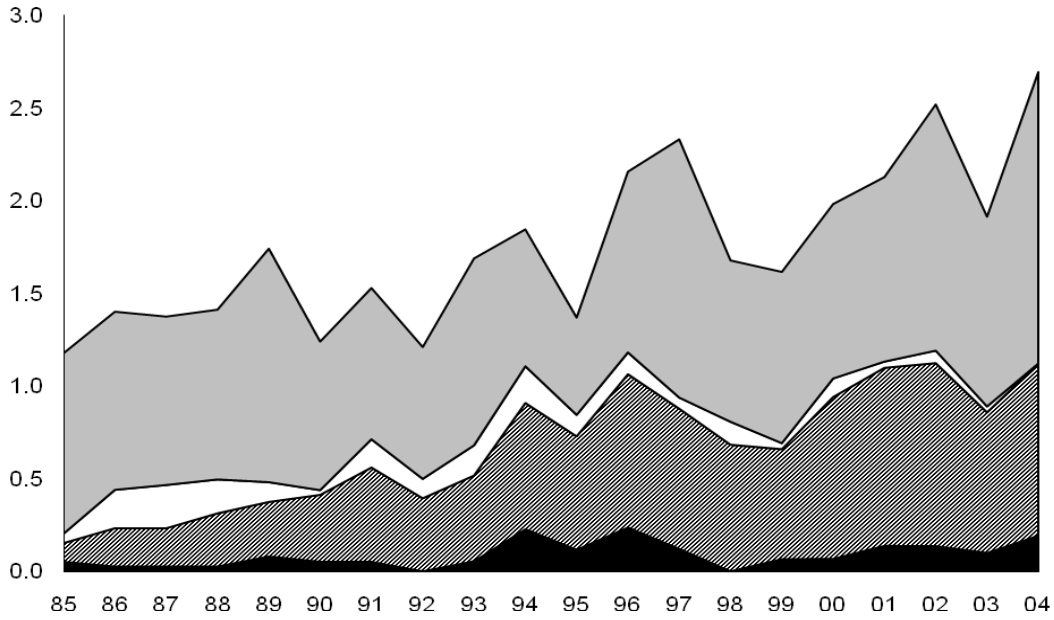

Fig 3.8. 20 year trends in birth prevalence of Down syndrome (per 1000 registered births) showing an overall doubling of the rate and the changing effect on live births.
Black = stillbirths, hatched = termination of pregnancy, white = live births with death in infancy, grey = live births alive after infancy.
(From Irving C, Basu A, Burn J, Wren C. Twenty-year trends in prevalence and survival of Down syndrome. *Eur J Hum Genet* 2008;16:1336-40.)

The overall theme of the first five papers was the use of sound, reliable data with high ascertainment rates and good validation from a defined population for descriptive and predictive analyses of the occurrence and influence of cardiovascular malformations. These themes were developed further in a series of linked reports discussed in more detail in chapter 4.

CHAPTER 4: PUBLISHED STUDIES ON THE EPIDEMIOLOGY OF CARDIOVASCULAR MALFORMATIONS

4.1 INTRODUCTION

The recent published output from analysis of data in the regional paediatric cardiology database is presented in this chapter. Ten papers published in high impact journals in 1999-2008 are included. The first three, which were published together, deal with the important topic of how congenital cardiovascular malformations come to notice. The fourth examines influences on intrinsic variability of birth prevalence and how ascertainment and classification of malformations affect apparent birth prevalence.

The fifth paper uses data on birth prevalence and survival to predict the growth of the population of adults with congenital heart disease and provides unique population-based data on post infant ascertainment of cardiovascular malformations. The next two focus on specific malformations – an analysis of outcome and quality of life in all forms of pulmonary atresia and a study of the influence of cardiovascular malformations on the outcome of infants with oesophageal atresia.

The next two papers examine the effects on the prevalence at live birth of cardiovascular malformations of maternal diabetes and prematurity.

The final paper, published since the original submission of this thesis, analyses trends in the presentation of life-threatening cardiovascular malformations in neonates over twenty years.

The ten papers employ similar methods to, and develop the themes of, the earlier studies presented in chapter three. They use population-based data with near complete ascertainment, accurate diagnosis and good validation and employ similar techniques of analysis and modelling. Their analyses and conclusions will influence other investigations currently in progress and planned for the future.

4.2 Ainsworth S, Wyllie J, Wren C. The prevalence and significance of cardiac murmurs detected at the routine newborn examination. *Arch Dis Child* 1999;80:F43-F45.

Background: The first of three papers, published together in *Archives of Disease in Childhood*, this two year prospective cohort study investigated the prevalence and significance of murmurs detected in more than 7000 neonates undergoing routine clinical examination by neonatal senior house officers in a large district general hospital. The regional paediatric cardiology database was used to identify those who presented earlier or later in infancy.

Key messages: Murmurs were detected in 6‰ (6 per 1000) neonates on routine examination before discharge and 25/46 (54)% had an underlying cardiovascular malformation. 32 presented later and 10 were diagnosed antenatally, or before routine examination, or after admission to the neonatal intensive care unit. Routine clinical examination detected only 44% of infant heart disease. The most important finding was that absence of a murmur does not exclude the presence of a serious cardiovascular malformation.

Impact: This report is a standard reference in all papers on neonatal heart defects and reviews of neonatal screening for cardiovascular malformations. Its findings have stimulated interest in the use of pulse oximetry to increase detection of serious malformation but real improvement is more likely to come from better antenatal diagnosis.

Citations: Google Scholar lists 49 citations at the end of 2007.

Arch Dis Child Fetal Neonatal Ed 1999;**80**:F43–F45

Prevalence and clinical significance of cardiac murmurs in neonates

Sean B Ainsworth, Jonathan P Wyllie, Christopher Wren

Abstract

***Aim*—To determine the prevalence and clinical significance of murmurs detected during routine neonatal examination.**

***Methods*—In a two year prospective study, 7204 newborn babies underwent routine examination by senior house officers. All those with murmurs underwent echocardiographic examination. All babies presenting later in infancy were also identified, to ascertain the total prevalence of congenital heart disease in infancy.**

***Results*—Murmurs were detected in 46 babies (0.6%) of whom 25 had a cardiac malformation. The most common diagnosis was a ventricular septal defect, although four babies had asymptomatic left heart outflow obstruction. A further 32 infants from the same birth cohort had a normal neonatal examination but were found to have a cardiac malformation before 12 months of age.**

***Conclusions*—The neonatal examination detects only 44% of cardiac malformations which present in infancy. If a murmur is heard there is a 54% chance of there being an underlying cardiac malformation. Parents and professionals should be aware that a normal neonatal examination does not preclude a clinically significant cardiac malformation. The detection of a murmur should prompt early referral to a paediatric cardiologist for diagnosis or appropriate reassurance.**

(*Arch Dis Child Fetal Neonatal Ed* 1999;**80**:F43–F45)

Keywords: congenital heart disease; neonatal examination; cardiac murmur; screening

Up to six in every 1000 live born babies have a cardiovascular malformation[1] which presents in infancy, but most are asymptomatic at birth.[1–4] Auscultation of the heart during routine examination before discharge from hospital provides an opportunity for early diagnosis and is recommended in the report of the Third Joint Working Party on Child Health Surveillance.[5] Despite this recommendation, routine auscultation has not been subjected to prospective evaluation.

The difficulties in detecting heart disease at neonatal examination are well known.[6 7] The neonatal examination takes place at a time of rapid change within the cardiovascular system as part of adaptation to extra uterine life.[8] These changes may produce murmurs which can be mistaken for heart disease.[9] Similarly, if transitional changes are slow to occur, presentation of congenital heart disease may be delayed.

The reported prevalence of murmurs in neonates varies from 0.9% to 77.4% and seems to be inversely related to the size of the study.[10–19] Detection of a murmur depends on the examiner's skill and experience, the timing and frequency of examination, and the conditions under which examination takes place. Most reports of the prevalence of neonatal murmurs come from early studies,[10–18] predating echocardiography which has improved the accuracy of diagnosis of congenital heart disease.[20] There is little in published findings that correlates murmurs during the newborn period with confirmed anatomical diagnosis.

This prospective study was undertaken to determine the prevalence and clinical significance of murmurs heard during routine examination of neonates and the contribution of the neonatal examination to detection of congenital heart disease in infancy.

Methods

The study comprised live born babies at a single large district general hospital between 1 January 1995 and 31 December 1996. Routine examination was undertaken by senior house officers in neonatal paediatrics or obstetrics within 48 hours of delivery. All had received identical training in neonatal examination. Infants who were either premature (<35 weeks of gestation) or ill, and who required neonatal intensive care, were excluded from analysis as their examination was not routine. Four cases in which antenatal diagnosis led to termination of pregnancy were also excluded.

Infants with murmurs were re-examined by a consultant (JPW) who performed an echocardiogram, usually within 24 hours of the murmur being heard. Where this was not possible, as in the case of early discharge, babies were brought back to an outpatient clinic or the neonatal unit within two to 14 days.

The echocardiogram permitted early accurate anatomical diagnosis either to reassure parents that the heart was normal, or where heart disease was detected, to explain the nature of the abnormality and, where necessary, to arrange referral for definitive treatment.

Infants who underwent echocardiography were categorised as either having: structural heart malformations; a physiological variant which would account for the murmur (such as left pulmonary artery branch stenosis or patent ductus arteriosus); a finding that in itself would not cause a murmur (such as cardiac hypertrophy secondary to maternal diabetes); or a completely normal echocardiogram. Congenital heart disease was defined as by Mitchell *et al*[21] as "a gross structural abnormality of the heart

Directorate of Neonatology South Cleveland Hospital Middlesbrough TS4 3BW
S B Ainsworth
J P Wyllie

Department of Paediatric Cardiology Freeman Hospital Newcastle upon Tyne
C Wren

Correspondence to:
Dr J P Wyllie.

Accepted 26 June 1998

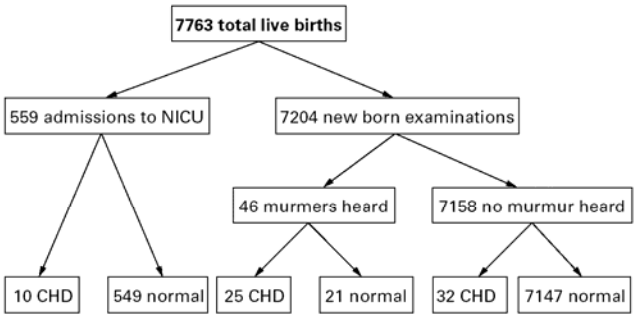

Figure 1 Flow diagram showing progress of all infants included in the study.

Table 1 Anatomical diagnosis and timing of diagnosis

	Antenatal	*Early*	*Intensive care*	*Newborn*	*Late*	*Total (%)*
VSD	0	0	2	15	19	36 (54)
Complex CHD	3	2	0	0	3	8 (12)
Left heart obstruction	0	0	0	4	1	5 (7)
Pulmonary stenosis	0	0	1	1	3	5 (7)
ASD	0	0	1	2	1	4 (6)
Tetralogy of Fallot	0	0	0	3	1	4 (6)
ASD/VSD	0	0	1	0	1	2 (3)
PDA	0	0	0	0	2	2 (3)
TAPVC	0	0	0	0	1	1 (1)
Totals	3	2	5	25	32	67 (100)

VSD = ventricular septal defect; CHD = congenital heart disease; ASD = atrial septal defect; PDA = patent ductus arteriosus; TAPVC = total anomalous pulmonary venous connection.

or intrathoracic great vessels that is actually or potentially of functional importance."

All infants presenting with congenital heart disease during the first year of life from the same birth cohort were identified from the regional paediatric cardiology database. Their hospital records were examined to ensure that murmurs had not been present at the time of the neonatal examination and they had not inadvertently been excluded from early echocardiography.

A randomly selected sample of 400 (6%) case files of infants without heart malformations were scrutinised to ensure no infant with a neonatal murmur had bypassed the study. All senior house officers were informed of the protocol before taking up their post and midwives could not discharge the baby without follow up checks being arranged for any congenital abnormality.

Statistical analysis was limited to calculation of sensitivity and specificity and the intervals of the proportions.

Results

During the study period, 7763 babies were live born at the hospital (fig 1). Of these, 559 were admitted to the neonatal intensive care unit, including two babies who became symptomatic before routine newborn examination, three known to have cardiac malformations antenatally, and five premature babies who were diagnosed during their stay in intensive care (other than patent ductus arteriosus associated with prematurity).

Table 2 Neonatal examination as a screening test

	Heart disease	*No heart disease*	*Totals*
Murmur present	25	21	46
Murmur absent	31	7127	7158
Totals	56	7148	7204

Key messages

- The prevalence of murmurs detected at routine examination of neonates is less than 1%.
- About half of murmurs are due to an underlying cardiovascular malformation
- Early referral of all newborn babies with murmurs for definitive diagnosis is recommended
- The absence of a murmur does not exclude serious heart disease

Of 7204 neonates who underwent routine examination, 46 (0.6%) were found to have a murmur (fig 1). All underwent echocardiography which confirmed a cardiac malformation in 25 and a structurally normal heart with physiological findings that would account for the presence of a murmur (such as patent ductus arteriosus or mild physiological pulmonary artery branch stenosis) in eight. Thirteen babies had normal hearts. All 25 babies with cardiac malformations were asymptomatic—15 had a ventricular septal defect, three had coarctation of the aorta, one had aortic valve stenosis, two had an atrial septal defect, one had pulmonary stenosis and three had tetralogy of Fallot (table 1).

A further 32 babies from the same birth cohort presented with congenital cardiac malformations after the routine neonatal examination and before the age of 1 year (table 1). Review of the hospital records of these infants confirmed that none had had a murmur at the time of neonatal examination. This identified 25 of 67 cases (37%) of structural heart disease diagnosed during infancy. The sensitivity of the examination for detection of congenital heart disease which became apparent during infancy was 44% (95% CI 31–58%), the specificity was 99.7%, and the positive predictive value was 54% (95% CI 39–69%) (table 2). The high specificity is simply a reflection of the low prevalence in the denominator population.

Discussion

Although congenital heart disease is present at birth, there are often no signs and most babies are asymptomatic. Detection of a murmur on routine examination may be a clue to the presence of heart disease and offers the possibility of early, presymptomatic diagnosis. Auscultation is, therefore, part of routine neonatal examination and is recommended in *Health for All Children*.[5] There is, however, a widespread misconception that murmurs are common in neonates, and that most are innocent or "physiological." This may explain why there seems to be reluctance to make early referral for definitive diagnosis of heart disease.[22]

Most neonatal examinations in the United Kingdom are performed by senior house officers who may see up to 20 babies a day, in conditions that are not ideal for auscultation. Given these limitations it is not surprising that

the prevalence of murmurs in this study is less than in previous reports. However, this study does reflect real life and its methodology did not change the system it studied. The prevalence of murmurs is consistent with the only previous published study relying on junior medical staff for detection of murmurs.[18] We found that murmurs were detected in 0.6% of babies undergoing routine examination. Fifty four per cent of babies with murmurs had a structural cardiovascular malformation. Most importantly, 9% of babies with murmurs required early cardiac surgery and were detected before they became symptomatic. This fact, if nothing else, would support the proposition that all babies with murmurs should undergo early paediatric cardiological assessment.

Early assessment of murmurs has been recommended,[23] but does not always happen. Abu-Harb *et al* found that 10 of 26 babies with obstructive left heart malformations who had been sent home, despite a murmur at neonatal examination, presented in heart failure before six weeks of age.[6] Similarly, Beebe *et al* found that 57% of neonates dying from cardiovascular malformations after discharge from hospital had had a murmur before discharge.[24] Thus given that murmurs are rare, and that many are a clue to the presence of asymptomatic heart disease, it seems appropriate to refer all such babies for early definitive diagnosis.

In this study the detection of a murmur at routine neonatal examination led to the diagnosis of 37% of all cases of congenital heart disease presenting in infancy. Another 15% presented before examination while 48% had no murmur and were diagnosed later in infancy. Routine neonatal examination thus has a sensitivity of 44% and the presence of a murmur has a positive predictive value of 54%. Ascertainment of heart disease was limited to infancy to ensure consistency with the methodology of other recent epidemiological studies.[1–3 22] Although neonatal auscultation does not perform particularly well as a screening test, it still offers the only real opportunity of early detection of heart disease. It should, however, be more widely recognised that about half of babies with congenital heart disease will have no signs when examined soon after birth. The low prevalence of murmurs in this study does not mean that murmurs went undetected, but rather that potentially serious heart disease may produce no physical signs early in life. Even in studies with a higher prevalence of murmurs there was no significantly greater detection of heart disease.[19]

The birth prevalence of congenital heart disease diagnosed in infancy in this study (9.3 per 1000 life births) is higher than in most large series.[1–4] This may be explained by a high prevalence of small ventricular septal defects as a result of the easy availability of early echocardiography. Two recent studies using neonatal echocardiography found a prevalence of ventricular septal defect as high as 20 and 53 per 1000 live births.[25 26] In both studies most babies were asymptomatic and most defects were small with early spontaneous closure rates of 76 and 89%, respectively.

This study has shown that a prevalence of murmurs of six in 1000 babies undergoing routine neonatal examination by junior paediatricians. About half of murmurs were due to underlying structural cardiac malformation and this examination led to recognition of 37% of all heart disease diagnosed in infancy. Identification and treatment of heart disease before development of symptoms offers the prospect of an improved outcome. Early referral of all asymptomatic babies with murmurs is recommended. The absence of a murmur does not exclude the presence of potentially serious heart disease.

The paediatric cardiology database is funded by the Children's Heart Unit Fund.

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4.3 Gregory J, Emslie A, Wyllie J, Wren C. Examination for cardiac malformations at six weeks of age. *Arch Dis Child* 1999;80:F46-F48.

Background: Clinical examination at 6-8 weeks of age, including auscultation of the heart, is a fundamental part of health surveillance. The second of a trilogy of papers, this was a retrospective cohort study to assess the efficacy of examination at six - eight weeks of age.

Key messages: Only 83% of babies eligible for examination attended and only 56% were examined at the intended time. Murmurs were heard in 8.7‰. After clinical assessment, half were referred for investigation and half of those were found a cardiovascular malformation. The 6-8 week examination led to the detection of 31% of cardiovascular malformations in the study population. Findings included significant abnormalities such as transposition of the great arteries and tetralogy of Fallot and this suggests that all infants with murmurs at this age should undergo further assessment.

Examination at 6-8 weeks could meet the criteria for a screening test. This study examined the efficacy of the examination as it is done rather than as it should be done. It found major deficiencies in what could be a useful screening test. Screening was performed with poor records, inconsistent action in the face of an abnormality, and no assessment of outcome.

Impact: This paper has some limitations, notably the inability to define a precise birth cohort, as the study was based on a population and was organised through the department of community paediatrics. Nevertheless, there is no other assessment of screening at 6-8 weeks in the literature.

Citations: Google Scholar lists 5 citations at the end of 2007.

Examination for cardiac malformations at six weeks of age

Jill Gregory, Alison Emslie, Jonathan Wyllie, Christopher Wren

Abstract

***Aim*—To attempt to define the prevalence and significance of murmurs detected on routine clinical examination at six to eight weeks.**

***Methods*—A retrospective review of the results of routine clinical examination of a cohort of 6 to 8 week old babies resident in Newcastle upon Tyne, was carried out in two 12 month periods. All cardiac defects diagnosed in infancy in the same cohort were ascertained.**

***Results*—7132 babies were eligible for routine examination; 83% of these were examined. Murmurs were heard in 47 of 5395 babies and in 11 of 25 referred for evaluation congenital heart disease was found. The six to eight week examination led to diagnosis of 11 of 35 cases (31%) of congenital heart disease in the study population.**

***Conclusions*—Nearly one baby in 100 had a murmur on routine examination at six to eight weeks. Nearly half of those with murmurs who were referred had a structural cardiovascular malformation.**

(*Arch Dis Child Fetal Neonatal Ed* 1999;**80**:F46–F48)

Keywords: congenital heart disease; screening; cardiac murmur

Department of Community Paediatrics Newcastle City Health NHS Trust
J Gregory

Department of Clinical Audit
A Emslie

Department of Paediatrics South Cleveland Hospital, Middlesbrough
J Wyllie

Department of Paediatric Cardiology Freeman Hospital, Newcastle upon Tyne
C Wren

Correspondence to:
Dr Christopher Wren
Department of Paediatric Cardiology
Freeman Hospital
Newcastle upon Tyne
NE7 7DN.

Accepted 26 June 1998

Examination for signs of cardiovascular malformation at six to eight weeks is part of the routine health surveillance of young infants.[1] Although the presence of a murmur at this age is potentially clinically significant and "prompt referral" for specialist assessment is recommended in national guidelines,[1] the efficacy of such a policy has not been formally evaluated. This study examines the performance of routine clinical examination at six to eight weeks for the detection of cardiovascular malformations.

Methods

The study was originally designed in two parts: a retrospective review of babies examined between January and December 1991, and a prospective assessment of those examined between July 1993 and June 1994. After analysis of the first cohort, general practitioners and community paediatricians were advised to refer all babies with murmurs in the second 12 month period for specialist examination. However, this advice was not followed and there was no difference in referral practice between the two groups, so the results are presented together.

All live born babies whose mothers were resident in Newcastle upon Tyne and who were eligible for examination at 6 to 8 weeks of age

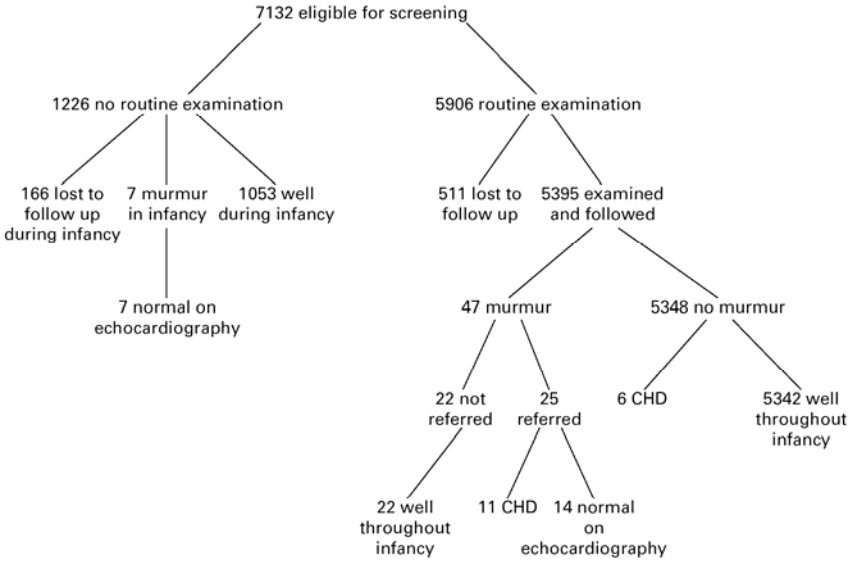

Figure 1 Flow diagram showing progress of the study from six to eight weeks to 12 months of age; CHD = coronary heart disease.

Table 1 Numbers and types of cardiovascular malformations identified in study population

Diagnosis		
Before 6 weeks	VSD	12
	PDA	2
	AVSD	1
	COA	1
	PS	1
	PA/VSD	1
6 to 8 weeks		
	VSD	7
	AVSD	2
	TGA	1
	TOF	1
After 6 to 8 weeks		
	PS	3
	VSD	2
	COA+VS D	1

VSD = ventricular septal defect; PDA = patent ductus arteriosus; AVSD = atrioventricular septal defect; COA = coarctation of aorta; PS = pulmonary valve stenosis; PA/VSD = pulmonary atresia with ventricular septal defect; TGA = transposition of the great arteries; TOF = tetralogy of Fallot.

between 1 January 1991 and 31 December 1991 and between 1 July 1993 and 30 June 1994 were identified. Routine clinical examination was performed by general practitioners and community paediatricians. The results of the examination (when performed) were identified by retrospective examination of records held at the Community Records Department, and the outcome of all those with murmurs was ascertained from the paediatric cardiology database.

The regional paediatric cardiology database provided information on all infants in the same cohort with congenital heart disease diagnosed by the age of 12 months. The database incorporates information from the regional perinatal and infant mortality survey to identify all cases dying before diagnosis.[2 3] The Freeman Hospital information system provided details of all infants evaluated for murmurs which were found to be benign. Congenital heart disease was defined as "a gross structural abnormality of the heart or intrathoracic vessels that is actually or potentially of functional significance".[4]

Results

In the two years of the study 7132 babies were eligible for routine clinical examination at six to eight weeks (fig 1). Of these 5906, (83%) were screened but 511 were lost to follow up or moved away before 12 months of age. The results of examination of the remaining 5395 are shown in the fig 1. Murmurs were heard in 47 babies (0.9%), but only 25 were referred for paediatric cardiological assessment. There is no information on how these babies were selected. As fig 1 shows, 11 of the 25 babies with murmurs who were referred had congenital heart disease and six with no murmur were subsequently found to have a cardiac defect during infancy. All diagnoses were confirmed by echocardiography. The 22 who were not referred remained well throughout infancy, and, as far as can be ascertained from the records, the murmurs all resolved spontaneously.

Of 1226 babies (17%) who did not undergo routine examination, seven (0.7%) were subsequently referred for evaluation of a murmur, 1053 were normal throughout infancy (in that they remained resident in Newcastle and did not present with heart disease during this time) and 166 were lost to follow up or moved away (fig 1).

Routine examination was not always carried out between 6 and 8 weeks of age. In this study 131 (2%) underwent what was considered to be a routine examination before 6 weeks, 1171 (20%) between 8 and 10 weeks, and 607 (10%) beyond 10 weeks.

Because of the study design it is not possible to define a birth cohort. However, congenital heart disease was recognised in babies born and resident in the catchment area throughout infancy in 18 (51%) before 6 weeks of age, as a result of the six week examination in 11 (31%), and between six weeks and 12 months of age in six (17%). Specific diagnoses made at various stages are shown in table 1.

Key messages

- Only 83% of eligible babies received routine examination for signs of heart disease and only 56% between 6 and 8 weeks of age.
- Murmurs were heard in roughly one baby in 100 (0.9%).
- About one quarter of babies with murmurs had structural heart disease but only about half were referred.
- Referral of all babies with murmurs at this age for expert evaluation is recommended.

Discussion

Routine examination for signs of congenital heart disease at 6 to 8 weeks of age is recommended in national guidelines[1] and is aimed at improving the outcome for babies with cardiovascular malformations, by detection at a pre-symptomatic stage. Although this policy potentially meets most of the criteria for a screening test,[5] its efficacy has not been formally evaluated before. Many babies with clinically significant abnormalities will have been identified before 6 weeks of age, although others may remain asymptomatic.[6] In a retrospective study of the presentation of a cohort of babies with cardiovascular malformations diagnosed in infancy, only 35% of those sent home without a definite diagnosis had achieved a diagnosis by 6 weeks of age.[6] After neonatal examination the six to eight week examination provides the only opportunity for detection of heart disease in infancy, other than opportunistic recognition of a murmur or the development of symptoms.

In retrospect, the design of our study could have been improved, particularly by the identification of a birth cohort which could then be followed up through infancy. Only 83% of babies who were eligible for examination underwent screening at all, and only 56% were examined between 6 and 8 weeks of age. Another weakness is that only 76% of the babies in the study population were examined at 6 to 8 weeks of age and were then available

for follow up throughout infancy (fig 1). Only 53% of those with murmurs were referred for expert assessment.

The 22 infants with murmurs who were not referred, the 5348 examined and found to have no murmur, and the 1053 not screened but who remained resident in the area can be assumed to have had no major cardiovascular problem as they were not referred to the only paediatric cardiology unit in the region and did not die. Whether they might have had a minor abnormality or none at all remains unknown. Most clinically significant congenital heart disease presents in infancy,[7 8] although some malformations, especially atrial septal defects and persistent arterial ducts, may not present until later. However, this study was aimed only at identifying problems which presented in infancy.

In this study 31% of all diagnoses made in infancy resulted from the six to eight week examination and 44% of babies with a murmur at this age turned out to have congenital heart disease. Routine examination did identify some clinically significant cardiac malformations but other significant problems were not detected (table 1). As with the neonatal examination,[6 9] it is important to recognise that absence of abnormal signs does not exclude abnormality.

Because of the design limitations we cannot clearly establish the population prevalence of murmurs at this age, although there is no obvious reason why the babies examined and followed up should be different from those who were not. For similar reasons it is difficult to define a precise birth prevalence of congenital heart disease diagnosed in infancy in this study. However, the figure of 35 cases from around 7000 births is consistent with those of previous studies with confirmed diagnoses only and ascertainment limited to infancy.[6 10–12] Despite its limitations, the study provides useful information for assessment of the routine six to eight week examination and for guidelines on what should be done if a murmur is heard.

This study set out to examine the efficacy of routine examination as it is performed rather than as it ideally should be performed. It highlights major deficiencies in the six to eight week examination as it is currently practised. Screening is performed with poor record keeping, inconsistent action in the face of an abnormality, and no assessment of outcome. There is obviously room for improvement.

The paediatric cardiology database is supported by the Children's Heart Unit Fund.

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4.4 Wren C, Richmond S, Donaldson L. Presentation of congenital heart disease in infancy – implications for routine examination. *Arch Dis Child* 1999;80:F49-F53.

Background: This is the third of three papers published together in *Archives of Disease in Childhood*. It was funded by the Northern Regional Health Authority and was a major retrospective review of the mode and timing of presentation of all infant heart disease in the region in eight years. Compared with the previous assessments of neonatal and 6-8 week routine examination, it looked at the detection of cardiovascular malformations from the other end of the telescope.

Key messages: Cardiovascular malformations were confirmed in 1590 infants (5.3 per 1000 live births). 33% came to notice before clinical examination because of symptoms or major non-cardiac abnormalities. Neonatal examination was abnormal in 45% but only a third of these were referred. 83% of babies were discharged without a diagnosis and a third of them presented with symptoms or died before the next scheduled examination at 6 weeks of age. Two thirds of those having a 6-8 week examination were abnormal but 31% of all infants remained undiagnosed by 12 weeks.

There was no correlation between the mortality for individual diagnoses and the likelihood of an abnormality being detected on examination. Detection rates were no higher in the four units providing neonatal intensive care than in smaller units.

The findings reinforce the difficulty of detecting cardiovascular malformations in asymptomatic infants and have encouraged the development of other screening strategies such as better antenatal diagnosis and routine pulse oximetry, although the efficacy of these methods is yet to be proven. The data from this study were used for further analysis in a recent HTA report: Knowles R, Griebsch I, Dezateux C, Brown J, Bull C, Wren C. Newborn screening for congenital heart defects: a systematic review and cost-effectiveness analysis. *Health Technol Assess* 2005;**9**(44).

Impact: This is a very important paper which has been widely quoted by many authorities, including ACC/AHA guidelines. It has had a major impact on clinical practice and has been used as evidence in defining national screening policy by the Royal College of Paediatrics and Child Health and the National Screening Committee.

Citations: Google Scholar lists 72 citations at the end of 2007.

Arch Dis Child Fetal Neonatal Ed 1999;**80**:F49–F53

Presentation of congenital heart disease in infancy: implications for routine examination

Christopher Wren, Sam Richmond, Liam Donaldson

Abstract

***Aim*—To investigate the performance of routine neonatal and 6 week examinations for detecting congenital heart disease.**

***Methods*—A retrospective review of findings on clinical examination was conducted of a cohort of live born infants with congenital heart disease in one health region in 1987–94**

***Results*—Of 1590 babies with congenital heart disease, 523 (33%) presented before neonatal examination because of symptoms or non-cardiac abnormalities. 1061 underwent routine neonatal examination which was abnormal in 476 (45%), but only 170 were referred directly for diagnosis. Of 876 discharged with no diagnosis, 306 presented or died undiagnosed before 6 weeks. At 6 weeks 252 of 569 babies underwent a second routine examination which was abnormal in 164 (65%).**

***Conclusions*—Routine neonatal examination fails to detect more than half of babies with heart disease; examination at 6 weeks misses one third. A normal examination does not exclude heart disease. Babies with murmurs at neonatal or 6 week examinations should be referred for early paediatric cardiological evaluation which will result either in a definitive diagnosis of congenital heart disease or in authoritative reassurance of normal cardiac anatomy and function.**

(*Arch Dis Child Fetal Neonatal Ed* 1999;**80**:F49–F53)

Keywords: congenital heart disease; cardiac murmur; screening.

Unrecognised neonatal heart disease carries a serious risk of avoidable mortality, morbidity, and handicap.[1] Examination before first discharge from hospital and of infants at 6 weeks of age for signs of congenital heart disease is recommended in *Health for All Children*.[2] We have already shown that most obstructive left heart malformations are not detected by these two examinations. Even when an abnormality (usually a murmur) is found, action is frequently not taken.[3]

We have now examined the performance of these two routine examinations in detecting all congenital heart disease within a large, geographically defined, population over a period of eight years.

Methods

We undertook a retrospective study of all cases of structural congenital heart disease diagnosed by the age of 12 months in babies live born in the northern health region of the UK between 1987 and 1994. This region covers a resident population of approximately 3.1 million in the counties of Cumbria, Northumberland, Tyne and Wear, Cleveland and Durham. Babies from south Cumbria are referred to another region and were excluded from this study. Cases were identified from the Northern Regional Congenital Abnormality Survey which was established in 1985 and which has collected cumulative records of all congenital malformations affecting babies born to mothers resident in the study population. A detailed description of its methodology has been published before.[4] A separate northern regional survey of perinatal, late neonatal, and infant mortality allowed babies with cardiovascular malformations who died before a cardiological diagnosis was made, to be identified.[5] Data on total births were obtained from the Office of National Statistics.

Congenital heart disease was taken to be "a gross structural abnormality of the heart or intrathoracic great vessels that is actually or potentially of functional significance," as defined by Mitchell *et al*.[6] Babies were included only if congenital heart disease was confirmed

Department of Paediatric Cardiology Freeman Hospital, Newcastle upon Tyne
C Wren

Neonatal Unit, Sunderland Royal Hospital
S Richmond

Department of Epidemiology and Public Health University of Newcastle upon Tyne
L Donaldson

Correspondence to:
Dr Christopher Wren
Department of Paediatric Cardiology, Freeman Hospital, Newcastle upon Tyne NE7 7DN.

Accepted 26 June 1998

Table 1 Diagnostic categories and total infant mortality

Diagnoses included	*Number*	*Total infant mortality n (%)*
Ventricular septal defect (VSD)	590	35 (6)
Pulmonary valve stenosis (PS)	135	5 (4)
Coarctation of aorta (COA)	108	17 (16)
Tetralogy of Fallot (TOF)	99	10 (10)
Simple transposition of great arteries (TGA)	84	17 (20)
Patent ductus arteriosus (PDA)	81	2 (2)
Complete atrioventricular septal defect (CAVSD)	81	33 (41)
Pulmonary atresia (PA)	73	25 (34)
Atrial septal defect, partial atrioventricular septal defect (ASD)	71	9 (13)
Aortic valve stenosis, subaortic stenosis, supravalvular stenosis (AS)	67	14 (21)
Hypoplastic left heart (HLH)	45	45 (100)
Total anomalous pulmonary venous connection (TAPVC)	27	8 (30)
Common arterial trunk (CAT)	24	17 (71)
Interruption of aortic arch (IAA)	24	16 (67)
Miscellaneous - other complex heart disease (MISC)	81	17 (21)
Total	1590	270 (17)

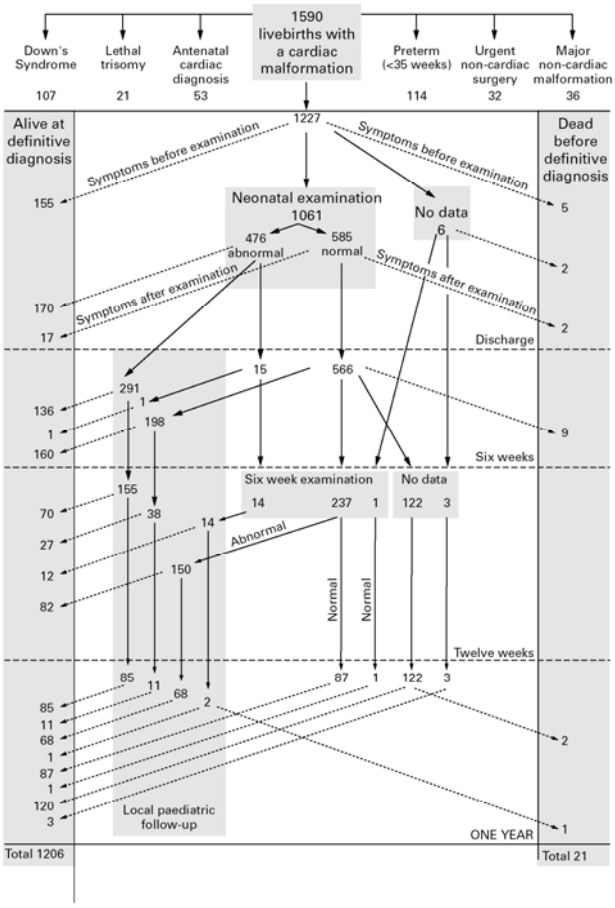

Figure 1 Flow chart showing how and when diagnosis of cardiovascular abnormality was achieved in all 1590 babies.

by echocardiography, cardiac catheterisation, surgery or necropsy, and cases were considered undiagnosed until diagnosis was made by one of these methods, even though the possibility of heart disease might have been recognised before this. Babies with isolated cardiac arrhythmias, patent ductus arteriosus complicating prematurity, and those with dilated cardiomyopathy and other acquired heart disease were excluded from analysis to permit comparison with previous studies.

All babies presenting beyond the age of 12 months were also excluded, in line with most population based epidemiological studies, because most clinically significant heart disease will have presented by this age. Two exceptions are atrial septal defect and patent ductus arteriosus which are included, although they are not really representative of the whole group of infants and children with these abnormalities—many such babies underwent evaluation because of other malformations or dysmorphic features rather than because of signs or symptoms on routine examination.

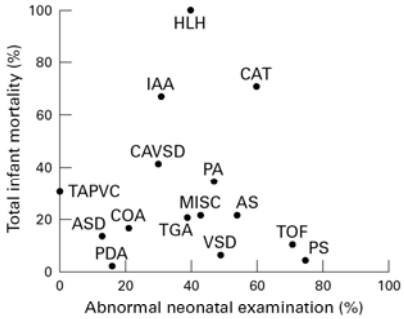

Figure 2 Relation between recognition of abnormality at routine neonatal examination and total infant mortality for each individual diagnostic group. Most deaths were due to cardiac malformation, with others accounted for by other abnormalities or a combination of factors.

The precise diagnosis was recorded. Babies with more than one cardiovascular abnormality were classified according to the malformation which precipitated presentation and which required earliest intervention.[7 8] For example, a baby with double inlet left ventricle and coarctation of the aorta was classified by the latter abnormality even though the former was the more severe malformation and more significant in determining the long term outcome. Details of routine neonatal examination were sought by retrospective review of the notes from the hospital where the baby had been born, the paediatric cardiology case notes, and the perinatal mortality survey records. For the purposes of this study a routine neonatal examination was taken to be the examination of a newborn baby before first discharge from hospital after birth, when the baby was assumed to be normal at the start of the examination. Such examinations were performed almost exclusively by paediatric senior house officers. Detailed examination of a baby to whom medical attention was drawn because of illness or abnormality was not considered a routine neonatal examination. All babies with other major non-cardiac malformation, lethal trisomy (13 or 18), urgent surgical abnormalities (such as oesophageal atresia), or babies who were significantly preterm (<1750 g or < 35 weeks of gestation) were excluded from general analysis on the grounds that our definition precluded a routine examination. Babies with Down's syndrome and all babies with an antenatal diagnosis of congenital heart disease were excluded for the same reason.

We attempted to trace results of examination at 6 to 8 weeks in all babies unless congenital heart disease had already been diagnosed, or the baby was under general paediatric follow up for suspected heart disease, before that age. We refer to this as the 6 week examination for the purposes of this report.

Results

Between 1987–94 300 102 babies were live born in the northern health region. Of 1590 who were found to have heart disease before the age of 12 months (table 1), we excluded from analysis 363 (23%) for the reasons

Table 2 Presentation of individual diagnoses, showing undiagnosed cases at each stage and performance of neonatal and 6 week examinations

Diagnostic group	*VSD*	*PS*	*COA*	*TOF*	*TGA*	*CAVSD*	*PDA*	*PA*	*ASD*	*AS*	*HLH*	*TAPV C*	*CAT*	*IAA*	*Miscellaneous*	*Totals*
Total cases (includes exclusions)	590	135	108	99	84	81	81	74	71	67	45	27	24	24	80	1590
All exclusions	101	23	13	27	8	62	26	10	33	9	10	5	6	5	25	363
Cases for analysis	489	112	95	72	76	19	55	64	38	58	35	22	18	19	55	1227
Not diagnosed before neonatal examination	483	108	82	63	18	19	54	32	38	57	18	20	16	13	46	1067
	99%	96%	86%	88%	24%	100%	98%	50%	100%	98%	51%	91%	89%	68%	84%	87%
Received neonatal examination	481	108	82	63	18	19	53	32	38	57	16	20	15	13	46	1061
Abnormal neonatal examination	237	61	17	45	7	3	16	15	5	31	6	0	9	4	20	476
Not diagnosed before discharge	407	90	72	41	13	15	47	20	36	49	12	19	11	9	35	876
	83%	80%	76%	57%	17%	79%	85%	31%	95%	84%	34%	86%	61%	47%	64%	71%
Not diagnosed before 6 weeks	289	66	26	20	3	8	44	7	31	39	0	11	5	0	21	570
	59%	59%	27%	28%	4%	42%	80%	11%	82%	67%		50%	28%		38%	46%
Received 6 week examination	136	24	18	7	1	6	19	2	14	13	0	2	1	0	9	252
Abnormal 6 week examination	101	15	7	6	1	4	6	1	8	10	0	2	1	0	2	164
Not diagnosed before 12 weeks	171	48	19	10	3	3	37	4	30	26	0	9	3	0	16	379
	35%	43%	20%	14%	4%	16%	67%	6%	79%	45%		41%	17%		29%	31%

explained above (fig 1). Of the remaining 1227 babies who were eligible for neonatal examination, 155 became symptomatic and were referred, and another five died undiagnosed, before routine neonatal examination. Thus 523 of 1590 (33%) were diagnosed before routine examination, leaving 1067 in the study (fig 1).

Figure 1 shows the progress of each baby through the process of postnatal assessment. Of 1067 babies now known to have had congenital heart disease diagnosed in infancy and who underwent routine neonatal examination, 876 (82%) had been discharged undiagnosed. General paediatric follow up had been arranged for 291 of the 306 recognised at the time as possibly having congenital heart disease. We found no evidence that the detection rate in the four units providing neonatal intensive care services to the region (220 of 475 cases, or 46%) was any better than that of small units (256 of 586 cases, or 44%).

By 6 weeks of age, 570 babies (54%) remained undiagnosed, of whom 193 had been recognised at neonatal examination and were under general paediatric review. By 12 weeks of age, 379 babies (36%) remained undiagnosed, 166 of whom had been recognised and were still under paediatric review.

We were unable to trace details of a neonatal examination in six of 1067 babies (0.6%). Details of the 6 week examination were sought only in the 377 babies who were neither diagnosed nor under paediatric review by that age, but details of the examination could not be traced in 125 (33%).

During the first year of life 21 babies died before diagnosis and a cardiovascular malformation was identified only at necropsy (fig 1). In 19 of 21 the malformation was sufficient to account for death.

Five died within 24 hours of birth—two with transposition of great arteries, one with hypoplastic left heart, one with coarctation of the aorta, and one baby who died from a non-cardiac cause, had a ventricular septal defect.

Four babies died between neonatal examination and discharge from hospital—two had a murmur before death (one with tetralogy of Fallot and one with hypoplastic left heart), and in two there were no data available (one with hypoplastic left heart and one with coarctation of the aorta).

Nine babies died between discharge and 6 weeks of age—three with interruption of the aortic arch, three with coarctation of the aorta, and one each with hypoplastic left heart, pulmonary stenosis, and pulmonary atresia. All died within three weeks of birth, either suddenly at home or after presenting to hospital in extremis following a short rapid deterioration.

Three babies died after 12 weeks of age—two had severe aortic stenosis and one

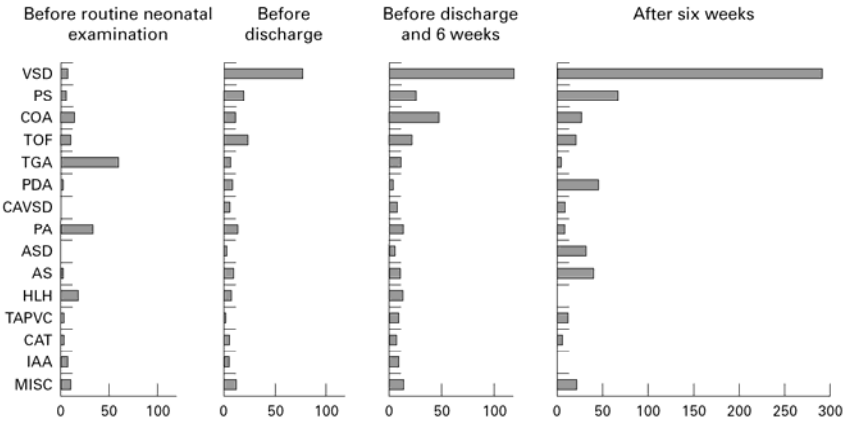

Figure 3 Timing of diagnosis and numbers of cases for each diagnostic group in 1277 babies eligible for routine examination. Displayed in this way, the spectrum of heart disease recognised at each stage is clearly shown.

sustained a sudden infant death and was found to have an atrial septal defect at necropsy. Figure 1 shows that one of these babies (with aortic stenosis) had been recognised as abnormal at both the neonatal and 6 week examinations.

Our data do not suggest that severe heart disease is any easier to detect on routine examination than less serious heart disease (fig 2).

Table 2 shows the mode and timing of diagnosis by individual diagnostic group. The neonatal examination was abnormal in 0% to 73% of babies, with the lowest prevalence of murmurs in atrial septal defect and total anomalous pulmonary venous connection and the highest in aortic stenosis, pulmonary stenosis, truncus arteriosus and tetralogy of Fallot. The examination was abnormal in 49% of babies with a ventricular septal defect but in only 16% of those with a complete atrioventricular septal defect. Most abnormalities detected at neonatal examination were murmurs but the higher abnormality rates for transposition of the great arteries and pulmonary atresia reflect the detection of cyanosis. Figure 3 shows the numbers and the spectrum of abnormalities diagnosed at each stage.

Babies with Down's syndrome and heart disease were not part of the main study cohort (see methods) but are described here for completeness. Of 107 babies, nine were preterm, five had urgent surgical problems, and in five heart disease was recognised antenatally, leaving 88 with "isolated" Down's syndrome. As babies with Down's syndrome have a high prevalence of heart disease,[9] the neonatal examination cannot be regarded as routine. Despite this, the cardiovascular abnormalities in this group were not readily detected. Only 41% had a clinical cardiovascular abnormality (almost always a murmur) on neonatal examination (table 3). Many babies were referred for early assessment and echocardiography simply because of Down's syndrome, yet 34% remained undiagnosed by 6 weeks of age and 24% by 12 weeks (table 3).

Key points

- More than half of babies with undiagnosed congenital heart disease which comes to light in infancy are missed by routine neonatal examination and more than one third by the 6 week examination
- Parents, community midwives, health visitors, general practitioners and paediatricians should recognise that a normal neonatal examination does not guarantee that the baby is normal and certainly does not exclude life threatening cardiovascular malformation
- Follow up of babies with murmurs without arranging for an early definitive (echocardiographic) diagnosis is of little value and can be risky
- Babies with murmurs at neonatal or 6 week examinations should be referred for early paediatric cardiological evaluation. This will result either in a definitive diagnosis of congenital heart disease or in authoritative reassurance of normal cardiac anatomy and function
- Babies with Down's syndrome have a high prevalence of congenital heart disease and all should be referred for early echocardiographic examination.

Discussion

Cardiovascular malformation is the most common group of congenital malformations. The prevalence at live birth diagnosed in infancy in this study was 5.3 cases per 1000 live births. This is consistent with previous large studies using similar methodology.[10–12] Our register of live born congenital heart disease was set up in 1990 with prospective ascertainment of all cases since then but retrospective ascertainment of cases in 1987–9. We are confident of complete ascertainment of all cases of complex or clinically significant heart disease throughout this study, but there was probably some under ascertainment of minor heart disease in 1987-1989. Recent prospective studies, with ready availability of early echocardiographic examination, have shown a higher of prevalence of live born heart disease, almost all of which is accounted for by the detection of more small ventricular septal defects.[13–15]

Early recognition of congenital heart disease is important because clinical presentation and deterioration may be sudden[2] and some treatable defects may even cause death before diagnosis.[3 16] Furthermore, in some cases early diagnosis can avoid irreversible pulmonary vascular disease. Clinical examination for signs of cardiovascular malformation is part of the recommended examination of neonates and 6 week old infants.[2]

We found that only 45% of babies with a cardiovascular malformation were considered to be abnormal on neonatal examination and in only 16% did the clinical findings lead to a

Table 3 Presentation of cardiovascular abnormalities in Down's syndrome, showing undiagnosed cases at each stage and performance of neonatal and 6 week examinations

Diagnostic group	*CAVSD*	*VSD*	*ASD*	*TOF*	*PDA*	*COA*	*PS*	*Miscellaneous*	*Totals*
Total cases	51	27	13	6	6	2	1	1	107
Not diagnosed before birth	47	26	13	6	6	2	1	1	102
Remaining after other exclusions	40	21	12	6	6	2	0	1	88
Not diagnosed before neonatal examination	36	20	12	4	6	2	0	1	81
Received neonatal examination	36	20	12	4	6	2	0	1	81
Abnormal neonatal examination	9	11	5	4	2	2	0	0	33
Not diagnosed before discharge	30	14	12	0	6	1	0	1	64
Not diagnosed before 6 weeks	18	12	5	0	1	0	0	0	36
Received 6 week examination	7	2	0	0	0	0	0	0	9
Abnormal 6 week examination	3	1	0	0	0	0	0	0	4
Not diagnosed before 12 weeks	13	8	4	0	1	0	0	0	26

diagnosis before discharge from hospital. Seventeen babies passed as normal on routine neonatal examination later developed symptoms and were diagnosed before discharge home. One third of these had duct dependent lesions. With the trend to increasingly early discharge after delivery, such babies will be more likely to develop symptoms at home rather than when still on a postnatal ward.

Of the babies discharged home undiagnosed, 35% were diagnosed by 6 weeks of age and 57% by 3 months. If every baby who was found to have signs or symptoms of congenital heart disease had been examined echocardiographically within four weeks of the abnormality first being noted, 58% could have been diagnosed by the time of the 6 week examination and 76% by three months. The nine babies who died undiagnosed between discharge and six weeks, would still not have been diagnosed in life as no signs of illness had been noted until immediately before death and all died before 4 weeks of age. However, one baby with aortic stenosis would have been diagnosed alive before six weeks instead of dying undiagnosed after 12 weeks.

In a previous study we showed that undiagnosed conditions most likely to lead to death soon after discharge from hospital were hypoplastic left heart, interruption of the aortic arch, and coarctation of the aorta.[3] In the present study there was no relation between the likelihood of detection of abnormality and infant mortality for individual diagnoses (fig 2). The main implication of this finding is that a normal neonatal examination does not exclude serious or life threatening cardiovascular malformation. As about half of the babies noted to have murmurs in the first few days of life have structural heart disease,[13] early referral of all such babies for cardiological assessment and echocardiography should be encouraged. We consider that continued local paediatric follow up in the absence of a confirmed diagnosis inappropriate.[1]

Many babies with life threatening cardiovascular malformation will have presented by 6 weeks of age (including all those with hypoplastic left heart or interruption of the aortic arch). However, in our study 27% of babies with coarctation were still undiagnosed by 6 weeks of age, and even by 3 months, 20% were still undiagnosed. Similarly, two thirds of babies with aortic valve stenosis were not diagnosed by six weeks and 45% by 12 weeks.

Data from the six week examination are not easily amenable to retrospective study. In many health districts there is no centralised record keeping. Despite an extensive search and good cooperation from local community paediatric departments, we could trace the results of the 6 week examination in only two thirds of the babies in whom we were interested. Even when an abnormality was suspected at the 6 week examination, this did not always lead to early diagnosis: only a third of those undiagnosed by six weeks were diagnosed by 12 weeks of age. Because about one quarter of babies noted to have a murmur at the six week examination have an underlying cardiovascular malformation,[17] we recommend the need for early referral.[1]

Early diagnosis of heart disease in Down's syndrome is important firstly because both the parents and the paediatrician need to know the implications of the heart defect. Secondly some major malformations with pulmonary hypertension may show no signs and may progress to irreversible pulmonary vascular disease before the heart defect has been recognised.[2] Despite this we found that in a third of babies with Down's syndrome and heart disease no diagnosis had been made by 6 weeks and a quarter remained undiagnosed as late as 3 months of age.

The study was funded by the former Northern and Yorkshire Regional Health Authority. The paediatric cardiology database is funded by the Children's Heart Unit Fund. We are indebted to Susan Fritz, who collected the data and to all our colleagues who provide sustained support for the regional perinatal, late neonatal, and infant mortality survey to allow collection of accurate mortality data.

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4.5 Wren C, Richmond S, Donaldson L. Temporal variability in birth prevalence of cardiovascular malformations. *Heart* 2000;83:414-9.

Background: This is a retrospective analysis of data which were collected (mostly prospectively) in 1985-1997. Its main aim was to examine year-to-year variations in numbers of individual malformations and to look for trends over time. A second aim was to compare the effect of "anatomical" and "physiological" diagnostic hierarchies on apparent numbers (discussed at more length in section 2.6). It has a denominator of almost half a million live births within the Northern Region.

Key messages: The number of diagnoses increased steadily over the study period. There was no change in complex or other significant malformations but a very significant rise in minor abnormalities, mainly small ventricular septal defects. Year-to-year variations in prevalence of rarer defects were more pronounced and make it impossible to ascribe short term change to anything other than natural variation, even in a study as large as this.

"Anatomical" hierarchies list cases with more than one diagnosis in relation to the major structural malformation. "Physiological" hierarchies give prominence to the abnormality with the greatest haemodynamic effect. The use of an anatomical hierarchy alone underestimates the numbers of pulmonary atresia by 27%, coarctation of the aorta by 39% and of interruption of the aortic arch by 100%. A physiological hierarchy alone underestimates the numbers of major structural malformations by 6%.

Impact: The apparent increase in prevalence at live birth of cardiovascular malformations had been reported in smaller series previously but was here shown to be entirely due to better ascertainment over time (largely because of easier recognition of small ventricular septal defects with colour Doppler echocardio-graphy). The "two-dimensional" hierarchy showed for the first time the effect on ascertainment of one or the other. The increase in termination of pregnancy after antenatal diagnosis was documented with no discernable effect on live births. The data in this study were further analysed by Hoffman and Kaplan's review of birth prevalence discussed in chapter 6.

Citations: Google Scholar lists 46 citations at the end of 2007.

Temporal variability in birth prevalence of cardiovascular malformations

C Wren, S Richmond, L Donaldson

Abstract
Objective—To investigate changes over time in the prevalence at live birth of cardiovascular malformations and to compare "anatomical" and "physiological" diagnostic hierarchies within a population.
Design—Retrospective and prospective ascertainment of all congenital cardiovascular malformations diagnosed in infancy.
Setting—The resident population of one health region.
Patients—All infants live born from 1985 to 1997 with cardiovascular malformations confirmed by echocardiography, cardiac catheterisation, surgery or autopsy.
Main outcome measures—Year to year variation in prevalence of individual malformations and of "complex", "significant", and "minor" groups.
Results—2671 babies with cardiovascular malformations were confirmed in a denominator population of 477 960 live births (5.6 per 1000). There was no change over 13 years in the birth prevalence of "complex" or "significant" defects, but a highly significant increase in "minor" defects ($p < 0.0001$), mainly small ventricular septal defects. Termination of pregnancy increased from no cases in 1985 to 16 in 1997 with no demonstrable effect on live born babies with heart defects. A one dimensional "anatomical" diagnostic hierarchy led to under ascertainment of pulmonary atresia by 27%, coarctation of the aorta by 39%, and interruption of the aorta by 100%.
Conclusions—The apparent increase in live born cardiovascular malformations results mainly from improved diagnosis of minor defects. There has been no change over time in birth prevalence of more serious defects. Spontaneous year to year variation in numbers will make it difficult to ascribe any short term changes to any particular intervention. A two dimensional diagnostic hierarchy is offered as a standard.
(*Heart* 2000;**83**:414–419)

Keywords: congenital heart defects; epidemiology; infancy; temporal variability

Department of Paediatric Cardiology, Freeman Hospital, Newcastle upon Tyne NE7 7DN, UK
C Wren

Neonatal Unit, Sunderland Royal Hospital, Sunderland, UK
S Richmond

Department of Epidemiology and Public Health, University of Newcastle upon Tyne, UK
L Donaldson

Correspondence to:
Dr Wren
email: Christopher.Wren@tfh.nuth.northy.nhs.uk

Accepted 6 January 2000

Cardiovascular malformations account for about 10% of all infant deaths and nearly half of all deaths from malformation.[1] As a group they are the most common type of congenital malformation.[2] The cause of an increasing number of cardiovascular malformations is known to be genetic and a few are environmental in origin, but for the majority the cause is unknown. The descriptive epidemiology of cardiovascular malformations has generated much interest over the last 30–40 years but has not so far provided major clues to aetiology. There have been many descriptions of disease frequency but comparison between them is hampered by the lack of a common methodology. Early studies are limited by their inclusion of many unconfirmed clinical diagnoses (before ultrasound was widely available)[3] and some more recent studies, which are institution based, are limited by their inability to define the population from which their patients were derived.[4] Comparisons between studies are also made difficult by uncertainties over ascertainment and because of the different diagnostic categories and diagnostic hierarchies employed.[5]

The pattern of cardiovascular malformation is likely to be changing with time. Recognition and description of this has important implications for the future provision of services but may also give clues to the cause. Increasing antenatal recognition of congenital heart disease and termination of affected pregnancies might be expected to reduce the prevalence at live birth of the more severe abnormalities.[6] Changes over time may also reflect the random effect of small numbers[5] or the increasing ascertainment of minor malformations with better non-invasive technology.[7 8] The recognised increased risk to offspring of survivors of congenital heart disease might be expected, all other things being equal, to lead to a significant increase in the birth prevalence in the population over several generations.[9]

Our study aimed to: (1) define the birth prevalence of cardiovascular malformations in a well defined population in the era of readily accessible non-invasive imaging; (2) propose an acceptable diagnostic hierarchy to enable comparison with previous and future reports; and (3) to examine temporal variability in the birth prevalence of cardiovascular malformations.

Methods

POPULATION

The former Northern Health Region comprises the counties of Cumbria, Northumberland, Tyne and Wear, Durham, and Cleveland, and has a population of just over three million people. Babies with suspected heart disease from the health district of South Cumbria are referred elsewhere for geographical reasons. All babies with suspected heart disease from the

other 15 of 16 health districts are referred to a single paediatric cardiology centre.[10]

DATA SOURCES

All cases of live born cardiovascular malformation diagnosed in the first 12 months of life were identified from the diagnostic database in the regional paediatric cardiology unit in the Freeman Hospital, Newcastle upon Tyne, and were cross checked with the northern congenital abnormality survey.[11] The paediatric cardiology database was established in 1990 with prospective registration of all congenital heart defects since then. Ascertainment of cases born in 1985 to 1989 was retrospective from ward admission lists, hospital diagnostic coding, and the northern regional perinatal, late neonatal, and infant mortality survey, and is thought to be complete for all complex and significant malformations (see below). There is likely to be some under ascertainment of minor malformations in the early part of the study. The perinatal, late neonatal, and infant mortality survey also provided information on all terminations of pregnancy where a heart defect had been recognised antenatally and all cardiovascular malformations in live born babies where death occurred before diagnosis had been made.[12] The Office of National Statistics provided data on the regional birth rate.

CASE DEFINITION

In this study, as in most previous studies, cardiovascular malformations were defined as by Mitchell and colleagues[13]—that is, "a gross structural abnormality of the heart or intrathoracic great vessels that is actually or potentially of functional importance". To enable comparison with previous studies, cases of isolated cardiac arrhythmia, cardiomyopathy, acquired heart disease, isolated bicuspid aortic valve, mitral valve prolapse without regurgitation, isolated dextrocardia, cardiac tumours, patent ductus arteriosus associated with prematurity (that is, ductus requiring surgical ligation within six weeks of the due date of delivery), atrial septal defect undergoing spontaneous closure in infancy, and mild physiological pulmonary artery branch stenosis were excluded. Ascertainment was limited to malformations diagnosed by the age of 12 months. While most significant heart disease has presented by this time, relatively few cases of patent ductus and atrial septal defect are diagnosed by 12 months of age and even fewer have undergone treatment by this age.[10] Because of this, data on isolated atrial septal defect and isolated patent ductus arteriosus diagnosed in infancy are presented separately.

DIAGNOSTIC HIERARCHY

Analysis of babies with multiple cardiovascular malformations is a difficult problem and all previous reports have allocated all cases a single diagnosis based on the malformation judged most important. There has been no consensus on an acceptable diagnostic hierarchy. Many previous studies have adopted either the classification proposed in the New England regional infant cardiac programme which defines a hierarchy based mainly on anatomical severity[14] or that in the Baltimore-Washington infant study in which priority is given to "the malformation components with the earliest embryonic disturbance".[15] In practice these two approaches using an "anatomical" hierarchy are broadly similar. Reports which are institution based and which cannot define the denominator population usually adopt a "physiological" hierarchy, taking as most

Table 1 Prevalence of individual cardiovascular malformations, including "anatomical" and "physiological" hierarchies

	PA	*IAA*	*CoA*	*TAPVC*	*ToF*	*All others*	*Total*	*Rate/1000 live births*
HLH						69	69	0.14
Mitral atresia	2		2	1		8	13	0.03
Tricuspid atresia	4		2			19	25	0.05
DIV	5	2	2			24	33	0.07
PA/IVS						23	23	0.05
PA/VSD				1		50	51	0.11
Truncus		6	1			37	44	0.09
CTGA	6					13	19	0.04
CAVSD	11		9	2	7	102	131	0.27
TGA		4	2			139	145	0.30
ToF						146	146	0.31
PAVSD			2			36	38	0.08
TAPVC			1			44	45	0.09
VSD op/or death		20	37			184	241	0.50
AS op/or death			6			40	46	0.10
PS op/or death			1			52	53	0.11
CoA						116	116	0.24
ASD			2			132	134	0.28
PDA						109	109	0.23
VSD						899	899	1.88
AS						47	47	0.10
PS						159	159	0.33
Miscellaneous		4	7			74	85	0.18
Total	28	36	74	4	7	2522	2671	5.59

PA, pulmonary atresia; IAA, interruption of the aortic arch; CoA, coarctation of the aortic arch; ToF, tetralogy of Fallot; HLH, hypoplastic left heart: DIV, double inlet ventricle; PA/IVS, pulmonary atresia with intact ventricular septum; PA/VSD, pulmonary atresia with ventricular septal defect; Truncus, truncus arteriosus; CTGA, congenitally corrected transposition of the great arteries; CAVSD, complete atrioventricular septal defect; TGA, transposition of the great arteries; PAVSD, partial atrioventricular septal defect; TAPVC, totally anomalous pulmonary venous connection; VSD op/or death, ventricular septal defect with operation or death in infancy; AS op/or death, aortic stenosis with operation or death in infancy; PS op/or death, pulmonary stenosis with operation or death in infancy; ASD, atrial septal defect; PDA, patent ductus arteriosus; VSD, ventricular septal defect with no operation or death in infancy; AS, aortic stenosis with no operation or death in infancy; PS, pulmonary stenosis with no operation or death in infancy.

Table 2 Year by year birth prevalence of individual cardiovascular malformations using and "anatomical" hierarchy

	85	*86*	*87*	*88*	*89*	*90*	*91*	*92*	*93*	*94*	*95*	*96*	*97*	*Total*
HLH	5	5	6	7	6	5	7	5	4	4	6	6	3	69
Mitral atresia	0	0	0	0	3	0	2	1	2	2	2	0	1	13
Tricuspid atresia	2	4	2	3	2	2	3	1	2	2	2	0	0	25
DIV	3	4	2	4	3	0	5	6	1	2	2	1	0	33
PA/IVS	2	2	2	2	2	3	2	2	1	3	2	0	0	23
PA/VSD	1	5	5	4	3	4	3	5	3	6	4	6	2	51
Truncus	4	2	5	9	3	1	2	2	4	3	2	3	4	44
CTGA	1	1	4	2	3	1	2	0	1	2	0	0	2	19
CAVSD	6	6	7	14	16	11	10	8	16	10	6	10	11	131
TGA	15	16	13	5	10	9	10	11	10	14	12	13	7	145
ToF	9	7	11	4	12	13	16	13	14	14	12	12	9	146
PAVSD	3	3	3	4	1	4	2	4	1	4	2	4	3	38
TAPVC	2	5	3	1	4	5	3	5	4	1	3	6	3	45
VSD op/or death	10	15	23	10	22	18	23	13	35	13	23	14	22	241
AS op/or death	5	5	6	2	2	3	2	3	1	7	3	2	5	46
PS op/or death	3	3	5	4	12	4	3	6	1	5	1	4	2	53
CoA	6	7	6	9	8	10	7	8	13	16	11	10	5	116
ASD	4	9	7	5	13	5	7	10	9	15	21	11	18	134
PDA	4	11	5	14	7	18	13	10	6	7	0	7	7	109
VSD	32	35	51	40	50	47	72	77	94	79	102	93	127	899
AS	0	1	3	7	3	8	5	6	3	2	3	3	3	47
PS	5	11	9	10	6	8	10	17	8	13	29	12	21	159
Miscellaneous	10	4	4	11	5	6	5	8	9	7	5	8	3	85
Total	132	161	182	171	196	185	214	221	242	231	253	225	258	2671

See table 1 for abbreviations.

significant that abnormality which requires the earliest intervention or which causes the most haemodynamic disturbance.[4]

In an effort to get round the limitations of each of these two approaches we have adopted a two dimensional classification, defining both the major structural abnormality and, where different, the abnormality precipitating clinical recognition of a cardiovascular malformation. For example, a baby with double inlet left ventricle and coarctation of the aorta would be classified by both these abnormalities, as would a baby with atrioventricular and ventriculoarterial discordance with pulmonary atresia. In both cases the former abnormality would be the more serious or fundamental malformation while the latter would precipitate presentation and diagnosis. All cases of ventricular septal defect, pulmonary stenosis or aortic stenosis were subdivided into those in which death occurred or intervention was required in infancy and those alive without intervention at 12 months. Deaths in these groups were few but in some cases the contribution of the heart defect to the death could not be ascertained retrospectively.

In order to provide larger numbers within each group for more reliable analysis of temporal variability, all cases (with the exception of patent ductus arteriosus and isolated atrial septal defect) were classified as being "complex", "significant", or "minor".[16] "Complex" heart disease included all cases of heterotaxy or atrial isomerism and all cases characterised by atresia or severe hypoplasia of a valve or chamber. Hearts with a common inlet valve (complete atrioventricular septal defect) or common outlet valve (truncus arteriosus) were also included in this group. Cases of "significant" cardiovascular malformation were those in which four valves and four chambers were present but where intervention was or would be required. This group, for example, includes all cases of simple transposition, tetralogy of Fallot, large ventricular septal defect, coarctation of the aorta, etc. "Minor" malformations were those where intervention would not be required. These were mainly mild or moderate aortic or pulmonary valve stenosis and smaller ventricular septal defects. Rarer malformations included in a miscellaneous group in tables 1 and 2 were also individually classified as complex, significant or minor.

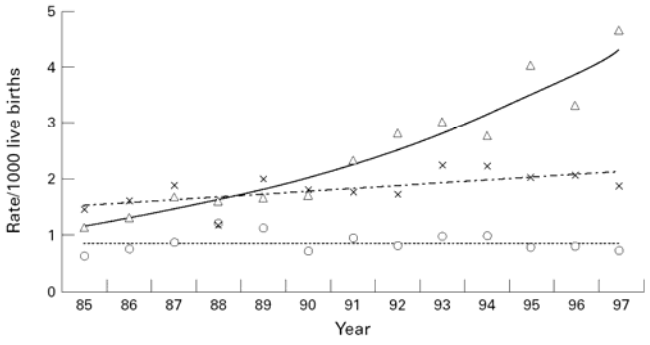

Figure 1 Year by year prevalence at live birth of 411 complex (open circles, dotted line), 870 significant (crosses, dashed line), and 1151 minor (open triangles, solid line) cardiovascular malformations. For definitions see text.

Where there were two or more malformations within the same broad diagnostic group (complex, significant or minor) the hierarchy was as shown by the order of listing in table 1. For example, a baby undergoing surgical closure of a ventricular septal defect and patent ductus was classified as having a ventricular septal defect, whereas a baby with a small ventricular septal defect requiring ligation of a ductus was classified as having a patent ductus arteriosus. As described above, isolated atrial septal defect and isolated patent ductus arteriosus were analysed separately and were not included in the complex, significant, and minor classification.

Simplified diagnostic hierarchies do not permit detailed subclassification of hearts with straddling atrioventricular valves or relative ventricular hypoplasia, features which will determine the surgical strategy and outcome but which are relatively rare. The diagnostic

hierarchy does not equate with a classification into those suitable for biventricular or univentricular repair. Our anatomical classification does not include double outlet right ventricle, a diagnostic label which fails to identify an anatomically or physiologically distinct group of heart malformations.

DIAGNOSIS

Cases were included only if they were live born. In all cases the diagnosis was confirmed by echocardiography, cardiac catheterisation, surgery or necropsy. Note was made of the total infant mortality in individual diagnostic categories.

Pregnancies terminated after antenatal diagnosis of congenital heart disease were listed separately.

Any study of cardiovascular malformations in a population would ideally include all affected fetuses and would therefore include complete ascertainment of pregnancies which ended in spontaneous abortion, termination or stillbirth. There is evidence of a high prevalence of cardiovascular malformations in stillbirths but reliable ascertainment is very difficult.[17] Small changes in fetal survival of some more severe malformations might be expected to have a major effect on birth prevalence.[18] Spontaneous fetal losses were not included in this analysis as there is no rigorous or reliable ascertainment of cardiovascular malformations in these groups in our population.

STATISTICS

Statistical analysis was limited to analysis of trends over time in the three main diagnostic groups using a Poisson model.

Results

DENOMINATOR POPULATION

From 1985 to 1997 there were 477 960 live births, a mean of 36 766 per year. There was a 15% decline in the birth rate from 38 592 in 1991 to 32 874 in 1997, exceeding the 9% fall in births in England and Wales between 1990 and 1997.[19]

BIRTH PREVALENCE

In the 13 years of the study 2671 live born cases of congenital heart disease were identified, a birth prevalence of 5.6 per 1000. Table 1 shows the prevalence of individual malformations using separate "anatomical" and "physiological" hierarchies. The use of a one dimensional anatomical classification alone would lead to under ascertainment of pulmonary atresia by 28/102 (27%) cases, of interruption of the aortic arch by all 36 (100%) cases, and of coarctation of the aorta by 74/190 (39%) cases, because they would be classified only according to the most significant intracardiac malformation.

TEMPORAL VARIATION OF LIVE BORN CARDIOVASCULAR MALFORMATION

Figure 1 shows the year by year prevalence of congenital heart disease within the three main diagnostic groups. There was a highly significant trend to increase in numbers of minor malformations over time ($p < 0.0001$), a slight trend towards increasing numbers of significant malformations which did not reach statistical significance ($p = 0.08$), and no change in complex cases ($p = 0.85$).

TEMPORAL VARIATION FOR INDIVIDUAL MALFORMATIONS

Table 2 shows the year to year variability in the prevalence of individual malformations using the main "anatomical" hierarchy. Figure 2 presents year to year variability for some individual diagnoses. The greatest variation was seen in interruption of the aortic arch, double inlet ventricle, and truncus arteriosus. More variability was apparent in diagnoses with smaller numbers but there was a relatively constant birth prevalence of hypoplastic left heart despite the small numbers. Figure 2 also shows a relatively small variation in the numbers of babies with tetralogy of Fallot or transposition of the great arteries, and a wider variability in the prevalence of complete atrioventricular septal defect. There appears to be a trend towards more cases of coarctation of the aorta, despite complete ascertainment. There is a real increase in the recognition and

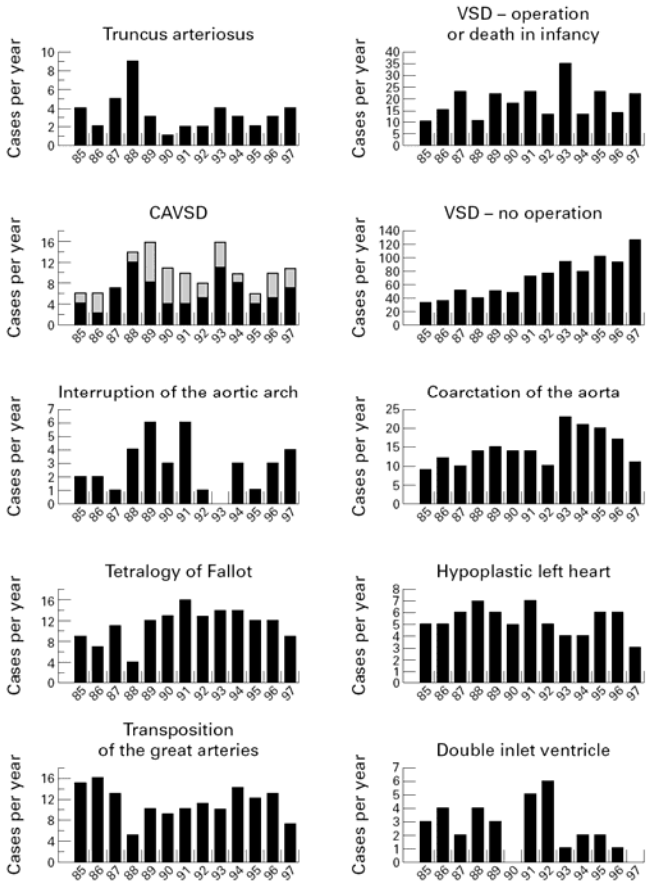

Figure 2 Year by year prevalence at live birth of selected individual diagnoses. VSD, ventricular septal defect; CAVSD, complete atrioventricular septal defect. Data for CAVSD are divided into those with trisomy 21 (black) and without (grey).

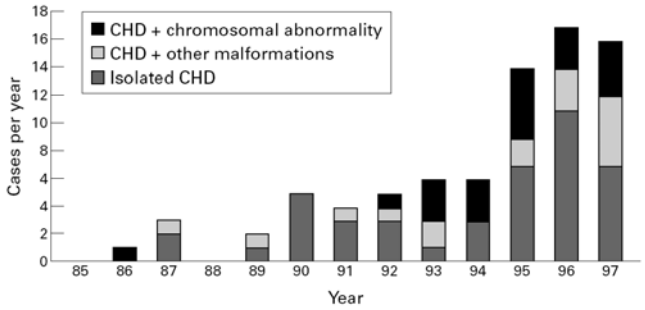

Figure 3 Year by year numbers of terminated pregnancies with congenital heart disease (CHD).

Table 3 Pregnancies with congenital heart disease terminated from 1985 to 1997

	CHD + chromosomal abnormality	*CHD + other malformation*	*Isolated CHD*
HLH	0	4	21
Isomerism	0	0	6
CAVSD	4	2	4
VSD	6	0	0
DIV	0	1	4
PA/VSD	1	3	0
ToF	4	1	0
PAVSD	2	1	0
Ectopia cordis	0	2	0
AS	0	0	2
Mitral atresia	0	0	3
Truncus	1	0	1
TGA	1	0	1
Ebstein/PA	0	0	1
Aortic atresia	0	0	1
CoA	0	1	0
PS	1	0	0
Total	20	15	44

CHD, congenital heart disease; Isomerism, atrial isomerism; Ebstein/PA, Epbstein's anomaly with pulmonary atresia. See table 1 for other abbreviations.

registration of ventricular septal defects not requiring operation in infancy, but no trend in larger ventricular septal defects requiring surgery or associated with death before the age of 12 months.

ANTENATAL DIAGNOSIS AND TERMINATION OF PREGNANCY

One possible effect on live born prevalence of congenital heart disease is a policy of termination of pregnancy after antenatal diagnosis. Figure 3 shows the increasing number of terminations during the study period. Of 79 fetuses whose pregnancies were terminated 20 had a cardiovascular malformation associated with a chromosomal abnormality, 15 with other major malformation, and 44 had isolated heart disease. Confirmed post mortem diagnoses are shown in table 3.

Discussion

Examination of published reports on the birth prevalence of congenital cardiovascular malformations emphasises the need for a constant method in order to be able to examine apparent differences.[5 20] There have been many reports but few meet the criteria of being population based, including only confirmed diagnoses, and limiting ascertainment to the first 12 months of life. There is also wide variation in the diagnostic hierarchies employed.[4 14 15 21] The differences in the birth prevalence of cardiovascular malformations in different populations might be a clue to a genetic or environmental cause, but the reported variation in prevalence is almost certainly accounted for by variation in ascertainment.[5 20] Even in large studies there are small numbers of the less common diagnoses and so no conclusions can be drawn from differences reported in the birth prevalence of rarer malformations.

This study is one of the largest to date with a denominator of nearly half a million live births. We think we have full ascertainment of "complex" and "significant" cardiovascular malformations, but there is inevitably some under ascertainment of minor malformations from the early years (1985 to 1989).

Diagnostic registers have a problem in classifying babies with multiple cardiovascular malformations. Institution based studies tend to deal with the abnormality which precipitates presentation or referral[4 10] whereas population based studies usually rank abnormalities according to anatomical severity.[14 15] Many older studies give no indication of how multiple malformations were dealt with. Other "embryological" hierarchies have been proposed but have not gained acceptance.[21] The diagnostic hierarchy presented here offers a standard and highlights the diagnoses likely to be under or over represented in studies using either anatomical or physiological hierarchies—that is, pulmonary atresia, interruption of the aortic arch, coarctation of the aorta, and total anomalous pulmonary venous connection.

This study also shows significant time related variation in the birth prevalence of cardiovascular malformations. The main reasons are better ascertainment with prospective registration, difficult retrospective ascertainment of minor malformations from the early years of the study, and increasing recognition of minor malformations using colour Doppler echocardiography, mainly of small ventricular septal defects.[7] Several previous studies have documented an increase over time in the identification of more minor cardiac malformations and have attributed the change to better ascertainment.[7 8 22–24] Year to year variation in the numbers of live born babies with less common malformations is quite striking (fig 2), but is almost certainly accounted for in the random variation of small numbers.

The increase in antenatal diagnosis of severe cardiovascular malformations and termination of affected pregnancies would be expected to lead to fewer cases being live born. So far it has been difficult to demonstrate this in any population based study.[6 25] The termination of pregnancy after antenatal diagnosis of cardiovascular malformation is increasing in our catchment area, as in other regions,[6 26] but we could show no effect of this on the prevalence at live birth of congenital heart disease. The natural history of heart disease diagnosed in utero is not clear and is obviously affected by termination of pregnancy. However, we cannot assume that those fetuses whose pregnancies were terminated would all have been live born. Fetal mortality varies considerably between

diagnoses[27] and there is a well recognised excess of cardiovascular malformations in stillbirths.[17 18] In the long run the increase in antenatal diagnosis and termination of pregnancy is likely to lead to fewer live born babies with cardiovascular malformations, but so far any effect is masked by the variation in small numbers and the decline in birth rate. Pregnancies terminated will tend to be those of fetuses with the most severe, and therefore most easily recognised, malformations and with the poorest prospect of natural survival.

Within a given population there are likely to be several influences on the birth prevalence of congenital heart disease. Better ascertainment, better non-invasive diagnosis, and survival into adult life with a higher risk to offspring are likely to increase the number of diagnoses, whereas antenatal diagnosis and termination of pregnancy will reduce the prevalence at live birth of the more severe forms of heart disease. Unknown environmental influences could have either effect. The prevalence of heart defects will also obviously be influenced by the overall birth rate. When individual diagnoses are considered, year to year variations in small numbers are likely to be large making it difficult to prove that any change results from any specific intervention.

We are indebted to Professor John N S Matthews of the department of statistics, University of Newcastle for statistical analysis, to Kati Whiteoak for data collection and compilation, and to the Children's Heart Unit Fund for financial support of the paediatric cardiology database.

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4.6 Wren C, O'Sullivan JJ. Survival with congenital heart disease and need for follow up in adult life. *Heart* 2001;85:438-43.

Background: The long term outlook for children with congenital cardiovascular malformations has improved steadily over the years, with more survivors with complex malformations. The care of "adults with congenital heart disease" has become a separate sub-specialty. By default the service is usually provided by paediatric cardiologists, although in recent years a few specially trained consultants have been appointed. Trainees are recruited from paediatric cardiology or adult cardiology. The provision of staff and resources has, predictably, lagged far behind the need. The aim of this project was to predict the future needs of the population of adults with congenital cardiovascular malformations.

Method: This was a modelling study, using data on cardiovascular malformations on children live born in 1985-1994. Unlike all the others in this series, it had open-ended ascertainment. We made correction for the variable length of ascertainment, depending on year of birth, and this allowed the proportion and spectrum of post infant diagnoses within a population to be defined for the first time. A theoretical birth-to-adult cohort was thus defined. Correction for the observed total infant mortality was applied. Survival to adult life for each individual malformation was then predicted from reports in the literature to define the number and spectrum of malformations in a population reaching adult life. The need for expert long term follow up was then defined for each diagnosis.

Key messages: The population of adults with congenital heart disease needing long term specialist review grows by 200 per 10^5 live births each year, ie by over 1600 per year in the UK. The complexity of malformations in the adult population is greater than in infancy or childhood. Increasing survival of even the most complex abnormalities means that the numbers and complexity will continue to grow for the foreseeable future.

Impact: This paper has been the most influential of all those in this series. It has had a major impact on planning services for adults with cardiovascular malformations. Its data have been used by planning taskforce groups in the UK (*Fifth report on the provision of services for patients with heart disease. Heart 2002;**88**:iii1-56*); Europe (*Deanfield J et al. The European task force on the management of grown up congenital heart disease. Eur Heart J 2003;**24**:1035-84*); and the USA (*Warnes CA, et al. Task Force 1: the changing profile of congenital heart disease in adult life. J Am Coll Cardiol 2001;**37**:1170-5*).

Citations: Google Scholar lists 76 citations by the end of 2007.

Heart 2001;**85**:438–443

Survival with congenital heart disease and need for follow up in adult life

C Wren, J J O'Sullivan

Abstract

Objective—To predict the growth in demand for long term follow up of adults with congenital heart disease.

Design—Observed diagnoses of congenital heart disease in infancy and childhood were adjusted for observed infant survival, predicted further survival to age 16 years, underascertainment in older childhood, and predicted need for long term follow up.

Setting—The resident population of one health region in the UK.

Patients—All confirmed cardiovascular malformations diagnosed in 1985 to 1999 in children born in 1985 to 1994.

Results—1942 cases of congenital heart disease were diagnosed in infancy in a population of 377 310 live births (5.2/1000). 1588 (82%) survived to 1 year and 1514 were predicted to survive to age 16. 605 further diagnoses were made in childhood—678 when adjusted for underascertainment. Thus, 2192 children were predicted to reach age 16, of whom 784 would require long term follow up in adult life. The adult population would comprise 28% complex, 54% significant, and 18% minor congenital heart disease. These figures predict the need for adult follow up of congenital heart disease of over 200 extra cases per 100 000 live births each year or over 1600 extra cases a year every year in the UK.

Conclusions—The need for follow up of congenital heart disease in adult life is likely to grow linearly, with increasing complexity and increasing need for reinvestigation and reintervention with time. Appropriate provision should be made for adequate manpower, resources, and facilities for care of these patients.

(*Heart* 2001;**85**:438–443)

Keywords: adult congenital heart disease; resources; patient survival

Improvements in diagnosis, medical treatment, and surgical repair are changing the pattern of survival of congenital heart disease. In recent years the survival of more complex types of congenital heart disease has improved, leading to an increasing work load for follow up, reinvestigation, and reoperation. Over the same time, the care of adults with congenital heart disease has begun to develop as a separate subspecialty.[1] It seems likely that all but those with the simplest forms of congenital heart disease will require specialist follow up, and this will be the main growth area in care of patients with congenital heart disease.[2] So far there has been inadequate planning for the future care of such patients and there are no population based data to assess the future growth of this subspecialty.[2 3] The aim of this study was, therefore, to predict the likely future growth of the population of survivors of congenital heart disease requiring follow up beyond the age of 16 years.

Department of Paediatric Cardiology, Freeman Hospital, Newcastle upon Tyne NE7 7DN, UK
C Wren
J J O'Sullivan

Correspondence to:
Dr Wren
Christopher.Wren@tfh.nuth.northy.nhs.uk

Accepted 5 December 2000

Methods

POPULATION

The former Northern Health Region comprises the counties of Cumbria, Northumberland, Tyne & Wear, Durham, and Cleveland and has a resident population of just over three million. All infants and children with suspected heart disease from 15 of the 16 health districts are referred to a single centralised paediatric cardiology centre.[4] Children from the health district of South Cumbria are referred elsewhere for geographical reasons and so were not included in this study.

DATA SOURCES

The paediatric cardiology database contains details of all infants and children with structural congenital heart disease born since 1 January 1985.[4] Ascertainment was prospective for all diagnoses made from 1990 onwards and retrospective for diagnoses made between 1985 and 1989. Ascertainment is thought to be complete for all significant and complex heart disease with some underascertainment of minor malformations in infancy in the early part of the study.[5]

Diagnoses made in infancy were limited to babies born to mothers resident in the region at the time of birth. There was no significant inflow or outflow of population within the first 12 months.[6] Diagnoses made after the first birthday were limited to those made in children resident in the region at the time of diagnosis. Infants and children moving into the region and referred for follow up of congenital heart disease that had already been recognised were not included. This allows us to compensate for immigration and emigration to other regions. National statistics show no significant net inflow or outflow of population during the period of the study.[6] The Office of National Statistics provided data on the regional birth rate.

CASE DEFINITION

Cardiovascular malformations were defined according to the generally accepted definition of "a gross structural abnormality of the heart

Table 1 Observed survival in infancy, predicted survival throughout childhood, and predicted requirement for follow up in adult life

	Observed infant survival	*Predicted survival 1 to 16 years*	*References*	*Predicted need for follow up beyond 16 years*	*References*
HLH	0.00	0.00	8,9	1.00	2
MA	0.80	0.40	10	1.00	2
TA	0.56	0.56	10	1.00	2
DIV	0.60	0.71	10,11	1.00	2
PA/IVS	0.43	0.71	12,13	1.00	2
PA/VSD	0.72	0.66	12,14,15	1.00	2,15
Truncus	0.34	0.92	16,17,18	1.00	2
CTGA	1.00	0.96	19	1.00	2
CAVSD	0.56	0.96	20,21,22	1.00	2
TGA	0.77	0.87	23,24,25	1.00	2
TOF	0.89	0.94	26,27,28	1.00	2
P-AVSD	0.79	0.91	29,30,31	1.00	2
TAPVC	0.73	0.97	32,33,34	0.05	2
VSD (S)	0.66	0.97	35,36,37	0.10	2,55
AS (S)	0.47	0.79	35,38,39	1.00	2,38,39
PS (S)	0.83	0.97	35,40,41	0.25	2
CoA	0.88	0.98	35,42,43	1.00	2,42
ASD	0.87	0.97	35,44,45	0.05	2
PDA	0.94	0.99	35,46	0.00	2
MR	0.57	0.94	47,48	1.00	2
VSD (M)	1.00	1.00	37,49	0.10	2,55
AS (M)	1.00	0.94	39,45,50	1.00	2,45,50
PS (M)	1.00	0.97	45	0.10	2
Misc	0.83	0.95	51,52,53,54	0.75	2
Total	0.82				

AS (M), aortic stenosis with no intervention in infancy; AS (S), aortic stenosis with intervention or death in infancy; ASD, atrial septal defect; CAVSD, complete atrioventricular septal defect; CoA, Coarctation of aorta; CTGA, congenitally corrected transposition of the great arteries; DIV, double inlet ventricle; HLH, hypoplastic left heart; MA, mitral atresia; MR, mitral regurgitation; Misc, miscellaneous; PA/IVS, pulmonary atresia with intact ventricular septum; P-AVSD, partial atrioventricular septal defect; PA/VSD, pulmonary atresia with ventricular septal defect; PDA, patent ductus arteriosus; PS (M), pulmonary stenosis with no intervention in infancy; PS (S), pulmonary stenosis with intervention or death in infancy; TA, tricuspid atresia; TAPVC, total anomalous pulmonary venous connection; TGA, transposition of the great arteries; TOF, tetralogy of Fallot; Truncus, truncus arteriosus; VSD (M), ventricular septal defect with no intervention in infancy; VSD (S), ventricular septal defect with intervention or death in infancy.

or intrathoracic great vessels that is actually or potentially of functional importance".[7] In keeping with previous population studies, children with isolated cardiac arrhythmias, cardiomyopathy, acquired heart disease, isolated bicuspid aortic valve, mitral valve prolapse without regurgitation, isolated dextrocardia, cardiac tumours, patent ductus associated with prematurity, and atrial septal defect undergoing spontaneous closure in infancy were excluded. All cases were classified according to the main anatomical diagnosis. Children with more than one cardiac malformation received a single diagnosis based on a previously described anatomical hierarchy.[5] Diagnoses classified as "miscellaneous" in tables 1 and 2 mainly included tricuspid valve abnormalities, pulmonary artery branch stenosis, great artery and coronary artery malformations, and left ventricular outflow obstruction. As described previously each anatomical diagnosis was also classified as complex, significant or minor.[5] Complex malformations were characterised by an absent, hypoplastic or common valve or chamber (including congenitally corrected transposition of the great arteries and complete atrioventricular septal defect); significant malformations involved hearts that had four valves and chambers but would require intervention; and minor defects were mainly smaller ventricular septal defects and less severe aortic or pulmonary valve stenosis. Patients with ventricular septal defect, aortic valve stenosis or pulmonary valve stenosis were divided into those dying or undergoing surgical repair in infancy (significant) and those alive and unoperated by one year or diagnosed after infancy (minor).[5] Late presentation of a large ventricular septal defect, inoperable because of pulmonary vascular disease, was not encountered in this study but would have been classified as significant.

MODEL DESIGN

Because the database contains data for patients live born since January 1985 the follow up ranged from a minimum of one year for babies born in 1998 to a minimum of 13 years for babies born in 1985.[5] The study was based on a theoretical population born in 1985 to 1994 with 10 years' ascertainment for all ages from birth to the 16th birthday (fig 1). These years were chosen because the oldest patients are about to graduate to the adult congenital heart clinic. They provide sufficient data for study,

Table 2 Observed cases, predicted survivors, and predicted need for follow up in adult life

	Live born diagnosed in infancy	*Survivors at 12 months*	*Predicted survival 1 to 16 years*	*Predicted total survivors from infancy*	*Observed post infant diagnoses*	*Adjusted post infant diagnoses*	*Total survivors to 16 years*	*Predicted need for adult follow up*	*Predicted extra adult follow up*	*Adult follow up per 10^5 live births*	*Extra adults per year in UK*
HLH	54	0	0.00	0	0	0	0	1.00	0	0	0
MA	10	8	0.40	3	0	0	3	1.00	3	1	6
TA	23	13	0.56	7	0	0	7	1.00	7	2	14
DIV	30	18	0.71	13	0	0	13	1.00	13	3	27
PA/IVS	21	9	0.71	6	0	0	6	1.00	6	2	12
PA/VSD	39	28	0.66	18	0	0	18	1.00	18	5	37
Truncus	35	12	0.92	11	0	0	11	1.00	11	3	22
CTGA	17	17	0.96	16	0	0	16	1.00	16	4	33
CAVSD	104	58	0.96	57	1	1	58	1.00	58	15	119
TGA	113	87	0.87	76	0	0	76	1.00	76	20	156
TOF	113	101	0.94	95	3	3	98	1.00	98	26	202
P-AVSD	29	23	0.91	21	15	15	36	1.00	36	10	74
TAPVC	33	24	0.97	23	2	2	25	0.05	3	1	6
VSD (S)	182	121	0.97	117	0	0	117	0.10	12	3	25
AS (S)	36	17	0.79	13	0	0	13	1.00	13	3	27
PS (S)	46	38	0.97	37	0	0	37	0.25	9	2	19
CoA	90	79	0.98	77	29	40	117	1.00	117	31	241
ASD	84	73	0.97	71	105	119	190	0.05	10	3	21
PDA	95	89	0.99	88	99	109	197	0.00	0	0	0
MR	7	4	0.94	4	24	29	33	1.00	33	9	68
VSD (M)	577	577	1.00	577	185	206	783	0.10	78	21	160
AS (M)	38	38	0.94	36	42	44	80	1.00	80	21	164
PS (M)	97	97	0.97	94	64	69	163	0.10	16	4	33
Misc	69	57	0.95	54	36	41	95	0.75	71	19	146
Total	1942	1588		1514	605	678	2192		784	208	1612

See table 1 for key to abbreviations.

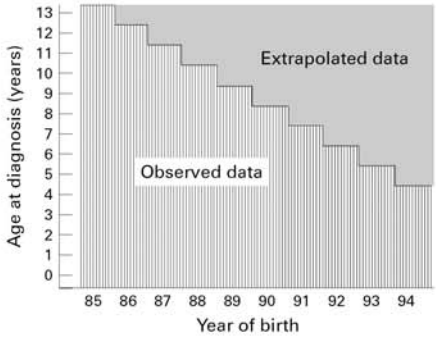

Figure 1 Data available on all diagnoses in babies and children born in 1985 to 1994. Ascertainment varies from 13 years for births in 1985 to four years for births in 1994. Data range from 10 years for 0–4 year olds to one year for 13 year olds. The figure shows data available (hatched) and data extrapolated (grey). The effect of the adjustment is shown in fig 2.

yet minimise the need for adjustment for underascertainment of diagnoses at older age. We have 100% ascertainment for the first five years of life and then diminishing ascertainment from 90% for 5 year olds to 10% for 13 year olds. To predict the size of the theoretical population, extrapolation from the observed population is required (fig 1) and assumes constant underascertainment. The required "correction factor" ranges from 1.1 for 5 year old children to 10.0 for 13 year old children to predict the situation if full ascertainment for 10 years at each age were achieved. The number of cases of each diagnosis identified at each age was determined from the database. Each age cohort was then corrected for underascertainment of each diagnosis (using the correction factor detailed above) and the total predicted numbers of each diagnosis at each age were then calculated.

There is potentially an increasing error with older age at diagnosis because of the increase in the correction factor required but, in fact, the number of diagnoses diminishes rapidly with increasing age. Figure 2 shows that the very large majority of diagnoses are made early in childhood so the potential error from extrapolation later in childhood is much reduced. Even with correction for underascertainment there are very few diagnoses over the age of 10 years (fig 2). Because of the design of the database we have no diagnoses in children aged 14 years and older. The likely error from excluding all children diagnosed at the age of 14 and 15 years is very small.

The study identified all live born newborns with heart disease during infancy and documented survivors at the end of the first year. The likely survival for each patient diagnosed from the age of 1 year to 16 years was predicted from the average of up to three published reports per diagnosis, which gave survival data as shown in table 1.[8-54] This gave a predicted theoretical population of 16 year old survivors of heart disease presenting in infancy. New diagnoses made at 1–13 years (corrected for underascertainment for 5–13 year olds as described above) produced a second theoretical childhood population, which was added to the infant survivors (table 2). It was assumed that all those diagnosed beyond infancy would survive until the age of 16 years. This produced a total number of patients reaching the age of 16 alive and a description of the spectrum of congenital heart disease they would have. Reports in the literature were used to predict the need for specialist follow up into adult life (table 1). This ranged from 100% for most serious forms of heart disease to 0% for patent ductus that was successfully closed or occluded in childhood. We have assumed, for instance, that 10% of children with ventricular septal defect would require continued follow up beyond 16 years of age, either for their ventricular septal defect or for associated aortic valve regurgitation, mitral valve regurgitation, repaired coarctation, subaortic stenosis, residual patch leak, permanent pacemaker, etc.[55] This might be considered to be either an under- or overestimate and could be adjusted accordingly. We could thus deduce the number of patients requiring follow up and from this the annual number for our population. Knowing the relation between our regional birth rate and national figures, we could also predict the requirements for the UK.[56]

Results

During the 10 year study period there were 377 310 live births in the population. The birth rate diminished from 38 865 in 1985 to 35 026 in 1994.

In the same population 1942 cases of congenital heart disease were diagnosed in infancy (5.2/1000) with 1588 (82%) still alive at the age of 1 year. Observed total infant survival varied from 0% for hypoplastic left heart to 100% for small ventricular septal defect, mild pulmonary stenosis, and mild aortic stenosis. The spectrum of congenital heart disease at birth and at the age of 1 year is shown in table 2.

The number of new diagnoses of congenital heart disease made after infancy diminished with age. Even after correction for underascertainment in later years (as described above and as shown in fig 2) it is still apparent that most childhood diagnoses are made before school age. As can be seen from fig 2, 74% of all cases are diagnosed in infancy, 18% before school age (age 1–4 years) and 8% in school age (age 5–13 years). The most common abnormalities diagnosed after infancy were ventricular septal defect, patent ductus arteriosus, atrial septal defect, and pulmonary valve stenosis (table 2), but there were also significant numbers of important malformations such as coarctation of the aorta and a few cases of more complex heart disease such as pulmonary atresia and tetralogy of Fallot.

Combining data for the survivors of heart disease diagnosed in infancy predicted to survive another 15 years with new diagnoses in childhood produces the spectrum of congenital heart disease in children reaching the age of 16 years (table 2). The predicted need for follow up into adult life ranged from 0% for closed patent ductus arteriosus to 100% for all major heart defects, and produced the predicted

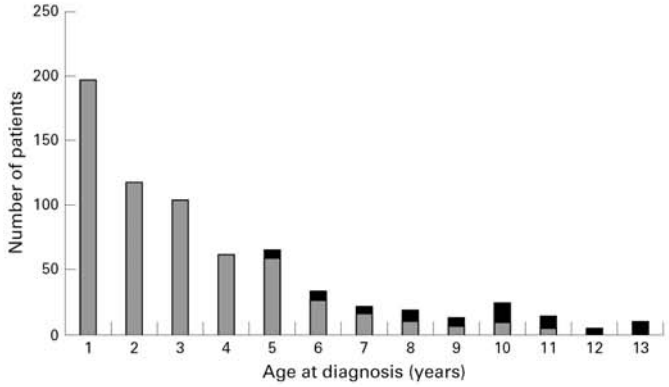

Figure 2 The effect of adjustment for underascertainment. All diagnoses at 1–13 years are shown (grey bars) with the effect of extrapolation to compensate for underascertainment at ages 5–13 years (solid bars). The difference between raw and adjusted figures is very small and is shown for individual diagnoses in table 2.

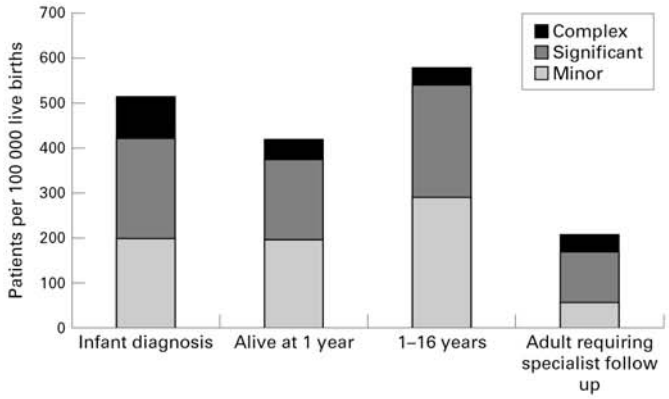

Figure 3 The spectrum of complexity of congenital heart disease at different stages of follow up. Complexity decreases during childhood but increases in adult life if children with minor malformations that do not require long term follow up are excluded.

spectrum of heart disease requiring long term follow up beyond 16 years of age (table 2).[2] As can be seen, the main diagnoses were repaired complete atrioventricular septal defect, atrial repair of transposition of the great arteries, repaired tetralogy of Fallot, repaired coarctation, and ventricular septal defect with significant numbers of mitral regurgitation, aortic stenosis, etc.

The birth rate in our catchment area comprises 4.86% of total births in the UK. The final column in table 2 predicts the total annual increment in patients requiring follow up of congenital heart disease into adult life in the UK.

Discussion

This study found that 74% of all congenital heart disease recognised in childhood is diagnosed in infancy. In 1985 to 1994 there was a total mortality in infancy of 18% but the predicted survival for a further 15 years for those surviving infancy is 96%. A further 18% of heart defects were diagnosed beyond infancy but before school age (1–4 years) so that 92% of all cases were recognised by the age of 4 years. Another 8% of children with cardiovascular malformations were first diagnosed during school age (5–13 years). Our study predicts the need for follow up beyond 16 years of age for repaired or unrepaired congenital heart disease in the UK of over 1600 cases extra each year or over 200 cases per 100 000 live births.

The spectrum of complexity of congenital heart disease diminishes throughout childhood—partly as a result of higher early mortality caused by serious malformations and partly because of later diagnosis of more minor abnormalities—but increases in adult life because many lesser defects do not require follow up (figure 3).

Numerically, the more complex malformations, including those suitable only for single ventricle repair (such as mitral atresia, tricuspid atresia, and double inlet ventricle) and others such as pulmonary atresia with ventricular septal defect or truncus arteriosus, are less common but they require more intensive follow up and will need more reinvestigation and repeat intervention.

We have restricted our analysis to structural heart disease but we recognise that children with cardiac tumours, Marfan's syndrome, cardiomyopathy, primary arrhythmia, and various other cardiac problems also require follow up. Thus we have underestimated the total number of patients graduating from the paediatric clinic to the adult congenital cardiology clinic. We also recognise that survival is constantly improving with advances in earlier diagnosis, surgery, and postoperative care so that the numbers of patients requiring follow up will continue to increase and the complexity of their cardiac problems will also increase.

In the very long term it is possible that a policy of antenatal diagnosis of cardiovascular malformation and termination of pregnancy will reduce the number of live born babies with complex malformations. The overall effect of this is likely to be very small[57] and would take many years to have a significant influence on the number of survivors in adult life. Such an effect on prevalence at live birth has so far not been demonstrated in our own region[5] or in other studies.[58]

Most congenital heart disease is now survivable and late deaths in childhood or early adult life are relatively few.[35 59] A review of adults with congenital heart disease followed up in Toronto, Canada showed an annual mortality rate of 13.9/1000 patient years (1.4%) so we can predict almost linear growth in the patient population in the foreseeable future.[60]

Few previous reports have considered the implications of this increasing workload. Gatzoulis and colleagues[61] reported a 269% expansion in the outpatient workload in 10 years (1987 to 1997) in Toronto. In our own unit we have seen a 400% growth in the number of clinics for adults with congenital heart disease in the past 10 years. In addition to development of facilities for outpatient surveillance[62] adults with congenital heart disease will require inpatient care, reinvestigation, and repeat surgery or catheter intervention.[63 64]

We have used the latest published survival data available. This may not reflect current survival figures but patients who are now 16 years old mostly had operations in infancy 15

years ago and so the choice of references to guide the predictions is justifiable. Improvements in care in the past 15 years mean that even more survivors will turn 16 each year, particularly those with more complex congenital heart diseases that require closer long term follow up and have a higher risk of late complications.

The main limitations of this study are the many assumptions we made as set out above. Our predictions were based on published reports and the methods we used are defined so that others can make any adjustments to the predictions that they deem appropriate. The design of our database means that we have progressive underascertainment in later childhood but we corrected for this and any error would be small. We did not include any cases diagnosed beyond 13 years of age but the effect of this would also be very small. We ignored heart disease other than structural congenital heart disease and we recognise that this leads to an underestimate of total numbers.

It was not the purpose of this study to enter into the discussion about the responsibility for continuing care of adults with congenital heart disease. At present this is undertaken mostly by paediatric cardiologists but in some places there are full time specialists in adult congenital cardiology[2] and in others there is a collaboration between paediatric cardiologists and interested adult cardiologists.[65] Whatever system is used it is important that appropriate arrangements be made for the handover of care of patients from the paediatric to the adult service.[66 67]

The predicted number of patients graduating to adult follow up each year is relatively small compared with the number of adults with heart disease. However, these patients, their families, and their cardiologists and surgeons have already invested greatly in time, effort, and resources. Rapid recent advances have led to the emergence of adult congenital heart disease as a distinct subspecialty and it is important to be able to predict its future growth to ensure appropriate provision of medical manpower, facilities, and resources for the care of adults with congenital heart disease.

We are indebted to Kati Whiteoak and Valerie Sutherland for data collection; to Kathryn Breeze for preparation of the tables, figures, and manuscript; and to the Children's Heart Unit Fund for financial support of the paediatric cardiology database.

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4.7 Leonard H, Derrick G, O'Sullivan J, Wren C. Natural and unnatural history of pulmonary atresia. *Heart* 2000;84:499-503.

Background: Pulmonary atresia is characterised by the absence of a direct connection between the heart and the lungs. It occurs in several situations – with a hypoplastic right ventricle (pulmonary atresia with intact ventricular septum - PA/IVS); as an extreme form of tetralogy of Fallot (pulmonary atresia with ventricular septal defect - PA/VSD); and in a wide variety of rare complex malformations (known in this report as complex pulmonary atresia - complex PA). Previous reports have all been either surgical series or from single institutions and dealt with only one of these groups. The main aim of this study was to define the prevalence and outcome for each type of pulmonary atresia within a defined population. Because these are severe malformations ascertainment is complete and we were able to collect data from 1980.

This was a descriptive cohort study. The combined birth prevalence of pulmonary atresia was $21/10^5$ live births with follow up of 555 patient years. We used innovative non-linear survival plots to provide a graphic illustration of outcome.

Key messages: These are rare and complex malformations. Overall survival was poor compared with many other malformations. Actuarial survival was better for PA/VSD and worse for complex-PA. Mortality was often before palliative surgery or from non-cardiac causes, but also reflects the era of the study. Current total mortality is lower and surgical survival is much higher. Despite this, these relatively rare patients need a disproportionate amount of hospital admissions, investigations and surgery to improve their outcome.

Impact: This was the first report to define the total prevalence of these rare conditions and to measure total mortality. Data are needed to inform discussion about management in the face of antenatal or postnatal diagnosis.

Citations: Google Scholar lists 25 citations at the end of 2007.

Heart 2000;**84**:499–503

Natural and unnatural history of pulmonary atresia

H Leonard, G Derrick, J O'Sullivan, C Wren

Abstract

Objective—To investigate mortality, cause of death, survival, and quality of life in all types of cardiac malformation with congenital pulmonary atresia.

Design—Retrospective analysis.

Setting—The resident population of one health region with a single tertiary referral centre.

Patients—All babies with pulmonary atresia live born in 1980 to 1995.

Main outcome measures—Anatomical classification, total mortality, cause of death, duration of survival, exercise ability. All cases were classified as pulmonary atresia with intact septum (PA-IVS), pulmonary atresia with ventricular septal defect (PA-VSD), or pulmonary atresia with complex cardiac malformation (complex pulmonary atresia).

Results—129 cardiac malformations with congenital pulmonary atresia were identified from 601 635 live births (21.4/100 000): 29 had PA-IVS, 60 had PA-VSD, and 40 had complex pulmonary atresia. Total mortality was 72/129 (56%), with 15 deaths in the first week and 49 in the first year. There were 23 surgical deaths, 33 hospital deaths (not related to surgery), and 16 sudden deaths, 12 of which remained unexplained. The sudden death rate was 29/1000 patient years of follow up. Of the 57 survivors, 39% have exercise ability I or II and 61% III or IV. Definitive surgical repair produced better exercise ability.

Conclusions—Early mortality is high in all types of pulmonary atresia, although survival has improved in recent years. Most children who have not undergone definitive repair have significant exercise limitation.

(*Heart* 2000;**84**:499–503)

Keywords: congenital heart disease; pulmonary atresia; sudden death; quality of life

Cardiac malformations with pulmonary atresia are rare but occupy a disproportionate amount of cardiological and surgical time and resources. Published reports have been confined to only one type of pulmonary atresia, either with intact ventricular septum[1–3] or with ventricular septal defect.[4–6] There is anatomical diversity within both these groups and bias may occur because of variations in anatomical selection criteria. Pulmonary atresia also occurs as part of more complex malformations, and such cases are excluded from other series.[2 3 5] Bias may occur in studies that report surgical series[7–11] or institution based data,[12–15] because of early deaths occurring before referral and inclusion of late referrals from other centres.

In this retrospective study we describe the outcome of all live born babies with pulmonary atresia within a defined population. Population based data give a more accurate picture of overall outcome than surgical series, institution based series, or reports limited to one variety of pulmonary atresia. They are thus important for planning management.

Department of Paediatric Cardiology, Freeman Hospital, Newcastle upon Tyne NE7 7DN, UK
H Leonard
G Derrick
J O'Sullivan
C Wren

Correspondence to:
Dr Leonard email:
Christopher.Wren@tfh.nuth.northy.nhs.uk

Accepted 3 May 2000

Methods

PATIENT IDENTIFICATION

The former Northern Health Region of England is geographically well defined and has a population of approximately three million. There is only one tertiary referral centre for paediatric cardiology and, with the exception of the health district of South Cumbria, which was excluded from this study, there is no cross border referral of infants with suspected heart disease.[16]

Patients were identified from the paediatric cardiology database, the Northern Region perinatal mortality survey,[17] the Northern Region congenital abnormality survey,[18] and fetal echocardiography records. The use of several sources allowed validation of data and ensured identification of any deaths occurring before referral to the regional cardiology centre. The total live birth rate for the region was obtained from the Office for National Statistics.

Patients included were those live born in 15 of the 16 districts of the Northern Health Region between 1980 and 1995 with congenital pulmonary atresia. Six pregnancies were terminated after antenatal diagnosis (four with additional non-cardiac malformations) and were excluded from the study.

ANATOMICAL CLASSIFICATION

Information about cardiac anatomy, age at diagnosis, interventions, and death was obtained from review of patient records and necropsy reports. Pulmonary arteries were classified by size (absent, small, or normal) and confluence (whether the right and left pulmonary arteries communicate directly with each other). The source of pulmonary blood supply (through the arterial duct or major aortopulmonary collaterals) and the presence of coronary artery fistulae were recorded. Retrospective analysis did not permit more accurate grading of pulmonary artery size (and was not possible in four cases) or measurement of right ventricular volume or tricuspid valve diameter.[1]

Patients were divided into three groups: those with intact ventricular septum (PA-IVS), those with ventricular septal defect (PA-VSD), and those with more complex malformations (complex pulmonary atresia). Patients were

Table 1 Cardiac diagnoses in complex pulmonary atresia

	Number of patients (survivors)
Atrial isomerism	8 (1)
Congenitally corrected transposition	6 (5)
Complete atrioventricular septal defect	5 (1)
Ebstein's anomaly	5 (0)
Tricuspid atresia	4 (2)
Mitral atresia	4 (2)
Double inlet left ventricle	3 (1)
Other	5 (2)

included in the PA-IVS group if the ventricular septum was intact and there were normal atria and atrioventricular connections. Those with additional Ebstein's malformation of the tricuspid valve and severe right ventricular dilatation were classified as complex pulmonary atresia (see below). Patients were included in the PA-VSD group if there was a ventricular septal defect with normal atria, atrioventricular valves, and atrioventricular connection, irrespective of ventriculoarterial connection. This group included cases described as tetralogy of Fallot with pulmonary atresia, transposition with pulmonary atresia, or double outlet right ventricle with pulmonary atresia, and included cases with major aortopulmonary collateral vessels irrespective of their contribution to pulmonary blood supply. Cases where pulmonary blood supply is entirely derived from aortopulmonary collateral vessels have been termed "complex pulmonary atresia" in other studies.[4] We reserved this description for cases that did not fit into the first two recognised groups because of abnormalities of atria, atrioventricular valves, and atrioventricular or pulmonary venous connections (table 1).

INTERVENTION

We considered palliative procedures to include total cavopulmonary connection, Fontan, Glenn, aortopulmonary shunt and stenting, ligation, or unifocalisation of major aortopulmonary collaterals.

EXERCISE ABILITY

Current exercise ability in survivors was assessed by a telephone questionnaire administered to parents of patients. Three patients with limitations because of non-cardiac problems and one with PA-IVS who had undergone cardiac transplantation were excluded from this analysis. Each child's exercise ability was described by one of the following categories: (I) unlimited compared with peers; (II) tires before peers during sports or games but unlimited when walking on level ground; (III) needs to stop and rest when walking on level ground; (IV) symptomatic at rest or on minimal exertion.

STATISTICS

Actuarial survival was calculated using the Kaplan–Meier technique.[19 20] The χ^2 method was used to compare mortality related to anatomical variations in the PA-VSD group (table 2).

Table 2 Mortality related to anatomical variation in pulmonary atresia associated with ventricular septal defect

	Survival at 1 year			Survival at end of study		
	Alive (n=45)	Dead (n=15)	p Value	Alive (n=32)	Dead (n=28)	p Value
MAPCAS						
Present	24	6		19	11	
Absent	21	9	> 0.3	13	17	> 0.1
Pulmonary artery size*						
Absent	3	2	> 0.5†	3	2	> 0.6†
Reduced	21	6	> 0.7‡	14	13	> 0.6‡
Normal	21	5		15	11	
Pulmonary arteries						
Confluent	40	13		28	25	
Non-confluent	5	2	> 0.8	4	3	> 0.8

*Unknown in two cases.
†Absent + reduced *v* normal.
‡Reduced *v* normal.
MAPCAS, major aortopulmonary collaterals.

Results

PREVALENCE AT LIVE BIRTH

Between 1980 and 1995 there were 129 cases of pulmonary atresia among 601 635 live births: 29 with PA-IVS (4.8/100 000), 60 with PA-VSD (10.0/100 000), and 40 with complex pulmonary atresia (6.6/100 000)—a total birth prevalence of 21.4/100 000 live births.

The median time to follow up (or death) was 1252 days (range 1–6119 days). The minimum follow up of survivors was two years, providing a total of 555 patient years follow up. Figure 1 provides a graphical representation of survival and changing pattern of survival in each diagnostic group.

MORTALITY

The total mortality of the group was 72/129 (56%). Mortality in the first year of life was 49/129 (38%): 15/29 (52%) for PA-IVS, 15/60 (25%) for PA-VSD, and 19/40 (48%) for complex pulmonary atresia. There were 15 deaths within the first week, eight of which occurred before surgical intervention could be offered. Kaplan–Meier survival plots are shown in fig 2.

For patients with PA-VSD, neither the presence nor absence of major aortopulmonary collateral vessels nor pulmonary artery size or confluence could be shown to have any influence on survival (table 2). The three surviving patients with no central pulmonary arteries had interventions: MAPCA (major aortopulmonary collateral arteries) stent (one patient) and shunt to vessels at lung hilum (two patients). The two who died had no intervention.

CAUSE OF DEATH

The cause of death was classified in three groups: deaths related to surgery, deaths in hospital from non-surgical causes, and sudden out of hospital deaths (table 3).

Surgical deaths

There were 23 surgical deaths (after 191 surgical procedures). They were defined as deaths in hospital within 30 days of surgery, but all except four occurred in the first 24 hours. In the PA-IVS group there were six deaths at a mean age of 65 days (range 3–345). In the PA-VSD group there were seven deaths at a mean age of 1209 days (range 3–2558). In the complex pulmonary atresia group there were 10 deaths at a mean age of 446 days (range 1–2278).

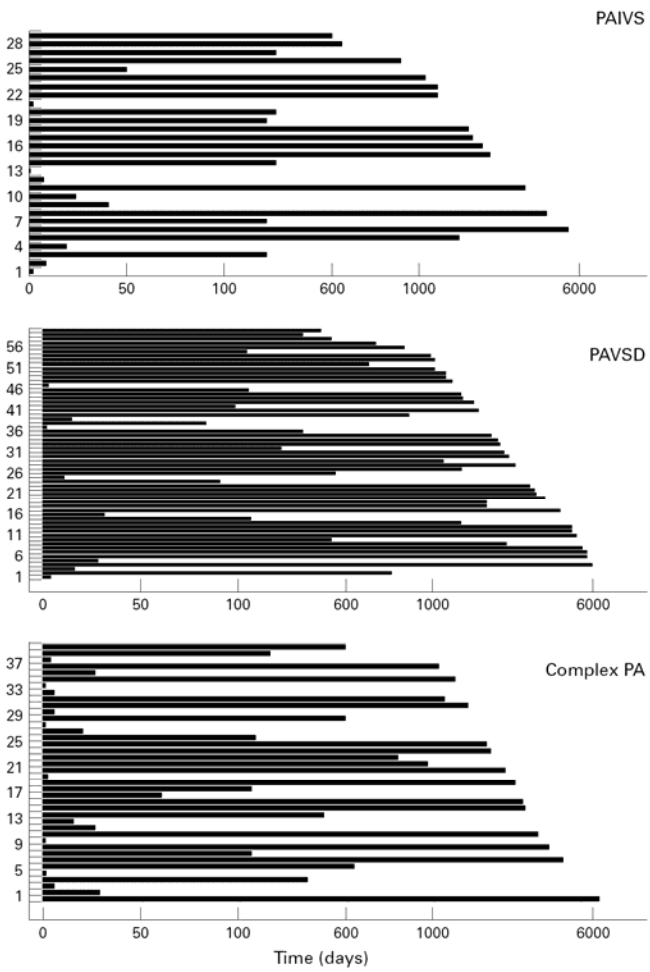

Figure 1 Survival plots for patients in all three groups. The length of the line shows time to follow up or death (in days). Patients are plotted in birth order on the y axis so that lines stopping short of the right hand outline indicate death, while those reaching the right hand outline indicate survival at latest follow up. Note that a three step linear scale is employed, as a logarithmic or linear scale would distort the plot.

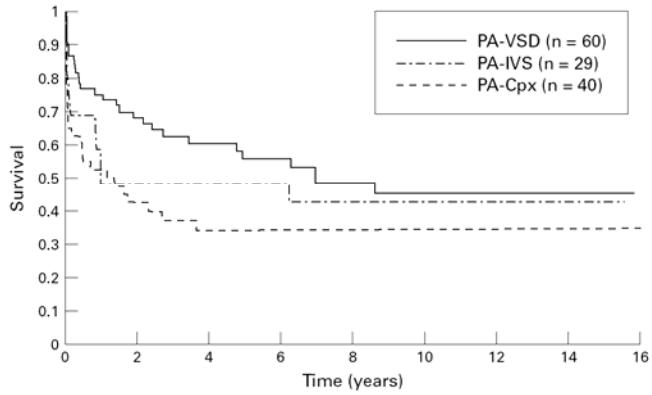

Figure 2 Kaplan–Meier survival plot for pulmonary atresia with intact septum (PA-IVS), pulmonary atresia with ventricular septal defect (PA-VSD), and complex pulmonary atresia (PA-Cpx).

Hospital deaths

Thirty three deaths occurred in hospital but were not related to surgery. Most occurred in children under one year of age and they were primarily cardiac in origin, although there were often added problems such as infection. Eight deaths were from non-cardiac problems: six patients (two in each group) died because of immunodeficiency and sepsis, and two neonates with complex pulmonary atresia died from pulmonary hypoplasia.

In the PA-IVS group there were seven deaths at a mean age of 127 days (range 1–345). In the PA-VSD group there were 14 deaths at a mean age of 421 days (range 1–2555). In the complex pulmonary atresia group there were 12 deaths at a mean age of 47 days (range 1–252).

Sudden deaths

Sixteen patients suffered sudden unexpected collapse and died before or shortly after arrival at hospital. Twelve of these 16 deaths remained unexplained after necropsy.

Three children with PA-IVS died suddenly at a mean age of 975 days (range 297–2279). All deaths were unexplained at necropsy. Seven children with PA-VSD died suddenly at a mean age of 850 days (range 90–3315). Five deaths were unexplained at necropsy; one child had severe gastroenteritis and one had a large pulmonary haemorrhage. Six children with complex pulmonary atresia died suddenly at a mean age of 590 days (range 26–1333). Four deaths were unexplained at necropsy; one was caused by occlusion of an aortopulmonary shunt and one infant had undiagnosed obstructed anomalous pulmonary venous connection.

Fifteen of the 16 patients who died suddenly had undergone previous surgery; 14 with an aortopulmonary and one with a Glenn shunt in situ. Only one had an occluded shunt at necropsy.

CURRENT STATUS

Non-cardiac anomalies that have an additional effect on their quality of life are present in 14 of the 72 survivors (19%). One child with PA-IVS had renal pelviureteric junction obstruction requiring surgery. Ten children with PA-VSD have the following problems: Di George syndrome (two), Alagille's syndrome, Shprintzen's syndrome, Coffin Lowry syndrome, mild hemiparesis (two), idiopathic thrombocytopenia, epilepsy, and choledochal cyst. In the complex pulmonary atresia group, two survivors have scoliosis and one has chronic glomerulonephritis.

CURRENT EXERCISE ABILITY IN SURVIVORS

Attempts were made to contact survivors (except four who were excluded from this analysis) and were successful in 44 of 53 cases (83%). Overall 12 children (27%) were in class I, five (11%) in class II, 25 (57%) in class III, and two (5%) in class IV. Details of exercise ability in individual diagnostic groups are given in table 4.

Children who had undergone definitive biventricular repair had a better exercise capacity

Table 3 Cause of death by age

	Surgical		Hospital		Sudden	
	< 1 year	> 1 year	< 1 year	> 1 year	< 1 year	> 1 year
PA-IVS	6	–	7	–	2	1
PA-VSD	3	4	10	4	2	5
Complex PA	5	5	12	–	2	4

IVS, intact interventricular septum; PA, pulmonary atresia; VSD, ventricular septal defect.

Table 4 Exercise ability in individual diagnostic groups

Exercise ability	I	II	III	IV
PA-IVS	4	1	2	0
PA-VSD	6	2	15	2
Complex PA	2	2	8	0
Total	12	5	25	2

IVS, intact interventricular sptum; PA, pulmonary atresia; VSD, ventricular septal defect. For exercise ability grades see text.

Table 5 Relation between exercise ability and postoperative status

		Exercise ability	
		I + II	III + IV
PA-IVS	2V	4	0
	1V	1	0
	Palliation	0	2
PA-VSD	2V	4	0
	1V	0	2
	Palliation	4	15
Complex PA	2V	0	0
	1V	3	2
	Palliation	1	6

IVS, intact interventricular septum; PA, pulmonary atresia; VSD, ventricular septal defect.
2V, biventricular repair; 1V, Fontan operation or equivalent; palliation, other palliative procedure or no intervention.

than those who had had palliative operations or no intervention (table 5).

Discussion

Published reports on pulmonary atresia are usually either surgical series[7–11] or based on experience from a single institution.[1 5] Data from institutions with a particular interest in the diagnosis will attract a disproportionate amount of more complicated referrals and introduce bias. Surgical series ignore cases where death occurs before intervention or where no intervention was feasible or thought necessary.

Most studies deal either with PA-IVS or PA-VSD and very few consider pulmonary atresia associated with other malformations. The anatomical inclusion or exclusion criteria vary (for example, hearts with Ebstein's malformation of the tricuspid valve may be included or excluded from series on PA-IVS), and apparently similar reports may not be comparable.[1–3] Complex pulmonary atresia is usually considered under the main associated cardiac malformation, even though the management (often aiming for a Fontan type circulation) is usually independent of the associated malformation. A recent report considering diagnostic hierarchies has shown that use of pulmonary atresia as a secondary diagnosis, as in our complex pulmonary atresia group, leads to an underascertainment of 27%.[21]

Our prevalence at live birth of PA-IVS (4.8/100 000) is consistent with the value of 4.5/100 000 live births found in the only other published detailed population based study.[22] However, we cannot really compare our total prevalence at live birth of all pulmonary atresia (21.4/1000 live births) with any previous reports. Population based epidemiological studies such as the New England infant cardiac program[23] and the Baltimore Washington infant study[24] do not define pulmonary atresia and have been criticised for underascertainment.

The present study provides details of mortality and survival for all types of pulmonary atresia in a birth cohort with complete ascertainment. This information is important when planning management after antenatal or postnatal diagnosis. Doctors counselling parents following an antenatal diagnosis sometimes only have a diagnosis of pulmonary atresia, with little additional anatomical data. The study shows the high early mortality in all three groups, especially PA-IVS and complex pulmonary atresia, with only about 50% medium term survival. In recent years there has been an improvement in survival in PA-IVS, little change in PA-VSD, and no improvement in complex pulmonary atresia (fig 1). Almost all the hospital non-surgical deaths and most of the surgical deaths occurred within the first year of life.

The incidence of out of hospital sudden death was surprisingly high, at 29/1000 patient years of follow up. This is much higher than reported after atrial repair of transposition of the great arteries or repair of tetralogy of Fallot.[25] Sudden death was encountered in all three groups, and 12 of 16 such deaths remained unexplained after necropsy. None of these three groups has previously been identified as having a significant risk of sudden death.

The exercise ability of survivors is disappointing, with three in four reporting limitation compared with their peers. As discussed above, some survivors have non-cardiac problems that also affect their quality of life. The exercise ability of children who have achieved biventricular repair is better than with a single ventricle repair or palliation. Some of the younger children currently palliated will undergo later definitive repair.

This study spans a period with considerable changes in management. Our own institutional bias has been towards conservative management, particularly in the early years of the study. These findings may indicate that a more aggressive surgical approach may be required.

CONCLUSIONS

Cardiac malformations with pulmonary atresia constitute a small proportion of congenital heart disease but require a large amount of medical attention. Despite this, results remain disappointing. Efforts to improve the outcome may be limited by early deaths before surgery, associated non-cardiac conditions, and late sudden death.

We are indebted to the Children's Heart Unit Fund for financial support of the paediatric cardiology database and to Kati Whiteoak for data collection. We are also grateful to Kathryn Breeze and Sheila Jamieson for producing the figures.

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4.8 Leonard H, Barrett AM, Scott JES, Wren C. The influence of congenital heart disease on survival of infants with oesophageal atresia. *Arch Dis Child* 2001;85:F204-F206.

Background: Oesophageal atresia is a rare condition causing immediate post-natal deterioration and requiring emergency surgery. It may be an isolated malformation but commonly occurs in babies with multiple abnormalities – most often congenital heart disease. Previous reports were all either surgical series or single institution reports. The aim of this study was to define the prevalence of oesophageal atresia within a population and to investigate the influence of cardiovascular malformations on outcome. This was a descriptive cohort study with a denominator of > 500,000 live births. It was performed in collaboration with the department of paediatric surgery. It is a good example of interdisciplinary co-operation in use of data in NorCAS.

Key messages: The prevalence of oesophageal atresia was 30 per 10^5 live births. One year survival was high, being 95% without and 67% with associated cardiovascular malformation. However, heart defects were mostly indicators of babies with multiple abnormalities and only 1 of 10 deaths was primarily cardiac. Most deaths were from associated pulmonary, renal or chromosomal abnormalities. Cardiovascular malformations were 23 times more common in babies with oesophageal atresia compared to normal and this high prevalence is an indication for early screening, even in the absence of cyanosis or a murmur.

Impact: Oesophageal atresia is a rare condition with a very good outcome as an isolated anomaly. This study is the largest of its kind and defines for the first time the influence of multiple abnormalities on survival.

Citations: Google Scholar lists 6 citations at the end of 2007.

Arch Dis Child Fetal Neonatal Ed 2001;**85**:F204–F206

The influence of congenital heart disease on survival of infants with oesophageal atresia

H Leonard, A M Barrett, J E S Scott, C Wren

Abstract

***Objective*—To examine the prevalence of congenital heart disease in babies with oesophageal atresia and its influence on outcome.**

***Design*—Retrospective analysis.**

***Setting*—The resident population of one health region.**

***Results*—A total of 153 babies with oesophageal atresia were identified from 509 975 live births (0.30 per 1000); 26 (17%) had cardiac defects. Survival of babies with normal hearts was 97%, 97%, and 95% at one week, one month, and one year. Survival of babies with congenital heart disease was 85%, 85%, and 67% at one week, one month, and one year, but only one of ten deaths was the result of the congenital heart disease. The remaining deaths were due to other congenital malformations, respiratory disease, or chromosome abnormalities.**

***Conclusions*—There is a high prevalence of congenital heart disease in babies with oesophageal atresia. Congenital heart disease is associated with a higher mortality in oesophageal atresia but it is not the cause of it.**

(*Arch Dis Child Fetal Neonatal Ed* 2001;**85**:F204–F206)

Keywords: heart disease; oesophageal atresia; congenital anomalies; mortality

Department of Paediatric Cardiology, Freeman Hospital, Newcastle upon Tyne, UK
H Leonard
C Wren

Department of Paediatric Surgery, Royal Victoria Infirmary, Newcastle upon Tyne
A M Barrett

Regional Maternity Survey Office, 25 Claremont Place, Newcastle upon Tyne
J E S Scott

Correspondence to:
Dr Leonard, Department of Paediatric Cardiology, Freeman Hospital, Newcastle upon Tyne NE7 7DN, UK
Christopher.Wren@tfh.nuth.northy.nhs.uk

Accepted 6 July 2001

Congenital heart disease is the most common congenital malformation associated with oesophageal atresia.[1–3] Previous reports have indicated a higher mortality for babies with oesophageal atresia if there is associated heart disease.[4–7] However, these institution based series are written from a surgical perspective and could be biased because of early deaths before referral to the centre or because institutions with an interest in the diagnosis may attract a disproportionate amount of more complicated referrals from other centres. Many of the cardiac abnormalities reported are minor and would be expected to have a low mortality,[8–10] so the pronounced influence of congenital heart disease on survival is surprising.

This retrospective population based study was performed to analyse the prevalence and type of cardiac anomalies associated with oesophageal atresia and their effect on outcome.

Methods

PATIENT IDENTIFICATION

The former Northern Health Region of England is geographically well defined and has a population of about three million. There is only one tertiary referral centre for paediatric cardiology and one for major paediatric surgery. With the exception of the health district of South Cumbria, which was excluded from this study, there is no cross border referral of infants with suspected heart or gastrointestinal malformation.

Patients with oesophageal atresia were identified from the Northern Regional Congenital Abnormality Survey, a register of all babies with congenital malformations born in the region. Its methodology has been described elsewhere and it includes all liveborn cases, even when diagnosis was made after death.[11] Babies with cardiovascular malformations were identified from the paediatric cardiology database and Northern Regional Congenital Abnormality Survey. Hospital records and operating theatre books were used to cross check data. The total live birth rate for the region was obtained from the Office for National Statistics.

Patients included are those live born with oesophageal atresia and/or cardiovascular malformation to mothers resident in the Northern Health Region between 1985 and 1998.

CLASSIFICATION OF CARDIAC DEFECTS

In common with most studies of congenital heart disease, cardiovascular malformations were defined as "a gross structural abnormality of the heart or intrathoracic vessels that is actually or potentially of functional importance".[12] We did not include isolated dextrocardia, right aortic arch, mild physiological pulmonary artery branch stenosis, isolated arrhythmia, cardiac tumours, bicuspid aortic valve with no stenosis, mitral valve prolapse with no regurgitation, cardiomyopathy, or patent ductus arteriosus that closed spontaneously in the first three months. Cardiac defects were classified as complex, significant, or minor. This methodology has been described elsewhere,[13] but, in brief, malformations are described as complex if they are characterised by atresia or hypoplasia of a valve or chamber, significant if four chambers and four valves were present but treatment was or would be necessary, and minor if no intervention was necessary. Atrial septal defects and patent ductus arteriosus requiring surgery were classified as significant.

STATISTICAL ANALYSIS

Standard relative risk method was used to assess prevalence of congenital heart disease in the background and population with oesophageal atresia.[14]

Table 1 Cardiac abnormalities in oesophageal atresia

Complex	4
Tricuspid atresia	1
Truncus arteriosus	1
Complete atrioventricular septal defect	2
Significant	15
Transposition of the great arteries	1
Tetralogy of Fallot	2
Large ventricular septal defect	8
Atrial septal defect	2
Patent ductus arteriosus and small ventricular septal defect	2
Minor	7
Small ventricular septal defect	7

Results

A total of 153 liveborn babies with oesophageal atresia were identified among 509 975 live births, giving a prevalence of oesophageal atresia of 0.30 per 1000 live births. Fourteen babies had atresia of the small or large intestine as well. Twenty six of 153 (170 per 1000) babies had cardiac defects. There were 3764 babies with congenital heart disease (7.38 per 1000) without oesophageal atresia in the same population. The relative risk for congenital heart disease in babies with oesophageal atresia compared with the background population was 23 (95% confidence interval (CI) 15.2 to 34.9).

During the period of the study, there were eight fetuses with oesophageal atresia and 104 fetuses with congenital heart disease whose pregnancies were terminated. All eight with oesophageal atresia had associated malformations: two had chromosomal abnormalities and three had congenital heart disease as well as other congenital malformations. Of the 104 fetuses with congenital heart disease, 20 had other malformations and 28 had a chromosomal abnormality. Fetuses where pregnancies where terminated were not included in further study.

TYPE OF CONGENITAL HEART DISEASE

Table 1 lists the 26 cardiac diagnoses in patients with oesophageal atresia. Four (15%) had complex heart disease, 15 (58%) significant heart disease, and seven (27%) minor heart disease.

The prevalence of complex, significant, and minor heart defects in the denominator population of 509 822 live births was 482, 1568, and 1714 respectively (3764 in total). In the 153 babies with oesophageal atresia, the relative risk of complex congenital heart disease was 32.1 (95% CI 12.2 to 84.6), the relative risk of significant congenital heart disease was 34.2 (95% CI 21.1 to 55.3), and the relative risk of minor congenital heart disease was 15.5 (95% CI 7.5 to 31.9) compared with the denominator population.

CHROMOSOMAL ABNORMALITIES

Four patients with oesophageal atresia and congenital heart disease had trisomy (three trisomy 21 and one trisomy 18), and one had Fanconi's anaemia. No patient with oesophageal atresia and a normal heart had a chromosomal abnormality.

OUTCOME FOR BABIES WITH OESOPHAGEAL ATRESIA AND NORMAL HEARTS

Two babies died on day 1, before operation or referral to the surgical unit: one from tracheal agenesis and one from bilateral renal agenesis.

Survival of babies with normal hearts was 97%, 97%, and 95% at one week, one month, and one year respectively. There were five deaths beyond a year; three from large aspiration and respiratory failure, one after sudden respiratory difficulties at home, and information was not available on the fifth.

OUTCOME FOR BABIES WITH OESOPHAGEAL ATRESIA AND CONGENITAL HEART DISEASE

Overall survival of babies with congenital heart disease at one week, one month, and one year was and 85%, 85%, and 65%. For those with significant or complex defects, survival was 79%, 79%, and 58%. There was one death beyond a year in a child undergoing repair of tetralogy of Fallot.

Table 2 gives information on cause of death for the ten patients with cardiac defects who died. Only one death was directly related to a cardiac problem.

Discussion

This is the largest study of its kind with a denominator population of over 500 000 live births and provides a precise birth prevalence of oesophageal atresia and associated cardiac defects within a population. Congenital heart disease is 23 times more common in association with oesophageal atresia. The spectrum of cardiac malformations in oesophageal atresia is not significantly different from that seen in babies without oesophageal atresia.

We believe ascertainment of oesophageal atresia is complete because it does not cause diagnostic ambiguity and cannot remain "covert". We have used several sources to cross

Table 2 Cause of death in babies with oesophageal atresia and cardiovascular malformations

	Atresia	*Cardiac defect*	*Age at death (days)*	*Cause of death*
1	OA	Truncus arteriosus	1	Bilateral renal dysgenesis/lung hypoplasia
2	OA	CAVSD	1	Trisomy 21 (no active treatment)
3	OA+AA	Large VSD	1	Bilateral renal agenesis/lung hypoplasia
4	OA	Large VSD	3	Trisomy 18 (no active treatment)
5	OA	Small VSD	69	Bronchomalacia/respiratory obstruction
6	OA	Tetralogy of Fallot	236	Oesophageal haemorrhage
7	OA+DA+AA	Large VSD (repaired age 5 months)	287	Large aspiration
8	OA	Tricuspid atresia	313	No information available
9	OA	Large VSD (repaired age 1 month)	352	Chronic lung disease/respiratory infection
10	OA	Tetralogy of Fallot	455	Cardiac surgery

CAVSD, Complete atrioventricular septal defect; VSD, ventricular septal defect; OA, oesophageal atresia; DA, duodenal atresia; AA, anorectal atresia.

check data. The birth prevalence of oesophageal atresia in our population is similar to that in previous studies.[10] However, the prevalence of cardiac defects in our patients with oesophageal atresia is towards the lower end of the range quoted in other studies (13.2–39%).[2 15] This is probably because other studies have included right aortic arch and dextrocardia, which may have surgical significance, but do not qualify as structural congenital heart disease and have no influence on mortality.

Survival in children with oesophageal atresia and normal hearts is excellent (particularly as we have included deaths before presentation to the referral centre). Other long term studies have noted appreciable improvements in survival in recent years.[3 16] This reflects advances in surgery and neonatal care of previously high risk groups such as low birth weight infants and infants with cardiac problems.[17 18] Survival in the group with congenital heart disease is poorer, but nine of ten deaths in this group were not related to the cardiac problem. These babies were much more likely to have an underlying syndrome or additional anomaly (such as renal dysgenesis) which had a direct effect on outcome. Four of the ten deaths were in babies who underwent no active treatment because of trisomy or renal agenesis.

The high prevalence of congenital heart disease is an indication for screening. Antenatal detection of oesophageal atresia should prompt referral for detailed fetal cardiac scanning. If there is no antenatal diagnosis, the timing of postnatal screening for cardiac disease (whether it should be performed urgently before surgery) is debatable and there are different recommendations about this.[19 20] We found no early deaths resulting from congenital heart disease and only one cardiac malformation that required early intervention (transposition of the great arteries). Therefore, if the baby is acyanotic with no signs of cardiac disease, we agree with Spitz *et al*[19] that a preoperative cardiac consultation is not mandatory and can be deferred until after oesophageal repair.

Antenatal or postnatal detection of congenital heart disease in association with oesophageal atresia is an indication for genetic testing and careful screening for other fetal abnormalities. If no other abnormalities are detected, congenital heart disease is unlikely to have a significant effect on mortality in babies with oesophageal atresia.

We are grateful to Marjorie Renwick, at the Regional Maternity Survey Office, and Kati Whiteoak, who maintains the paediatric cardiology database, for the collection and retrieval of data. We are indebted to the Children's Heart Unit Fund for financial support of the paediatric cardiology database.

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4.9 Wren C, Birrell G, Hawthorne G. Cardiovascular malformations in infants of diabetic mothers. *Heart* 2003;89:1217-20.

Background: The cause of most cardiovascular malformations is unknown although about 5% are thought to have an environmental origin. The increased risk to infants of diabetic mothers is recognised but not well defined.

This six-year prospective cohort study had a denominator of almost 20020 ,000 live births. It was performed in collaboration with the Northern Diabetic Pregnancy Register, which was set up in 1993 to investigate the outcome of pregnancy in women with pre-existing insulin-dependent diabetes.

Key messages: Cardiovascular malformations were present in 36‰ live births with diabetic mothers compared with 7‰ without (odds ratio 5.0). Because individual malformations are rare, we combined our data with the five previously published reports for more detailed analysis. The prevalence at live birth of transposition is 518 per 100 000 in maternal diabetes compared with 30 per 100 000 for non-diabetic mothers – a 17 fold excess. We also looked for coding of maternal diabetes in 180 consecutive live born babies with transposition in 1985-2000. Although retrospective coding of maternal diabetes might be incomplete, it was recorded in 2.8% of mothers of infants with transposition, compared with a population prevalence of 0.32% in our main study.

Impact: This study is the largest, most complete, and only prospective study of cardiovascular malformations in infants of diabetic mothers. It reinforces advice that diabetic mothers should have an expert fetal echocardiogram. It poses interesting questions but does not tell us why cardiovascular malformations, in particular transposition, are so common.

Citations: Google Scholar lists 20 citations at the end of 2007.

CONGENITAL HEART DISEASE

Cardiovascular malformations in infants of diabetic mothers

C Wren, G Birrell, G Hawthorne

Heart 2003;**89**:1217–1220

See end of article for authors' affiliations

Correspondence to: Dr C Wren, Department of Paediatric Cardiology, Freeman Hospital, Newcastle upon Tyne NE7 7DN, UK; Christopher.Wren@tfh.nuth.northy.nhs.uk

Accepted 17 April 2003

Objective: To compare the prevalence at live birth and the spectrum of cardiovascular malformations in infants born to diabetic mothers with pre-existing diabetes with that in infants of non-diabetic mothers.

Design: Prospective study of all live births in the resident population of one health region, with recording of details of the outcome of all pregnancies of women with pre-existing diabetes and of all live born babies with cardiovascular malformations.

Results: In the six years 1995–2000 there were 192 618 live births in the study population. Cardiovascular malformations were confirmed in 22 of 609 (3.6%) babies with diabetic mothers and in 1417 of 192 009 (0.74%) babies with non-diabetic mothers. The odds ratio for a cardiovascular malformation with maternal diabetes was 5.0 (95% confidence interval 3.3 to 7.8). Combination of these results with previous reports and comparison with the spectrum of cardiovascular malformations in infants of non-diabetic mothers shows a greater than threefold excess of transposition of the great arteries, truncus arteriosus, and tricuspid atresia.

Conclusions: Pre-existing maternal diabetes is associated with a fivefold increase in risk of cardiovascular malformations. Transposition of the great arteries, truncus arteriosus, and tricuspid atresia are overrepresented to produce a substantial excess of these malformations.

Congenital cardiovascular malformations form the most prevalent group of birth defects, affecting around 6–8 per 1000 live births.[1] In most cases the cause is unknown although some are genetic in origin and a few are known to have an environmental cause. Only 1% of cases are caused by maternal diseases.[2] Maternal diabetes is known to have a teratogenic effect on the cardiovascular system with a reported risk of malformation in published studies of 1.7–4.0%.[3–8] A prospective population based study of live born infants of diabetic mothers has not previously been reported. Our aim in this study was to determine the prevalence at live birth of structural cardiovascular malformations in babies born to mothers with pre-existing diabetes and to compare the findings in babies of non-diabetic mothers.

METHODS

Population base

We based the study on the population of the former Northern Health Region of England, which comprised the counties of Cumbria, Northumberland, Tyne & Wear, Cleveland, and Durham. All babies with suspected congenital heart disease from 15 of the 16 health districts are referred to a single paediatric cardiology centre. Babies from the small health district of South Cumbria are referred elsewhere for geographical reasons and they were excluded from the study.[9] The population is stable and geographically well defined with a recent average live birth rate of around 32 000 a year.

Study population

We included in this study all live born babies whose mothers had pre-existing diabetes and who were born between 1 January 1995 and 31 December 2000. The data were cross referenced with the paediatric cardiology database to identify all those with a cardiovascular malformation. The Northern Diabetic Audit was set up in 1993 to collect data prospectively on the outcome of all pregnancies in women with pre-existing diabetes. Its design and findings have been reported previously.[10] All terminations of pregnancy for fetal heart defects also were noted.

Denominator population

The Regional Paediatric Cardiology Database has registered all congenital cardiovascular malformations in live born children within the former Northern Health Region since 1985 with prospective ascertainment since 1990.[9] We identified all babies born alive with a cardiovascular malformation to non-diabetic mothers between 1 January 1995 and 31 December 2000. The Office for National Statistics provided data on the regional birth rate in the same period. Although this study concentrated on pregnancies ending in live birth, termination of pregnancy for fetal heart disease was also noted in the non-diabetic denominator population from data provided by the Northern Congenital Abnormality Survey.[11]

In a separate retrospective investigation we obtained details of the pregnancies of all mothers of babies with transposition live born between 1985 and 2000 from data held at the Northern Congenital Abnormality Survey.[11]

Case definition

In common with most previous epidemiological studies we defined a cardiovascular malformation as a "gross structural abnormality of the heart or intrathoracic great vessels that is actually or potentially of functional importance".[12] We limited ascertainment to cases diagnosed before the baby was 12 months old, as the majority of significant structural heart disease has presented by this age.[13] We included only live born infants, as the natural history of cardiovascular malformations in the fetus is unclear.[1] We excluded babies with diabetic cardiomyopathy, as this is often a self limiting problem with no clinical consequence and is not a structural malformation of the heart. We also excluded from the study babies with mild physiological pulmonary artery branch stenosis, persistent foramen ovale, persistent ductus in prematurity, atrial septal defect undergoing spontaneous closure in infancy, isolated cardiac arrhythmia, isolated bicuspid aortic valve, mitral valve

Table 1 Cardiovascular malformations in live born babies with diabetic and non-diabetic mothers

	Diabetic	Non-diabetic	Total
CVM	22	1417	1439
Normal	587	190592	191179
Total	609	192009	192618

CVM, cardiovascular malformation.

prolapse without mitral regurgitation, isolated dextrocardia, and cardiac tumours.

Statistical analysis

Statistical analysis was limited to calculation of the odds ratio for comparison of risk of malformation in diabetic pregnancies.[14]

RESULTS

During the six years 1995–2000 there were 192 618 live births in the study population. In 192 009 babies born to non-diabetic mothers, there were 1417 with a cardiovascular malformation diagnosed before the age of 12 months, a prevalence at live birth of 7.4 per 1000 (0.74%). In 609 babies live born to diabetic mothers, there were 22 with cardiovascular malformations, a prevalence at live birth of 36 per 1000 (3.6%). Table 1 gives the details. The odds ratio for a cardiovascular malformation in the offspring of diabetic mothers compared with the non-diabetic population was 5.0 (95% confidence interval (CI) 3.3 to 7.8).

Table 2 gives details of the specific cardiovascular malformations in infants of diabetic mothers in our study population and in five previous reports.[3 5–8] Table 3 compares the spectrum of cardiac defects in maternal diabetes derived from the six studies in table 2 with results from our own non-diabetic population. The methodological differences between previous reports make this an approximation only and detailed statistical comparison is inappropriate. Because our own data for offspring of non-diabetic mothers relate to 1995–2000, table 3 also includes the percentage distribution of various specific cardiovascular malformations as described in a recent analysis by Hoffman[1] of 35 reports of the descriptive epidemiology of cardiac defects published in 1964–1998. It is worthy of note that transposition of the great arteries, tricuspid atresia, and truncus arteriosus are seen three or more times more frequently than expected in the infants of diabetic mothers than in either our own data from non-diabetic mothers or in Hoffman's compiled data.

Few babies in table 2 had tricuspid atresia or truncus arteriosus. However, transposition accounts for 14.4% of all heart defects, which have a prevalence at live birth of 36 per 1000, giving a prevalence of transposition of 518 per 100 000. This compares with 4.3% of 7 per 1000 in the non-diabetic population, a prevalence of 30 per 100 000. Thus, there is a roughly 17-fold excess of transposition in live born babies of mothers with pre-existing diabetes.

To investigate further the link between maternal diabetes and transposition we retrospectively investigated all mothers of babies with transposition who were live born in 1985–2000 from data held at the Northern Congenital Abnormality Survey. There were 180 babies with transposition in that 16 year period, of whom 5 (2.8%, 95% CI 0.9% to 6.4%) had mothers who could be identified retrospectively as having pre-existing diabetes. Given that only 609 of 192 618 (0.32%, 95% CI 0.29% to 0.34%) mothers in the six years of our main study had diabetes, this confirms the increased risk of transposition in infants of diabetic mothers.

All women in the Northern Diabetic Audit have diabetes before conception. In the six years of this study there were 774 pregnancies, of which 609 resulted in live birth: 562 of 609 (92%) women were treated with insulin throughout the pregnancy and 552 of 609 (91%) had insulin dependent diabetes.

There were 24 pregnancies in diabetic women with a fetal or postnatal recognition of a cardiovascular malformation. One ended in an early spontaneous abortion, no pregnancies were terminated, and there was one antepartum stillbirth. Both dead fetuses had left atrial isomerism. A diagnosis of a cardiovascular malformation was confirmed or suspected antenatally in 10 of 22 (45%) pregnancies resulting in live birth. During the same time 92 pregnancies were terminated with cardiovascular malformations (53 with isolated cardiac defects, 17 with multiple malformations, and 22 with associated chromosomal abnormalities).

DISCUSSION

Although the increased risk of cardiovascular malformations associated with maternal diabetes is recognised, this is the

Table 2 Details of cardiovascular malformations in live born babies with maternal diabetes in the present and previous reports

	Pederson *et al* 1964[3]	Rowland *et al* 1973[5]	Mills *et al* 1988[6]	Ferencz *et al* 1990[7]	Becerra *et al* 1990[8]	This study 2003	Total
HLH	0	0	0	2	0	0	2(1.6%)
MA	0	0	1	0	0	0	1(0.8%)
TA	2	1	0	1	0	0	4(3.2%)
DIV	0	0	0	0	0	1	1(0.8%)
PA	0	1	0	0	1	2	4(3.2%)
CAT	1	1	1	2	0	0	5(4.0%)
AVSD	0	0	0	2	0	1	3(2.4%)
TGA	3	3	5	2	2	3	18(14.4%)
ToF	2	0	0	5	0	2	9(7.2%)
VSD	3	3	8	10	5	6	35(28.0%)
AS	0	0	1	1	0	0	2(1.6%)
PS	1	1	1	1	0	3	7(5.6%)
CoA	1	3	2	2	0	3	11(8.8%)
ASD	0	2	1	2	2	1	8(6.4%)
PDA	2	1	0	0	0	0	3(2.4%)
Misc	0	3	1	5	3	0	12(9.6%)
Total	15	19	21	35	13	22	125(100)

AS, aortic stenosis; ASD, atrial septal defect; AVSD, atrioventricular septal defect; CAT, common atrial trunk; CoA, coarctation of the aorta; CVM, cardiovascular malformations; DIV, double inlet ventricle; HLH, hypoplastic left heart; MA, mitral atresia; Misc, miscellaneous; PA, pulmonary atresia; PDA, patent ductus arteriosus; PS, pulmonary stenosis; TA, tricuspid atresia; TGA, transposition of the great arteries; ToF, tetralogy of Fallot; VSD, ventricular septal defect.

Table 3 Comparison of frequency of individual cardiovascular malformations in live born babies of non-diabetic mothers

	CVM in offspring of non-diabetic mothers (%)	Overall CVM Hoffman (%)	CVM in maternal diabetes (%)*
HLH	1.5	2.8	1.6
MA	0.3	–	0.8
TA	**0.4**	–	**3.2**
DIV	0.4	1.3	0.8
PA	2.0	–	3.2
CAT	**0.9**	**1.4**	**4.0**
AVSD	5.0	3.8	2.4
TGA	**4.3**	**4.4**	**14.4**
ToF	4.5	5.2	7.2
VSD	51.8	32.4	28.0
AS	2.2	3.9	1.6
PS	7.1	7.0	5.6
CoA	3.4	4.8	8.8
ASD	7.3	7.5	6.4
PDA	5.7	6.8	2.4
Misc	3.9	–	9.6

*Summarised from six studies in table 2.
Individual malformations with the most notable excess in infants of diabetic mothers are shown in bold.

first prospective population based study to compare the prevalence at live birth of congenital heart disease in infants of mothers with pre-existing diabetes with that in infants of non-diabetic mothers. We have found a significant excess of cardiovascular malformations with an odds ratio of 5.0. However, the total number of cardiovascular malformations in babies with diabetic mothers in our study is small (22) and so precludes detailed analysis of individual diagnoses. To overcome this we combined our findings with those in previous publications containing sufficient data for analysis.[3 5-8]

Pedersen and colleagues[3] reported malformations visible to "the naked eye" present on clinical examination in the offspring of diabetic mothers born in 1926–1963. No data relating to cardiovascular malformations are given in the original report but Rowe and colleagues[15] provided the data from Pederson's study cohort in 1981. Rowland and associates[5] reported a population based study of diabetic pregnancy but included both still births and post-infant ascertainment of congenital heart disease up to the age of 7 years in 1973. Mills and colleagues[6] reported a case–control study of malformations of infants of diabetic mothers in 1988. The abnormalities reported were apparently detected by a single examination at three days of age, although the diagnoses included anomalous origin of the left coronary artery from the pulmonary artery, coarctation of the aorta, and atrial septal defect, malformations that are not usually apparent at this early age. Ferencz and colleagues[7] in 1990 reported a case–control study of congenital heart disease, so the denominator of normal babies of diabetic mothers was not available. "Overt" diabetes was present in 0.5% of mothers of babies with heart defects but four of 35 mothers denied ever taking insulin and there was no means of validating the diagnosis. Ferencz and colleagues[7] reported an excess of cases of double outlet right ventricle, a diagnostic category not used in any of the other studies. Double outlet right ventricle defines one part of a malformation, which is of importance when contemplating surgical repair, but it does not have a constant definition[16 17] and does not define an anatomically or physiologically distinct group of malformations.[17] It includes diagnoses that may otherwise be described as transposition of the great arteries, tetralogy of Fallot, etc. Unlike most other studies, that of Ferencz and colleagues[7] did not find an excess of babies with transposition of the great arteries, possibly as a result of the use of double outlet right ventricle as a diagnostic category. Becerra and associates[8] reported a case–control study of babies with birth defects in 1990. Their study group also included stillbirths and because this was a case–control study the number of normal babies born to diabetic mothers is unknown.

Combining our findings with those previously reported, the excess of cardiovascular malformations in infants of diabetic mothers is confirmed (table 2). Although methodological differences between previous reports preclude detailed statistical analysis, the more than threefold excess of diagnoses such as transposition of the great arteries, truncus arteriosus, and tricuspid atresia, coupled with the fivefold excess of cardiovascular malformations overall, implies that these specific malformations are perhaps at least 15 times more prevalent than in offspring of non-diabetic pregnancies.

In a case–control study of infants with "conotruncal" defects (which included truncus arteriosus, tetralogy of Fallot, transposition of the great arteries, and double outlet right ventricle) in Atlanta, Adams and colleagues[18] found an increased risk associated with maternal diabetes with an odds ratio of 5.6 overall (7.1 for truncus arteriosus and 9.1 for transposition of the great arteries). However, there was no validation of the diagnosis of diabetes (only four of six mothers admitted to taking "medication") and there was no separation of pre-existing diabetes and gestational diabetes. Although Adams and colleagues[18] confirm the excess of transposition of the great arteries and truncus arteriosus, there is little justification for grouping conotruncal defects together, as they are different types of malformations and are unlikely to have a common cause.

Studies of antenatal echocardiography and diabetic pregnancy also report an excess of cardiovascular malformations. Gladman and colleagues[19] identified fetal heart disease in seven of 328 diabetic pregnancies. Four pregnancies resulted in live birth, giving a prevalence at live birth of congenital heart disease of 1.2%. The authors concluded that "the incidence of fetal cardiac abnormalities is low and not significantly related to maternal diabetic control". Meyer-Wittkopf and colleagues[20] reported a prevalence of fetal cardiac abnormalities of 3.1% in diabetic mothers. Five babies were live born, giving a live birth prevalence of 1.5%. The authors concluded that the "increased risk" of cardiovascular malformation in infants of diabetic mothers was an indication for fetal echocardiography.

In common with previous studies, ours included babies with persistent ductus arteriosus and atrial septal defect recognised in infancy. Both of these are usually asymptomatic in the infant or young child and both are more commonly recognised beyond infancy. In a previous study we found that 47% of cases of persistent ductus arteriosus and 41% of atrial septal defects were diagnosed in children in the first 12 months of

life compared with 80% of all other cardiovascular malformations.[13] Infants born to diabetic mothers may be subjected to greater scrutiny and may therefore be more likely to have asymptomatic cardiovascular malformations recognised. Despite that, it can be seen from table 3 that atrial septal defect and persistent ductus are not overrepresented in the spectrum of cardiovascular malformations.

In this study we did not assess the quality of control of diabetes during pregnancy because of the lack of standardisation of normal haemoglobin A_1c assays in different laboratories in the region until recently.[10]

Our prospective population based study of infants of diabetic mothers has confirmed the increased risk of cardiovascular malformations and the greatly increased risk of some specific malformations, notably transposition of the great arteries. It supports existing recommendations that all pregnant women with diabetes should be offered a specialist fetal echocardiogram.[20] This advice is reinforced by published evidence that antenatal diagnosis of transposition leads to an improved postnatal outcome.[21]

ACKNOWLEDGEMENTS

We are indebted to Marjorie Renwick of the maternity survey office for collection of data on diabetic pregnancies, to Valerie Sutherland for collection of data on all cardiovascular malformations, and to the Children's Heart Unit Fund for financial support of the database. The Northern Diabetic Pregnancy Survey is financially supported by NovoNordisk.

Authors' affiliations

C Wren, G Birrell, Department of Paediatric Cardiology, Freeman Hospital, Newcastle upon Tyne, UK
G Hawthorne, Northern Diabetic Pregnancy Register, Regional Maternity Survey Office, Newcastle upon Tyne, UK

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4.10 Tanner K, Sabrine N, Wren C. Cardiovascular malformations among preterm infants. *Pediatrics* 2005;116:e833-e838.

Background: Preterm birth and cardiovascular malformations are the two leading causes of neonatal and infant mortality. This is the first population-based report of the association between them. The aim was to compare the prevalence of cardiovascular malformations in preterm and term infants and to look at the influence of prematurity on mortality.

This was a retrospective cohort study with a denominator of >500,000 live births. Gestation data were cross-checked with NorCAS. Atrial septal defect and patent ductus arteriosus were excluded to prevent ascertainment bias.

Key messages: Cardiovascular malformations were present in 12.5‰ preterm and 5‰ term infants (odds ratio (OR) 2.4). 16% of all babies with cardiovascular malformations were preterm. Increasing prematurity is associated with an increasing mortality risk. The presence of a cardiovascular malformation further increases the risk (OR 1.8 at <28 weeks gestation) but the effect is much greater at term (OR 35.6) because the one year mortality for term normal babies is so low.

Analysis of gestation in all infants in NorCAS with Down syndrome showed that the increased prevalence of prematurity partly explains the association with atrioventricular septal defect. Cardiovascular malformations are thought to be more common in twins and 50% of twins are preterm. Analysis of NorCAS data showed that this association does not explain the association between cardiovascular malformations and preterm birth.

Impact: This paper defines the association between preterm birth and cardiovascular malformations for the first time and shows the excess mortality risk. The reason for the association is not clear.

Citations: Google Scholar lists 7 citations by the end of 2007.

Cardiovascular Malformations Among Preterm Infants

Kirsty Tanner, MBBS; Nilofer Sabrine, MBChB; and Christopher Wren, MBChB

ABSTRACT. *Objective.* Preterm birth and cardiovascular malformations are the 2 most common causes of neonatal and infant death, but there are no published population-based reports on the relationship between them. We undertook this study to determine the prevalence and spectrum of cardiovascular malformations in a preterm population, the prevalence of prematurity among infants with cardiovascular malformations, and the influence of prematurity and cardiovascular malformations on outcomes.

Methods. We based the study on the population of the former Northern Health Region of England. We identified all live-born infants with cardiovascular malformations diagnosed in the first 1 year of life from the regional pediatric cardiology database, which includes the gestational age and details of the diagnosis. We limited ascertainment to malformations diagnosed by the age of 12 months. Infants with isolated patent ductus arteriosus or atrial septal defect were excluded, to avoid ascertainment bias. Infants with ventricular septal defect were classified according to whether they required surgery in the first 1 year. There are no population data on gestational ages for all births in our population for the era of this study; therefore, we used data published in the literature for populations similar to our own to predict that 0.4% of live births occur at <28 weeks of gestation, 0.9% at 28 to 31 weeks, and 6% at 32 to 36 weeks. Overall, 7.3% of live-born infants are preterm.

Results. Of 521 619 live-born infants in 1987–2001, 2964 had cardiovascular malformations (prevalence: 5.7 cases per 1000 live births). Cardiovascular malformations were present at 5.1 cases per 1000 term infants and 12.5 cases per 1000 preterm infants. The odds ratio (OR) for a cardiovascular malformation in prematurity was 2.4 (95% confidence interval [CI]: 2.2–2.7). We found that 474 infants (16%) with cardiovascular malformations were born at <37 weeks of gestation, giving an OR for prematurity among infants with a cardiovascular malformation of 2.4 (95% CI: 2.2–2.7). More infants were born preterm with diagnoses of pulmonary atresia with ventricular septal defect (23%), complete atrioventricular septal defect (22%), and coarctation of the aorta, tetralogy of Fallot, and pulmonary valve stenosis (each 20%). Fewer were born preterm with diagnoses of pulmonary atresia and intact ventricular septum (7%), transposition of the great arteries (8%), and single ventricle (9%). We found that 18% of infants with ventricular septal defect requiring surgery were preterm, compared with 13% in the nonsurgical group. Preterm infants with ventricular septal defect required surgery in 30% of cases, compared with 23% of term infants with ventricular septal defect. These figures show that the excess of cardiovascular malformations among preterm infants cannot be explained by greater ascertainment of minor ventricular septal defects. In our denominator population, 646 live-born infants were recognized as having trisomy 21, and gestational age data were available for 609. Of these, 149 (25%; 95% CI: 21–28%) were preterm. Approximately two thirds of infants with complete atrioventricular septal defect have trisomy 21. Complete atrioventricular septal defect was no more common among preterm infants with trisomy 21 (16%) than among term infants with trisomy 21. However, the increased incidence of prematurity among infants with trisomy 21 probably explains some of the excess of preterm births among infants with complete atrioventricular septal defect. Only 4 (11%) of 38 infants with 22q11 deletion were born preterm. None of those infants had pulmonary atresia with ventricular septal defect; therefore, 22q11 deletion does not explain the excess of preterm births in pulmonary atresia with ventricular septal defect. The OR for death in the first 1 year in the presence of a cardiovascular malformation was 4.4 (95% CI: 3.1–5.5) overall; ORs were 1.8 at <28 weeks of gestation, 3.7 at 28 to 31 weeks, 11.0 at 32 to 36 weeks, and 35.6 at term.

Conclusions. This study showed that preterm infants have more than twice as many cardiovascular malformations as do infants born at term and that 16% of all infants with cardiovascular malformations are preterm. It also showed, not surprisingly, that there is an increased mortality rate among infants born preterm with a cardiovascular malformation. The additional effect of cardiovascular malformations on mortality rates is most marked for term and near-term infants, for whom mortality rates are otherwise low. The excess of cardiovascular malformations among preterm infants is intriguing but not easy to explain. Previous studies of birth weight among infants with cardiovascular malformations reported a significant increase in the likelihood of being small for gestational age among infants with tetralogy of Fallot, complete atrioventricular septal defect, hypoplastic left heart, or large ventricular septal defect. There is an obvious relationship between birth weight and gestational age, and those studies also showed an increased prevalence of prematurity among infants with tetralogy of Fallot, pulmonary stenosis, aortic stenosis, coarctation of the aorta, complete atrioventricular septal defect, or ventricular septal defect. There is also a high prevalence of cardiovascular malformations among late stillbirths, with major differences in the number and spectrum of cardiovascular malformations, compared with those seen in postnatal life. In particular, there is a greater incidence of coarctation of the aorta, double-inlet left ventricle, hypoplastic left heart, truncus arteriosus, double-outlet right ventricle, and atrioventricular septal defect among stillbirths. This spectrum of malformations is similar to that in our study and to those in other reports. Whether

From the Department of Paediatric Cardiology, Freeman Hospital, Newcastle upon Tyne, United Kingdom.
Accepted for publication Jun 24, 2005.
doi:10.1542/peds.2005-0397
No conflict of interest declared.
Address correspondence to Christopher Wren, MD, Department of Paediatric Cardiology, Freeman Hospital, Newcastle upon Tyne, NE7 7DN, United Kingdom. E-mail: christopher.wren@nuth.nhs.uk

the increased prevalence of cardiovascular malformations among preterm infants and the increase in stillbirths suggest clues to the cause is difficult to say. The influence of preterm birth should be taken into account in risk assessment and risk stratification for surgical repair. *Pediatrics* **2005;116:e833–e838. URL: www.pediatrics.org/cgi/doi/10.1542/peds.2005-0397;** ***cardiovascular malformation, prematurity.***

ABBREVIATIONS. OR, odds ratio; CI, confidence interval.

Cardiovascular malformations affect ~6 to 8 infants per every 1000 live births.[1] Cardiovascular malformations and prematurity are the 2 most common causes of neonatal and infant death, but there are no published population-based reports of the relationship between them.[2,3] We undertook this study to determine the prevalence and spectrum of cardiovascular malformations in a preterm population, the prevalence of prematurity among infants with cardiovascular malformations, and the influence of prematurity and cardiovascular malformations on outcomes.

METHODS

Population Base

We based this study on the population of the former Northern Health Region of England, which includes North and East Cumbria, Northumberland, Tyne and Wear, Durham, and Cleveland. All infants with suspected cardiovascular malformations are referred to a single pediatric cardiology center. The population of ~3 million is stable and geographically well defined. The recent average annual live birth rate has been ~35 000 births per year. The ethnic composition of the population is 97.6% white, 0.1% black, 1.5% Asian, 0.5% mixed, and 0.3% other.[4]

We included all live-born infants with cardiovascular malformations diagnosed in the first 1 year of life. The infants were identified from the regional pediatric cardiology database, which includes the gestational age and details of the diagnosis. The database has had prospective ascertainment since 1990, with retrospective ascertainment back to 1985.[5]

Case Definition

In common with most previous epidemiologic studies, we defined a cardiovascular malformation as "a gross structural abnormality of the heart or intrathoracic great vessels that is actually or potentially of functional importance."[6] We limited ascertainment to malformations diagnosed by the age of 12 months. Although most significant heart disease has presented by this time, relatively few cases of patent ductus arteriosus and atrial septal defect are diagnosed in the first 1 year.[7] Therefore, both of these diagnoses were excluded, to avoid ascertainment bias, particularly because preterm infants are more likely to have patent ductus arteriosus and are more likely to undergo echocardiography in a NICU. We also excluded from the study infants with physiologic pulmonary artery branch stenosis, patent foramen ovale, isolated cardiac arrhythmia, isolated bicuspid aortic valve, mitral valve prolapse without regurgitation, isolated dextrocardia, and cardiac tumors. Because of their relative rarity, we grouped together under the diagnostic label "single ventricle" infants with mitral atresia, tricuspid atresia, and double-inlet left ventricle. Ventricular septal defects were classified according to whether they required surgery in the first 1 year. This subanalysis was limited to surviving infants because the contribution of the ventricular septal defect to death could not be determined retrospectively, especially for preterm infants. Analysis of ventricular septal defects including deaths yielded findings very similar to those described below.

We defined gestational age as the number of completed weeks from the first day of the mother's last menstrual period to the day of delivery. If the menstrual history was in doubt, then gestational age was estimated from obstetric assessments, including physical examination and ultrasonography.[8]

The Northern Congenital Abnormality Survey provided data on the numbers of live births and total infant mortality rates.[9] There are no data for our population on the gestational age at birth for all infants or on total infant mortality rates according to gestational age. To be able to predict the size of the denominator groups, we plotted data for populations similar to our own described in the literature[10–13] and in the All Wales Perinatal Survey (1993–2000)[14] (Fig 1). Data points from the various publications were given equal weight and, from the line of best fit in Fig 1, we predicted that 0.4% of live births occur at <28 weeks of gestation, 0.9% at 28 to 31 weeks, and 6% at 32 to 36 weeks. Therefore, overall 7.3% of live-born infants are preterm. Some of these studies also provided data on the relationship between preterm birth and mortality rates.[10,11] The study was approved by the Newcastle and North Tyneside Local Research Ethics Committee.

Statistical Analyses

We limited statistical analysis to calculation of odds ratios (ORs) and their associated confidence intervals (CIs)[15] and comparisons of proportions with the χ^2 test.

RESULTS

Cardiovascular Malformations Among Preterm Infants

Of 521 619 live births in the study population in 1987–2001, 2964 infants were recognized as having a cardiovascular malformation (excluding atrial septal defect and patent ductus arteriosus) in infancy (Table 1). This gives a prevalence of 5.7 cases per 1000 live births. With our assumption that 7.3% of all live births are preterm, the prevalence at live birth of cardiovascular malformations among preterm infants was 12.5 cases per 1000 live births. In comparison, cardiovascular malformations were present at 5.1 cases per 1000 term infants, giving an OR for cardiovascular malformations in prematurity of 2.4 (95% CI: 2.2–2.7). Cardiovascular malformations

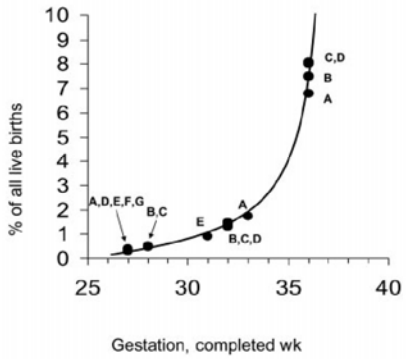

Fig 1. Prevalence of live births at various gestational ages of <37 weeks in 5 publications regarding populations similar to our own. Data points represent estimates of frequency at less than the indicated gestational age. The reports show sufficient consistency for us to derive predictions of the prevalence of preterm birth at <28 weeks, <32 weeks, and <37 weeks from the line of best fit. We assumed that 0.4% of live births in our own denominator population were at <28 weeks, 0.9% at 28 to 31 weeks, and 6.0% at 32 to 36 weeks and thus the cumulative prevalence of preterm birth was 0.4% at <28 weeks, 1.3% at <32 weeks, and 7.3% at <37 weeks. Data points are as follows: A, Joseph et al,[12] 1992–1994; B, Centers for Disease Control and Prevention,[13] 1989; C, Centers for Disease Control and Prevention,[13] 1996; D, Alexander et al,[10] 1995–1997; E, All Wales Perinatal Survey,[14] 1993–2000; F, Tin et al,[11] 1987–1990; G, Tin et al,[11] 1991–1994.

TABLE 1. Proportion of Live-Born Infants and Prevalence at Live Birth of Cardiovascular Malformations in Each Gestational Age Group

Gestational Age, wk	No. (%; 95% CI)	
	Live Births	Infants With Cardiovascular Malformations
<28	2086 (0.4)	13 (0.62; 0.37–1.06)
28–31	4695 (0.9)	60 (1.28; 0.99–1.64)
32–36	31 297 (6.0)	401 (1.28; 1.16–1.41)
≥37	483 541 (92.7)	2490 (0.51; 0.50–0.54)
Total	521 619 (100)	2964 (0.57; 0.55–0.59)

were present at 12.8 cases per 1000 infants born at 32 to 36 weeks of gestation, 12.8 cases per 1000 infants born at 28 to 31 weeks of gestation, and 6.2 cases per 1000 infants born at <28 weeks of gestation (Table 1). There was no strong evidence of a real difference between these groups because of the small number of infants born at <28 weeks of gestation.

Preterm Births Among Infants With Cardiovascular Malformations

Using published data, we assumed that 7.3% of all infants are born at <37 weeks of gestation (Fig 1). We found that 474 infants (16%) with cardiovascular malformations were born before 37 weeks of gestation, giving an OR for prematurity among infants with cardiovascular malformations of 2.4 (95% CI: 2.2–2.7). More infants were born preterm with diagnoses of pulmonary atresia with ventricular septal defect (23%), complete atrioventricular septal defect (22%), and coarctation of the aorta, tetralogy of Fallot, and pulmonary valve stenosis (each 20%) (Table 2 and Fig 2). Fewer were born preterm with diagnoses of pulmonary atresia and intact ventricular septum (7%), transposition of the great arteries (8%), and single ventricle (9%). Statistical analysis showed

TABLE 2. Numbers of Preterm Infants and Total Live Births for Individual Cardiovascular Malformations

Diagnosis	No. Preterm	No. Total	Proportion Preterm, %	95% CI, %
PA/VSD	13	57	23	14–35
CAVSD	33	150	22	16–29
CoA	29	144	20	14–27
ToF	34	174	20	14–26
PS	48	237	20	16–26
VSD	228	1538	15	13–17
AS	15	100	15	9–23
TAPVC	7	46	15	8–28
CAT	6	46	13	6–26
HLH	7	66	11	5–20
SV	6	68	9	4–18
TGA	13	162	8	5–13
PA/IVS	2	27	7	2–23
Total CVMs	474	2964	16	15–17
No CVM	37 861	518 655	7.3	7.2–7.4

PA/VSD indicates pulmonary atresia with ventricular septal defect; CAVSD, complete atrioventricular septal defect; CoA, coarctation of the aorta; ToF, tetralogy of Fallot; PS, pulmonary valve stenosis; VSD, ventricular septal defect; AS, aortic valve stenosis; TAPVC, total anomalous pulmonary venous connection; CAT, common arterial trunk; HLH, hypoplastic left heart; SV, single ventricle; TGA, transposition of the great arteries; PA/IVS, pulmonary atresia with intact ventricular septum; CVM, cardiovascular malformation.

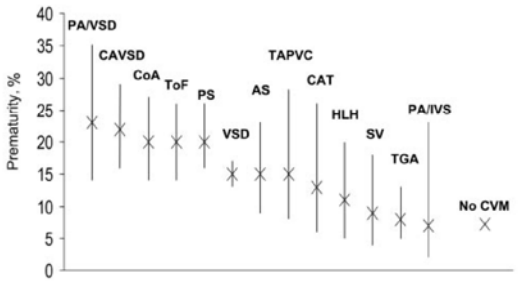

Fig 2. Prevalence of premature births among infants with specific cardiovascular malformations, ranked according to the prevalence of prematurity, and among infants without cardiovascular malformations. Vertical bars indicate 95% CIs. PA/VSD indicates pulmonary atresia with ventricular septal defect; CAVSD, complete atrioventricular septal defect; CoA, coarctation of the aorta; ToF, tetralogy of Fallot; PS, pulmonary valve stenosis; VSD, ventricular septal defect; AS, aortic valve stenosis; TAPVC, total anomalous pulmonary venous connection; CAT, common arterial trunk; HLH, hypoplastic left heart; SV, single ventricle; TGA, transposition of the great arteries; PA/IVS, pulmonary atresia with intact ventricular septum; CVM cardiovascular malformation.

that the differences between these diagnostic groups were significant ($\chi^2 = 28.0$, $P = .005$).

To investigate the possibility of an ascertainment bias toward increased detection of more minor malformations among preterm infants because of increased medical surveillance early in life, infants with ventricular septal defect were analyzed according to the need for surgery in the first 1 year. We found that 18% of infants in the surgical group were preterm, compared with 13% in the nonsurgical group. Preterm infants with ventricular septal defect required surgery in 30% of cases, compared with 23% of term infants with ventricular septal defect. These figures show that the excess of cardiovascular malformations among preterm infants cannot be explained by greater ascertainment of minor ventricular septal defects. Most of the other malformations considered (with the exception of some cases of aortic valve stenosis and pulmonary valve stenosis) are major and would have complete ascertainment in infancy regardless of gestational age. The median age at diagnosis for preterm infants was 19 days (interquartile range: 4–59 days), and that for term infants was 12 days (interquartile range: 4–74 days).

Other Influences

The strong associations between complete atrioventricular septal defect and trisomy 21 and between pulmonary atresia with ventricular septal defect and 22q11 deletion are well recognized. To investigate the possible contribution of chromosomal abnormalities to preterm birth in these groups, we analyzed the gestational age of all infants with trisomy 21 or with 22q11 deletion in the same population. In our 15-year study period, 646 live-born infants were recognized as having trisomy 21; gestational age data were available for 609. Of these, 149 (25%; 95% CI: 21–28%) were born preterm. Complete atrioventricular septal defect was diagnosed for 16% of preterm

infants with trisomy 21 and 16% of term infants with trisomy 21. Previously published work from this unit showed that approximately two thirds of infants with complete atrioventricular septal defect have trisomy 21.[16] Therefore, the increase in preterm births among infants with trisomy 21 probably explains some of the excess of preterm births among infants with complete atrioventricular septal defect.

Only 4 of 38 infants (11%; 95% CI: 4–24%) with 22q11 deletion were born preterm. None of those infants had pulmonary atresia with ventricular septal defect; therefore, 22q11 deletion does not explain the excess of preterm births among infants with pulmonary atresia with ventricular septal defect.

To investigate the possible influence of prematurity of twins on our findings, we analyzed data from the Northern Multiple Pregnancy Register.[17] Since 1998, this survey has collected prospective data on all multiple pregnancies for the same population as in our study. In 1998–2002, there were 4115 live-born twins, representing 2.7% of all live births. This is consistent with findings in published reports dealing with the same years.[18] Most reports showed an increase in the incidence of live-born twins from ~2% in the 1980s to ~3% in the 1990s; therefore, a more accurate twin rate over the 15 years of our study might be 2.5%.[18] In the Northern Multiple Pregnancy Register data, 46 of 4115 live-born twins were recognized as having a cardiovascular malformation in the first 1 year of life, a rate of 1.1 case per 1000 live births. In the same data, 52% of twin maternities (pregnancies resulting in ≥1 live birth or stillbirth) were delivered preterm. This finding is also consistent with reports in the literature showing that ~50% of twins are born before 37 weeks of gestation.[19] In our study, 112 of 2964 infants with cardiovascular malformations were twins (3.8%) and 88 of these (79%) were born preterm. From these data, we can conclude that 18% of all preterm infants are twins, 1.3% of all term infants are twins, 23% of preterm infants with cardiovascular malformations are twins, and 1.3% of term infants with cardiovascular malformations are twins. Therefore, twins do not contribute significantly to the excess of cardiovascular malformations we observed among preterm infants.

Influence on Outcomes

The total 1-year mortality rate for infants of all gestational ages with cardiovascular malformations was 393 of 2964 infants (13%), and that for preterm infants with cardiovascular malformations was 97 of 494 infants (20%). Published studies of preterm infants, including our own population, predict that the overall 1-year mortality rate for preterm infants is 5.8%.[10,11,14] In a comparison of our data for preterm infants with cardiovascular malformations with these population data, the OR for death in prematurity with cardiovascular malformations was 4.2 (95% CI: 3.1–5.5). Specific mortality rates for gestational age groups with and without cardiovascular malformations are shown in Fig 3. The mortality rate was higher at all gestational ages, but the effect was most marked for near-term (OR: 11.0) and term (OR: 35.6) infants.

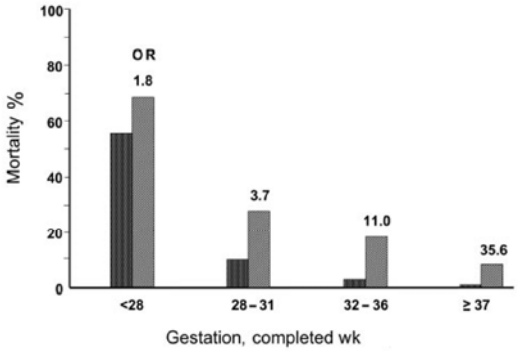

Fig 3. Total infant (12-month) mortality rates for different gestational age groups. Dark bars indicate infants without cardiovascular malformations; light bars, infants with cardiovascular malformations. ORs are for excess deaths among infants with cardiovascular malformations in each gestational age group.

DISCUSSION

This study showed that preterm infants have more than twice as many cardiovascular malformations as do infants born at term and that 1 of 6 infants with cardiovascular malformations is born preterm. It also showed, not surprisingly, that there is an increased mortality rate for infants born both preterm and with a cardiovascular malformation. The additional effect of cardiovascular malformations on mortality rates is most marked for term and near-term infants, for whom mortality rates are otherwise low. All mortality rates quoted in this study are from all causes in the first 1 year of life, not necessarily as a result of the cardiovascular malformation. We were not able to determine retrospectively the contribution of the cardiovascular malformations to the deaths. In a previous study of infants with esophageal atresia, we showed a sevenfold increase in mortality rates for those who also had a cardiovascular malformation but the heart defect was mainly a marker of multiple abnormalities and other syndromes, rather than being the cause of death.[20]

Infants with some malformations (notably pulmonary atresia with ventricular septal defect and complete atrioventricular septal defect) had a higher prevalence of prematurity; for those with other malformations (such as transposition of the great arteries), preterm birth was less common, and the differences were statistically significant (Fig 2). The association between trisomy 21 and prematurity shown in this study goes some way to explain the excess rate of prematurity in complete atrioventricular septal defect, but the larger number of preterm births in pulmonary atresia with ventricular septal defect is not explained by the association with 22q11 deletion. The associations between other chromosomal abnormalities or syndromes and specific cardiovascular malformations are less common, which precludes detailed analysis.

One obvious limitation of our study is that we have no local population data on gestational ages or mortality rates according to gestational age. No such data are collected nationally in the United King-

dom.[21] We therefore used 6 published reports from matching time periods and from populations with similar ethnic distributions (using non-Hispanic white infants from US studies[13]) to derive the proportions of infants born at various gestational ages and the mortality rates according to gestational age. The very close agreement between these studies shown in Fig 1 gives us confidence in using our assumed proportions of infants born in each gestational age group.

There has been no previous comparable population-based study with ascertainment of cardiovascular malformations among both preterm and term infants. In a small study from a single neonatal unit, Kecskes and Cartwright[22] reported a prevalence at live birth of cardiovascular malformations of 23 cases per 1000 infants of <1500 g born at gestational ages of 24 to 36 weeks. Those authors found the most common abnormalities to be ventricular septal defect and coarctation, a finding not confirmed in our study. Their study had no denominator group of term infants, no ascertainment of diagnoses made after initial discharge from the hospital, and no correction for ascertainment bias related to referral patterns. Dees et al,[23] in a larger study of admissions to a single NICU, found 16 per 1000 infants had cardiovascular malformations. There was no denominator of term infants and no population data, but those authors did report an increased prevalence of "conotruncal defects," compared with the Baltimore-Washington Infant Study[24] (which itself had a fairly low overall ascertainment rate). Dees et al[23] found that the in-hospital mortality rate for preterm infants was increased by a factor of 2.6 by the presence of a cardiovascular malformation and the risk of necrotizing enterocolitis was increased by a factor of 1.7. The mortality rate for cardiac surgery was twice as high among preterm infants, compared with term infants. We also found an increase in the mortality rate for preterm infants with cardiovascular malformations, but we did not investigate the relative contributions of different causes of death. Reddy,[25] in a report on cardiac surgery among infants of <2500 g, noted a significant increase in the mortality rate, compared with larger infants undergoing similar surgical repair. However, 2 recent European retrospective reports of cardiac surgery among neonates weighing <2500 g found that, although nearly one half were preterm, this was not an additional risk factor for early death.[26,27] Jenkins et al[28] used data sets from the Pediatric Cardiac Care Consortium and hospital discharge data from Illinois, Massachusetts, and California to develop and to validate a risk adjustment score for surgery to treat congenital heart disease. The prevalence rates of codes for prematurity in the 2 data sets were 7.8% and 1.7%, respectively. Prematurity was an additional predictor of risk (after type of operation, age at operation, and presence of major noncardiac malformation), with ORs for in-hospital death of 1.8 (95% CI: 1.3–2.6) and 2.9 (95% CI: 1.5–6.0), respectively, in the 2 data sets. McElhinney et al,[29] in a study of neonatal admissions to a cardiac ICU, found that prematurity was associated with an OR of 3.9 for development of necrotizing enterocolitis.

We analyzed the data in this study according to anatomic diagnosis. Several methods have been proposed to group anatomic diagnoses into speculative etiologic groups. They include a "mechanistic classification"[24] and a "potential morphogenetic classification."[30] There are similarities but also inconsistencies between these classifications, and they group together malformations that may be unrelated embryologically, etiologically, or physiologically; therefore, we did not apply such an analysis to our data.

There has been interest in the relationship between birth weight and prevalence at live birth of cardiovascular malformations, and there is an obvious relationship between birth weight and gestational age.[21] Although birth weight was recorded for all cases in our register, our analysis was on the basis of gestational age alone. Rosenthal et al[31] reported a case-control study of birth weight in relation to estimated gestational age among singleton infants with a limited range of isolated cardiovascular malformations. They found a significant increase in the likelihood of being small for gestational age among infants with tetralogy of Fallot, complete atrioventricular septal defect, hypoplastic left heart, or large ventricular septal defect. Their data also showed an increased prevalence of prematurity among infants with tetralogy of Fallot, pulmonary stenosis, aortic stenosis, coarctation of the aorta, or ventricular septal defect. Kramer et al[32] reported birth weights for 842 infants with cardiovascular malformations. They also found an increase in the chance of being small for gestational age among infants with tetralogy of Fallot, complete atrioventricular septal defect, or pulmonary stenosis. A larger proportion of infants with pulmonary stenosis and complete atrioventricular septal defect were premature, although the differences were not significant.

In common with most centers, we have an increasing number of infants born live after prenatal diagnosis of a cardiovascular malformation. It is unlikely that this has any significant influence on gestational age at delivery, because our policy is not to recommend premature delivery. Published evidence does not suggest that infants with prenatal diagnoses of cardiovascular malformations are born significantly earlier than those without.[33]

The excess of cardiovascular malformations among preterm infants shown in this study is intriguing but not easy to explain. Hoffman,[34] in a review of cardiovascular malformations in prenatal life, reported a much increased prevalence among late stillbirths. Early fetal losses are often associated with chromosomal abnormalities, many of which involve cardiovascular malformations, but chromosomal abnormalities are much less common after 20 weeks of gestation. The review by Hoffman[34] states that it is difficult to give an accurate estimate of the frequency of cardiovascular malformations, because of the disparate nature of reports available, but there are major differences in the number and spectrum of cardiovascular malformations, compared with those seen in postnatal life. In particular, there are higher

incidence rates of coarctation of the aorta, double-inlet left ventricle, hypoplastic left heart, truncus arteriosus, double-outlet right ventricle (a diagnostic category we did not use), and atrioventricular septal defect among stillbirths. Interestingly, this spectrum of malformations is similar to that shown in Fig 2 and those reported by Rosenthal et al[31] and Kramer et al,[32] as discussed above. Whether the increased prevalence of cardiovascular malformations among preterm infants and the increase in stillbirths reported by Hoffman[34] suggest clues to the cause is difficult to say. In many cases, it is not clear that the cardiovascular malformation led to preterm birth or stillbirth; we know that most cardiovascular malformations have little effect on the developing fetus and become hemodynamically significant only after birth.[35,36] There is also no evidence that cardiovascular malformations are associated with any compromise of placental function that might precipitate preterm delivery or cause stillbirth.

ACKNOWLEDGMENTS

We are indebted to the Children's Heart Unit Fund for financial support for the pediatric cardiology database, to Valerie Sutherland for help with data collection, to the Northern Congenital Abnormality Survey for additional data, and to Professor John Matthews for statistical advice.

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4.11 Wren C, Reinhardt Z, Khawaja K. Twenty-year trends in diagnosis of life-threatening neonatal cardiovascular malformations. *Arch Dis Child* 2008;93:F33-F35.

This paper was published after the original submission of this thesis and was originally included in full text unpublished form. It analyses temporal trends in the timing and mode of cardiovascular malformations in neonates. It finds that around 30% of infants with potentially life-threatening maformations were undiagnosed at discharge from hospital. Specific malformations most likely to go unrecognised were coarctation of the aorta (54%), interruption of the aortic arch (44%), aortic valve stenosis (41%), and total anomalous pulmonary venous connection (37%).

Original article

Twenty-year trends in diagnosis of life-threatening neonatal cardiovascular malformations

C Wren, Z Reinhardt, K Khawaja

Freeman Hospital, Newcastle upon Tyne, UK

Correspondence to:
Dr C Wren, Department of Paediatric Cardiology, Freeman Hospital, Newcastle upon Tyne NE7 7DN, UK; christopher.wren@nuth.nhs.uk

Accepted 10 May 2007
Published Online First 7 June 2007

ABSTRACT

Background: Infants with cardiovascular malformations are usually asymptomatic at birth. Earlier diagnosis is likely to improve outcome.

Objective: To examine trends in the diagnosis of potentially life-threatening cardiovascular malformations.

Methods: Ascertainment of all cardiovascular malformations diagnosed in infancy in the resident population of one English health region between 1985 and 2004. Infants with life-threatening cardiovascular malformations were all with hypoplastic left heart, pulmonary atresia with intact ventricular septum, transposition of the great arteries or interruption of the aortic arch; and those dying or undergoing operation within 28 days with coarctation of the aorta, aortic stenosis, pulmonary stenosis, tetralogy of Fallot, pulmonary atresia with ventricular septal defect or total anomalous pulmonary venous connection.

Results: Cardiovascular malformations were diagnosed in infancy in 4444 of 690 215 live births (6.4 per 1000) and were potentially life threatening in 669 (15%). Overall, 55 (8%) were recognised prenatally, 416 (62%) postnatally before discharge from hospital, 168 (25%) in living infants after discharge and 30 (5%) after death. Antenatal diagnoses increased from 0 to around 20% and no case was first diagnosed after death in the past 6 years. However, the proportion going home without a diagnosis remains around 25%. Malformations most likely to remain undiagnosed at discharge were coarctation of the aorta (54%), interruption of the aortic arch (44%), aortic valve stenosis (40%) and total anomalous pulmonary venous connection (37%).

Conclusions: One in three infants with a potentially life-threatening cardiovascular malformation left hospital undiagnosed. Better early diagnosis is likely to be achieved by further improvements in antenatal diagnosis and more widespread use of routine pulse oximetry.

Cardiovascular malformations are the commonest type of congenital malformation, accounting for 6–10% of all infant deaths and 20–40% of all infant deaths from malformation.[1 2] Most babies with serious cardiovascular malformations are asymptomatic at birth.[3] Some of them deteriorate or die before the diagnosis is recognised.[2] Earlier diagnosis, before clinical deterioration, ought to lead to an improvement in outcome.[4]

All babies are examined after birth before discharge from hospital. Although this examination is commonly regarded as a screening test, it is known to perform poorly in babies with life-threatening cardiovascular malformations, as there may be no abnormal physical signs before the development of symptoms.[5 6] The opportunity for presymptomatic diagnosis may also be reduced by earlier discharge from hospital after delivery.

This study examines trends in the time of diagnosis of potentially life-threatening cardiovascular malformations over a 20-year period.

PATIENTS AND METHODS

Study population

We based this study on the former Northern Health Region of England. The resident population is approximately 3.1 million with a recent average of 35 000 live births per year. All babies with suspected congenital heart disease are referred to a single paediatric cardiology centre. We identified all live born babies with a cardiovascular malformation from the regional paediatric cardiology database.[7] We identified all those dying before diagnosis by the Northern Congenital Abnormality Survey.[8] This survey also provided data on terminations of pregnancy for antenatally diagnosed heart defects and on total live births.

Case definition

We included all live born infants with potentially life-threatening cardiovascular malformations born in 1985–2004. We considered as having a potentially life-threatening abnormality all infants with a diagnosis of hypoplastic left heart, pulmonary atresia with intact ventricular septum, simple transposition of the great arteries, or interruption of the aortic arch and all infants dying or undergoing an operation within the first 28 days of life with the following diagnoses: coarctation of the aorta, aortic valve stenosis, pulmonary valve stenosis, tetralogy of Fallot, pulmonary atresia with ventricular septal defect, or total anomalous pulmonary venous connection. In infants with two life-threatening malformations the first presenting was coded (eg, an infant with transposition of the great arteries and coarctation of the aorta was coded as transposition). We used the 28-day limit for pragmatic reasons, although we recognise that the risk of death from undiagnosed cardiovascular malformations may be present after that age. In a previous report we documented sudden death from critical aortic valve stenosis in two babies at the age of 2 months.[2]

The Newcastle and North Tyneside Local Research Ethics Committee approved the study.

RESULTS

In 1985–2004 there were 690 215 live births in the study population. A diagnosis of a cardiovascular malformation was made in 4444 (6.4 per 1000) and 669 (15%) of these met our criteria for life-threatening congenital cardiovascular malformation defined above. There was a 20% fall in the live birth rate from nearly 39 000 to around 30 000 per year, but there was no change in the prevalence at live

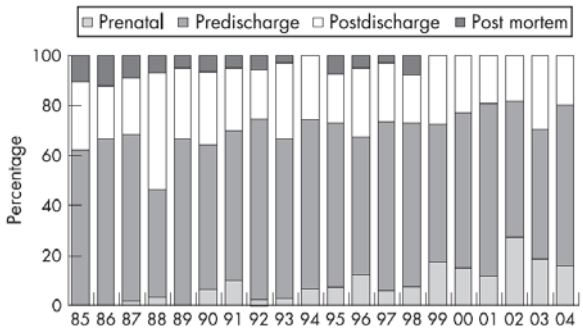

Figure 1 Time of diagnosis by year of birth 1985–2004.

birth of life-threatening cardiovascular malformations over the 20 years of the study, with a mean of 0.97 per 1000 live births.

Of 669 infants with life-threatening cardiovascular malformations, 55 (8%) had an antenatal diagnosis, 416 (62%) had a postnatal diagnosis before discharge from hospital, 168 (25%) were diagnosed in living infants after discharge from hospital and 30 (5%) were diagnosed only at autopsy. Figure 1 shows that over 20 years the proportion with an antenatal diagnosis increased to about 20% and overall there was a decrease in the proportion of cases diagnosed before discharge from hospital.

Cardiovascular malformations were undiagnosed at the time of discharge from hospital in 198 infants (30%) and in 30 of these the diagnosis was made only after death. Table 1 shows the timing of diagnosis of individual malformations. Figure 2 shows that the diagnoses most likely to be unrecognised at the time of discharge included coarctation of the aorta (54%), interruption of the aortic arch (44%), aortic valve stenosis and total anomalous pulmonary venous connection (37%).

Over 20 years the all-causes 12-month mortality for live born infants with life-threatening cardiovascular malformations fell from around 50% to around 20%.

There were 139 terminations of pregnancy in fetuses with a cardiovascular malformation. The majority had associated major chromosomal or other non-cardiac abnormalities, but 60 had isolated cardiovascular malformations which would meet our criteria for being potentially life-threatening in postnatal life. The rate of termination increased, with 14 in the first 10 years and 46 in the second 10 years.

We have no regional data on the length of hospital stay after birth.

DISCUSSION

Our study has found that around 30% of infants with potentially life-threatening cardiovascular malformations were undiagnosed at the time of discharge from hospital. This proportion fell to around 25% in recent years. Terminations of pregnancy increased, but there was no change in the prevalence at live birth of life-threatening cardiovascular malformations, which remained at around 1 in 1000 live births. Despite this, the total infant mortality for such babies has reduced substantially.

Earlier postnatal recognition of potentially serious cardiovascular malformations should contribute to reduction in morbidity and mortality.[4 9] There is also evidence that prenatal diagnosis improves postnatal outcome for a number of malformations, including transposition of the great arteries,[10] hypoplastic left heart[11] and coarctation of the aorta.[12]

There have been few other studies of the timing of diagnosis of potentially life-threatening cardiovascular malformations. In a recent report Mellander and Sunnegårdh investigated post-discharge diagnosis in neonates and young infants with critical heart disease.[13] They included all infants requiring surgery or catheter intervention in the first 2 months of life and thus had a wider range of diagnoses over a longer time period than our study. Mellander and Sunnegårdh found that 50% of their patients had duct-dependent systemic circulation, 41% had duct-dependent pulmonary circulation and 9% were not duct dependent. The proportion of their patients diagnosed after discharge from hospital averaged 20% but doubled over 9 years. Their study did not include patients not referred for surgery or dying before diagnosis and could not take account of changes in prenatal diagnosis or termination of pregnancy.

In a much smaller study from a hospital with only 2300 births a year Meberg *et al* reported a lower rate of late diagnosis.[14] They also found that coarctation of the aorta and aortic valve stenosis were the potentially dangerous malformations most likely to be overlooked before discharge.

Influences on the speed of recognition of life-threatening cardiovascular malformations include antenatal diagnosis, the speed of referral of babies with a clinical suspicion of congenital heart disease and the length of stay in the maternity hospital after birth. We are unaware of any published data from the United Kingdom on age at discharge, but reports from Sweden, the United States and Canada show a reduction from 4 or 5 days in the 1980s to 1–3 days in the 1990s.[15–19] It is likely that the trend towards earlier discharge in our population mirrors that in the UK nationally, with an increasing proportion of babies being sent home 6–12 hours after delivery.

Table 1 Timing of diagnosis for individual malformations

Malfomation	Prenatal	Before discharge	After discharge	Post mortem	Total
PA/VSD	3	42	2	1	48
PA/IVS	7	22	4	0	33
ToF	4	25	3	1	33
PS	1	17	2	1	21
TGA	5	136	23	6	170
HLH	19	45	9	10	83
TAPVC	0	24	12	2	38
AS	4	15	13	0	32
IAA	1	22	13	5	41
CoA	11	68	87	4	170
Total	55	416	168	30	669

AS, aortic valve stenosis; CoA, coarctation of the aorta; HLH, hypoplastic left heart; IAA, interruption of the aortic arch; PA/IVS, pulmonary atresia with intact ventricular septum; PA/VSD, pulmonary atresia with ventricular septal defect; PS, pulmonary stenosis; TAPVC, total anomalous pulmonary venous connection; TGA, transposition of the great arteries; ToF, tetralogy of Fallot.

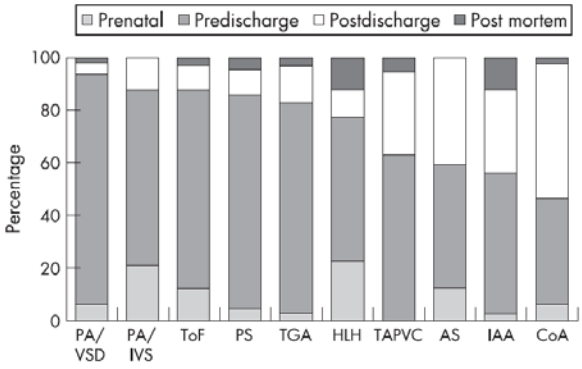

Figure 2 Time of diagnosis for individual malformations (ranked according to probability of predischarge diagnosis). For abbreviations see table 1.

What is already known on this topic

- Early diagnosis of asymptomatic cardiovascular malformations is difficult as clinical examination performs poorly as a screening test.
- Earlier diagnosis improves outcome.

What this study adds

- Life-threatening cardiovascular malformations are present at live birth in 1 baby in 1000, but 25% of these are discharged without being diagnosed.
- Coarctation of the aorta, interruption of the aortic arch, total anomalous pulmonary venous connection and aortic valve stenosis are the diagnoses most likely to be overlooked.

In a previous study we found that the diagnosis of cardiovascular malformations is often delayed despite the detection of a murmur at the first neonatal examination.[5] It is impractical to refer all neonates with murmurs for urgent paediatric cardiology assessment, but if a significant murmur is detected and echocardiography skills are available in the neonatal unit, earlier diagnosis of potentially serious cardiovascular malformation ought to lead to a better outcome.[20 21]

Given the failure of clinical examination to increase the number of babies with serious heart disease detected before discharge, any improvement is likely to come from a different strategy. This will include further improvements in antenatal diagnosis,[22] more widespread adoption of routine pulse oximetry in the newborn,[23–25] and better education of midwives and other primary healthcare professionals that the absence of physical signs at birth does not mean that there is no life-threatening problem.[3] The trend towards a shorter postnatal length of stay is likely to continue.

Acknowledgements: We are indebted to Valerie Sutherland for helping with data extraction, to the Children's Heart Unit Fund for financial support of the paediatric cardiology database and to the Northern Congenital Abnormality Survey for providing additional data.

Competing interests: None.

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CHAPTER 5: PREVALENCE AT LIVE BIRTH OF CONGENITAL CARDIOVASCULAR MALFORMATIONS: A SYSTEMATIC REVIEW

5.1 INTRODUCTION

The prevalence at live birth of cardiovascular malformations was a subject of interest even before paediatric cardiology became a recognised specialty. Reports have been published on different populations around the world over the last fifty years but many early papers do not contain sufficient detail to be useful for analysis. Although attempts have been made at comparison between studies, their usefulness is limited by the absence of a common methodology. [Ferencz 1990]

The cause of most cardiovascular malformations is unknown. Some have genetic causes [Lin 2005, Pierpont 2007], others are environmental in origin [Mone 2004, Jenkins 2007], but most have traditionally been regarded as "idiopathic" or "multifactorial" [Nora 1968]. Comparisons between different populations are potentially valuable because different environmental exposure, diet, or genetic make-up might produce a true variation in the prevalence and/or spectrum of cardiovascular malformations. However, before populations can usefully be compared, there has to be a proper evaluation of other possible reasons for differences between reports.

The aims of this study were:

1. To identify all published observational studies of the prevalence of congenital cardiovascular malformations.
2. To examine these studies for potential sources of bias.
3. To predict which malformations are most liable to ascertainment bias and to test the prediction against analysis of variation in the published prevalence rates.
4. To identify studies with sufficiently common methodology for further analysis.
5. To investigate whether there is evidence of a real difference between populations.
6. To produce recommendations for consistent methodology for future reports to allow proper comparison between different populations.

5.2 SYSTEMATIC REVIEWS

Improvements in the conduct and reporting of research over time led to the development of the concept of evidence-based medicine. Various levels of evidence are defined, depending on the validity of the research underlying them.

The levels range from level 1A which might be a systematic review of randomised controlled trials to level 5 which is expert opinion without explicit critical appraisal. Criteria for the conduct and reporting of randomised control trials and for meta-analysis of randomised control trials were published in *Lancet* in 1999 by the QUOROM (Quality of Reporting of Meta-Analyses) Group. [Moher 1999] Editors of most major medical journals now require compliance with these recommendations.

Similar concepts have since been applied to the conduct and reporting of observational epidemiological studies. Proposals have been published by the MOOSE (Meta-analysis of Observational Studies in Epidemiology) Group in *JAMA* in 2000 and are reproduced in appendix A. [Stroup 2000]

A systematic review is a review which is prepared using a strategy to avoid bias and which defines the materials and methods to make the process transparent. A systematic review may or may not include a meta-analysis, which is "a statistical analysis which combines or integrates the results of several independent clinical trials considered by the analyst to be 'combinable'". [Egger 2003]

Systematic reviews are not infallible. Some which address the same subject have reached opposite conclusions. [Higgins 2006] Two factors which are central to the validity of systematic reviews and meta-analyses are:

- Inclusion of all relevant studies (or an unbiased sample of relevant studies).
- The methodological quality of the component studies.

The STROBE (Standards for the Reporting of Observational Studies in Epidemiology) Group have published a checklist of essential items to be taken into account when publishing an observational epidemiological study or when performing a systematic review of such studies – see appendix B. [von Elm 2007]

5.3 REPORTING BIAS

It has been recognised for a long time that only a proportion of research projects performed are eventually published in an indexed journal and thus become available and identifiable for systemic review. The fact that not all research results are published is a major concern, more so for meta-analyses of randomised controlled trials rather than for systematic reviews of epidemiological studies. "Positive" results are more likely to be published, more likely to published quickly, more likely to be published in English, more likely to be published more than once, and more likely to

be cited. These problems are grouped together under the heading of reporting bias. Types of reporting bias are listed in table 5.1.

Table 5.1. Types of reporting bias. Adapted from Egger 2003.

Type of reporting bias	Definition
Publication bias	The publication or non-publication of research findings depending on the nature and direction of results.
Multiple publication bias	The multiple or singular publication of research findings, depending on the nature and direction of results.
Language bias	The publication of research findings in a particular language, depending on the nature and direction of the results. This is often more likely to be English if the findings are positive.
Database bias	The inclusion or exclusion of research findings from widely used bibliographic databases such as MEDLINE, depending on the nature and direction of results.
Citation bias	The citation or non-citation of research findings, depending on the nature and direction of results.
Outcome reporting bias	The selective reporting of some outcomes, but not others, depending on the nature and direction of results.

Other types of bias in the raw material of clinical trials also threaten the validity of systematic meta-analysis. They include selection bias, performance bias, detection bias, and attrition bias. [Egger 2003].

Assessment for bias

Several methods have been developed for assessment of the impact of various biases on randomised control trials and systematic reviews. One in particular is the funnel plot which is used to measure publication bias. The smaller a study is, the larger the treatment effect that will be needed for the results to be considered “statistically significant”. Bias in a systematic review may therefore be present if there is an association between treatment effect and study size. This is assessed using a funnel plot which is a scatter plot of treatment effect in individual studies against study size or standard error. In the absence of bias the plot will be symmetrical. Bias produced by failure to report, publish or include smaller studies showing no significant effect will produce asymmetry in the funnel plot. However, an asymmetrical funnel plot may be due to study factors other than publication bias. [Cochrane Collaboration 2002]. These include other types of selection bias,

poor methodological quality or design of smaller studies, inadequate analysis, fraud, chance, artefact and true heterogeneity. Egger *et al* used these techniques to assess the importance of comprehensive literature searches and assessment of trial quality in systematic reviews. [Egger 2003] They found that systematic reviews based on easily accessible English languages reports often produced results similar to those from more comprehensive reviews free from language bias. They also found that trial results which were difficult to locate were often of low quality, raising the prospect that a more diligent systematic review might introduce rather than reduce bias, by inclusion of studies of dubious worth. Egger *et al* also confirmed the usefulness of the funnel plot and used a regression method to assess funnel plot asymmetry in the detection of small study effects – that is the tendency for smaller studies to show larger treatment effects.

5.4 BIAS IN DESCRIPTIVE EPIDEMIOLOGY

Descriptive epidemiological studies are also susceptible to bias of various types. Whilst this may include publication bias, the main concern is that reports of the prevalence at live birth of cardiovascular malformations may be affected by various types of ascertainment bias. Table 5.2 lists various types of bias which may affect such epidemiological studies, most of which were discussed in chapter 1.

From the list in table 5.2 it seems very likely that some specific cardiovascular malformations will be more susceptible to certain types of bias than others. For example, ventricular septal defect is the most common diagnosis in every reported survey. One would expect ventricular septal defects to be affected by ascertainment bias (more intensive surveillance or more recent colour Doppler echocardiography studies will be expected to find a higher number of very small ventricular septal defects) and classification bias (ie there may be fewer large ventricular septal defects using a physiological hierarchy - see section 2.6). Hypoplastic left heart has a relatively constant definition but is likely to be affected by variable ascertainment as it will be influenced by termination of pregnancy and by death before diagnosis, probably both relatively minor effects. Double outlet right ventricle and pulmonary atresia with ventricular septal defect suffer from the problem of variable definition and variable use in different studies. The Baltimore-Washington Infant Study considered pulmonary atresia with ventricular septal defect to be a variant of tetralogy of Fallot and didn't code it separately. [Ferencz 1993] However, this report did use double outlet right ventricle, a diagnostic group ignored by many others.

Double outlet right ventricle covers a variety of malformations that in other reports are variously coded as transposition of the great arteries, tetralogy of Fallot etc.

Table 5.2. Types of ascertainment bias.

Type of bias	Example
Population or institution based	Whole population including all live births preferred.
	Bias from single institution – may not reflect whole population.
	Bias from social group (e.g. health care insurance).
Referral bias	Historical referral pattern.
	Mild disease not referred.
	Severe disease not recognised before death.
	Failure to refer because of co-existing severe non-cardiac disease (e.g. lethal trisomy).
Ascertainment bias	Limited availability of paediatric cardiologists in less affluent countries.
	“Screening” by murmur, echocardiography etc.
	Small studies with more intensive surveillance.
	Inclusion or exclusion of terminations, stillbirths.
Diagnostic bias	No echocardiography in early era, with failure to diagnose minor malformations or inclusion of unconfirmed clinical diagnoses.
	Variable inclusion/exclusion criteria (e.g. bicuspid aortic valve, mitral valve prolapse, preterm patent ductus, arrhythmia, cardiomyopathy, etc.) – see text.
	Inclusion of patent foramen ovale / atrial septal defect / very mild valve stenosis.
Selection bias	Limited or open-ended ascertainment.
	Antenatal diagnosis and termination of pregnancy.
	Down’s syndrome screening and termination of pregnancy.
Classification bias	Variable diagnostic classification – e.g. pulmonary atresia, double outlet right ventricle etc – see text.
	Effect of hierarchy.

5.5 METHODS

The design of this study was influenced by guidelines published by the Health Technology Assessment programme [Sutton 1998], the NHS Centre for Reviews and Dissemination (CRD) [CRD 2001], the Meta-analysis of Observational Studies in Epidemiology group (MOOSE) [Stroup 2000], and Standards for the Reporting of Observational Studies in Epidemiology (STROBE) [STROBE 2006]. A prior search of the Cochrane database was made to ensure that no similar investigation had already been done.

Criteria for considering studies

The objective was to identify all cohort studies reporting the prevalence at live birth of cardiovascular malformations in 1950-2005. Copies were obtained of all published reports and many colleagues helped with translating those not published in English (see Acknowledgements page xi).

The literature search strategy

The author performed a database search of MEDLINE (PubMed and OVID) and Google Scholar to identify all reports relating to the prevalence, incidence or epidemiology of congenital heart disease or cardiovascular malformations published before the end of December 2005. Hand searching of references cited in published review articles [Ferencz 1990, Hoffman 1995, Loffredo 2000, Hoffman 2002] and in each of the included primary reports was also performed. In a few cases where key information was missing from a report apparently otherwise suitable for inclusion or analysis, authors were contacted directly for advice or additional data. Publications in all languages were included and copies were obtained with the help of the staff of Freeman Hospital library. PubMed was specifically searched for papers in German, Spanish, Russian, Chinese and Japanese to minimise language bias. In a very few cases, for example papers published in Russia or India in the 1960s, reports were untraceable and, therefore, had to be excluded (they are unlikely to have contained useful information). Many papers in languages other than English contained sufficient information in the English abstract to assess whether they were suitable for analysis (e.g. if they were autopsy series they were not useful for inclusion). Full copies of potentially useful publications in languages other than English were obtained. Unpublished reports or those appearing only as abstracts were not included.

Appraisal of studies

All studies were examined to determine whether a denominator population could be identified. Those dealing with consecutive births in a single hospital or group of hospitals covering a defined population were included but papers describing admissions to, or attendance at, a hospital or clinic were excluded. Also excluded were papers reporting only neonates or only symptomatic infants or diagnoses made only in children beyond infancy (e.g. in schoolchildren) and those dealing only with selected malformations. Where there was more than one report from the same institution or population, only the later one was included.

Analysis

Particular note was made of whether studies (a) limited diagnoses to those made in the first year of life or had open ended ascertainment; (b) included only confirmed diagnoses (by echocardiography, cardiac catheterisation, surgery or autopsy); and (c) had a defined denominator population of live births. Studies which included stillbirths and/or terminations of pregnancy in the numerator, and in which data for live born babies could not be identified separately were excluded from secondary analysis. Also excluded from secondary analysis were studies which did not include infants with chromosomal or genetic abnormalities [Borman 1987, Mayberry 1990] as these account for up to 10-15% of cardiovascular malformations [Ferencz 1989, Johnson 1997]. For each of the reports the prevalence at live birth of cardiovascular malformations was calculated and the diagnostic hierarchy used for classification of patients with more than one main malformation was analysed.

Further analysis of prevalence at live birth of specific malformations

The 15 papers that included only live-births, limited ascertainment to infancy, excluded clinical diagnoses, and had a population base to permit calculation of birth prevalence were grouped for further analysis.

Prediction of susceptibility of individual cardiovascular malformations to ascertainment bias

Before analysis of any results from the selected reports, each individual cardiovascular malformation was assessed for susceptibility to various types of ascertainment bias (Table 5.3). In particular, a prospective assessment was made of whether ascertainment was lively to be influenced by:

- Variable ascertainment (ie more diligent diagnosis of, or coding of, minor malformations)

- Variable definition
- Variable (or undefined) diagnostic hierarchy
- Rarity
- Reduced live birth prevalence because of termination of pregnancy after antenatal diagnosis
- Death before diagnosis
- Post-infant open-ended ascertainment

As can be seen from table 5.3, the malformations predicted to be least likely to be affected by these factors are transposition of the great arteries, tetralogy of Fallot, complete atrioventricular septal defect and hypoplastic left heart. These were selected for more detailed analysis of prevalence, along with coarctation of the aorta (predicted to be more susceptible to factors affecting ascertainment – most notably the effects of diagnostic hierarchy and open ended ascertainment), and ventricular septal defect (because it is the most common and is predicted to be one of the most affected by the variables in table 5.3).

Statistical analysis

Most of the statistics used are descriptive. They include presentation of data with means, medians and range. Box and whisker plots were produced in Microsoft Excel. Funnel plots were produced with the help of data analysis programmes produced by the Eastern Region Public Heath Observatory, ERPHO, (http://www.erpho.org.uk/) and available at: http://www.erpho.org.uk/tools.aspx.

Table 5.3. Susceptibility of individual malformations to various types of ascertainment or selection bias. Malformations are listed in order of an anatomical hierarchy, with decreasing morphological "severity".

Malformation	Ascertainment	Definition	Hierarchy	Rarity	Termination of pregnancy	Death before diagnosis	Post infant ascertainment
Hypoplastic left heart (HLH)		x			x	x	
Mitral Atresia (MA)				**X**	x		
Tricuspid Atresia (TA)				**X**	x		
Double Inlet Left Ventricle (DILV)				**X**	x		
Pulmonary Atresia with Intact Ventricular Septum (PA/IVS)				**X**	x		
Pulmonary Atresia with Ventricular Septal Defect (PA/VSD)		**X**	x		x		
Congenitally Corrected Transposition of the Great Arteries (CCTGA)			x	**X**			
Truncus arteriosus (CAT)				**X**	x		
Total Anomalous Pulmonary Venous Connection (TAPVC)			**X**	**X**			
Hypoplastic Right Heart (HRH)		**X**		**X**	x		
Double Outlet Right Ventricle (DORV)		**X**	**X**				
Complete Atrioventricular Septal Defect (CAVSD)			x		x		
Partial Atrioventricular Septal Defect (P/AVSD)				**X**			**X**
Tetralogy of Fallot (ToF)		x					
Transposition of the Great Arteries (TGA)							
Interruption of the Aortic Arch (IAA)			**X**	**X**		x	
Coarctation of the Aorta (CoA)			**X**			x	**X**
Ventricular Septal Defect (VSD)	**X**	x	**X**				**X**
Aortic Valve Stenosis (AS)	**X**	**X**				x	**X**
Pulmonary Valve Stenosis (PS)	**X**	**X**	**X**				**X**
Atrial Septal Defect (ASD)	**X**	**X**	**X**				**X**
Persistent Ductus Arteriosus (PDA)	**X**						**X**
	X	major effect					
	x	minor effect					

5.6 RESULTS

Papers examined

The initial literature search identified 317 papers from 67 countries published in 1951-2005 that reported the prevalence or incidence of cardiovascular malformations. Figure 5.1 shows their geographical distribution. Of the 317 papers, 233 (74%) either had no identifiable birth cohort or included only neonates or only children and were excluded from detailed analysis. These papers are listed in appendix C.

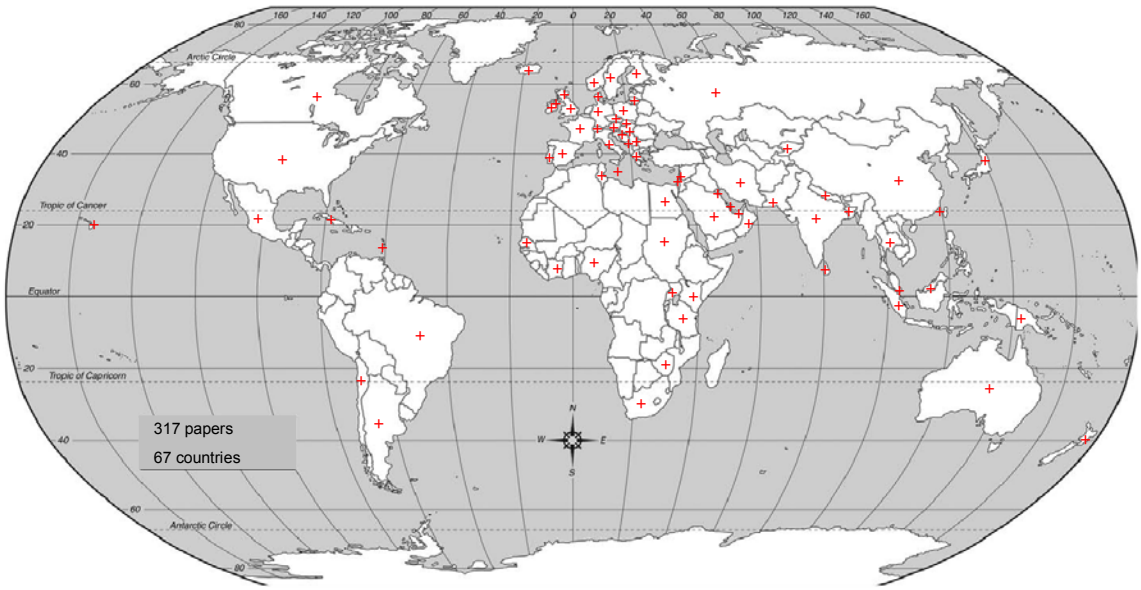

Figure 5.1. The geographical spread of the 67 countries producing reports on cardiovascular malformations. Sources of individual papers are not shown.

Description of papers included in analysis

Eighty-four papers from 38 countries published between 1951 and 2005 contained sufficiently detailed data for inclusion. Figure 5.2 shows the geographical distribution of these papers. As one might predict, reports from Western countries predominate.

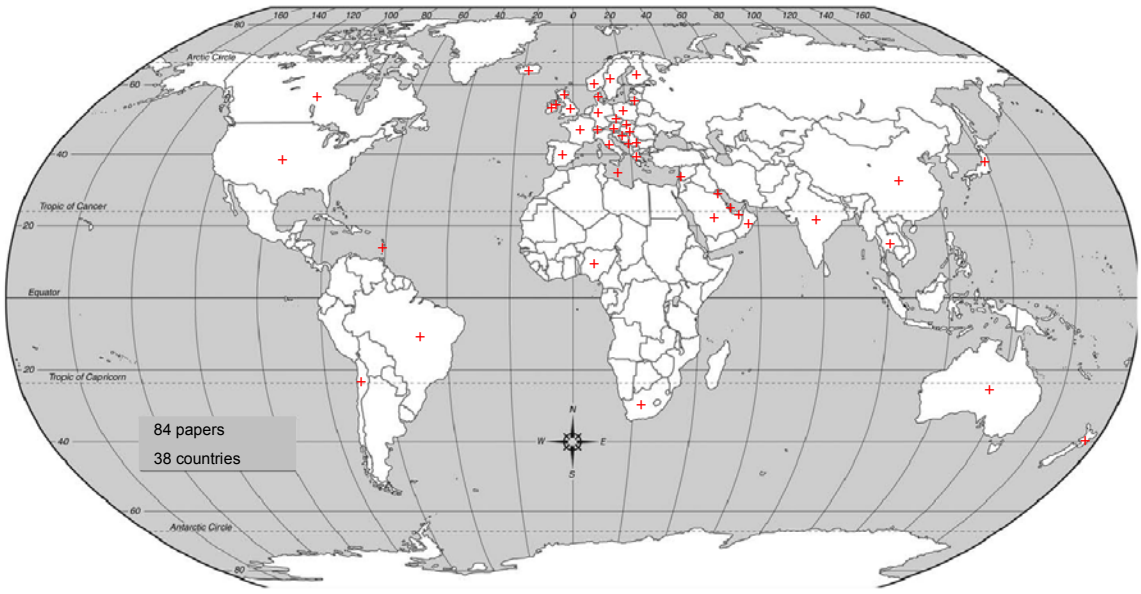

Figure 5.2. The geographical spread of the 38 countries producing reports suitable for analysis. Sources of individual papers are not shown.

The denominator populations in the 84 papers ranged from 2,500 to over 2,000,000 and totalled over 18,500,000. They included over 100,000 cases of cardiovascular malformation. The 84 papers are listed in table 5.4 along with their main characteristics. The country abbreviations are taken from the United Nations abbreviations - details are at: http://unstats.un.org/unsd/methods/m49/m49alpha.htm

Of the 84 papers, 47 (56%) included clinical (i.e. unconfirmed) diagnoses, 19 (23%) included stillbirths and/or terminations of pregnancy in the denominator and/or numerator, and 48 (57%) extended ascertainment beyond infancy (the first year of life). Most papers excluded isolated bicuspid aortic valve with no stenosis, patent ductus arteriosus in prematurity, cardiomyopathy, isolated positional abnormalities of the heart, isolated cardiac arrhythmias, and tumours but others also excluded trisomies and syndromes [Borman 1987, Mayberry 1990], and specific ethnic groups [Arbour 2004].

In some cases precise numbers of stillbirths or of abnormalities such as cardio-myopathy or bicuspid aortic valve were given so that they could be removed for more appropriate analysis. In a few cases the exact birth cohort was not defined but could be calculated fairly precisely as both the number of cardiovascular malformations and the birth prevalence were given. [Tikkanen 1990, Roy 1994, Pradat 2003, Abushaban 2003]

Table 5.4. The 84 papers in the main analysis.

1st Author	Year	Country	Era	Births	No of CVM	Prevalence	Infant diagnosis?	Confirmed diagnosis?	Population-based?	All live born?	Hierarchy
Gardiner	1951	CAN	48-49	134367	291	2.2	no	no	yes	yes	none
Richards	1955	USA	46-53	5652	42	7.4	yes	no	yes	yes	none
Carlgren	1959	SWE	41-50	58105	369	6.4	no	no	yes	yes	none
Renwick	1964	CAN	55-60	34138	973	4.3	no	no	yes	no	none
Gupta	1967	NGA	64	4054	10	2.5	no	no	hosp	yes	none
Howie	1970	NZL	64-67	16103	80	4.7	yes	no	hosp	no	"most important"
Feldt	1971	USA	50-69	32393	186	4.9	no	no	yes	yes	none
Bound	1971	GBR	57-71	56982	338	5.9	no	no	yes	yes	none
Mitchell	1971	USA	58-65	54765	420	7.7	no	no	yes	yes	none
Darsinos	1971	GRC	54-68	99254	369	3.7	yes	no	hosp	yes	list
Hay	1971	USA	63	58686	233	4.0	yes	no	yes	no	none
Czeizel	1972	HUN	63-65	52549	371	7.1	no	yes	yes	no	most grave
O'Brien	1972	IRL	66-71	32978	125	3.8	yes	no	hosp	yes	most severe
Levin	1973	ZAF	66-70	21810	141	6.5	no	no	yes	yes	none
Kenna	1974	GBR	60-69	163692	1081	6.5	no	no	yes	no	"pecking order"
Henriksen	1974	NOR	67-68	133719	716	5.4	no	no	yes	yes	none
Pentek	1975	HUN	55-69	97482	744	7.6	yes	no	yes	yes	none
Ishihara	1974	JPN	69-71	36554	205	5.6	no	no	yes	yes	none
Gravinghoff	1975	DEU	69	22605	152	6.7	no	no	yes	?	none
Hoffman	1978	USA	59-66	19044	163	8.8	no	no	yes	yes	none
Pongpanich	1978	THA	69-75	26152	70	2.7	yes	no	hosp	yes	none
Kopecka	1979	CZA	75-77	756335	3213	4.3	no	no	yes	yes	none
Zajadacz	1979	POL	65-77	8564	57	6.7	no	no	yes	yes	specific
Laursen	1980	DNK	63-73	854886	5249	6.1	no	no	yes	yes	none
Stocker	1980	CHE	75	78464	494	6.3	yes	no	yes	yes	none
Fyler	1980	USA	68-74	1083083	2190	2.0	yes	yes	yes	yes	anatomical
Dickinson	1981	GBR	60-69	160480	884	5.5	no	no	yes	yes	none
Squarcia	1981	ITA	72-80	33245	327	9.8	?	no	yes	yes	none
Dolara	1981	ITA	75-80	32561	337	10.3	yes	no	yes	yes	none
Philippi	1986	CHL	83	7360	99	13.5	no	no	yes	yes	none
Nakazawa	1986	JPN	84-85	72745	773	10.6	yes	no	yes	yes	none
Borman	1987	NZL	78	51777	181	3.5	yes	no	yes	yes	predominant
Carlgren	1987	SWE	81	93678	708	7.6	yes	yes	yes	no	none
Grabitz	1988	CAN	81-84	103411	573	5.5	yes	yes	yes	yes	embryological
Stoll	1989	FRA	79-86	105299	757	7.2	yes	yes	yes	no	none
Diez Tomas	1989	ESP	76-85	53578	282	5.2	no	no	yes	yes	none
Schmidt	1989	DEU	71-80	229846	1638	7.1	no	no	yes	yes	none
Mayberry	1990	USA	70-88	16474	120	7.3	no	no	yes	yes	physiological
Tikkanen	1990	FIN	82-83	132993	583	4.4	yes	yes	yes	no	none
Klimentova	1990	CZE	81-87	61420	480	7.8	yes	no	yes	yes	first
Fixler	1990	USA	71-84	379561	2509	6.6	no	no	yes	yes	embryological
Fischer	1991	AUT	79-83	41725	341	8.2	no	no	yes	yes	none
Sung	1991	CHN	87-89	20928	125	6.0	yes	yes	yes	yes	none

Table 5.4 continued.

1st Author	Year	Country	Era	Births	No of CVM	Prevalence	Infant diagnosis?	Confirmed diagnosis?	Population-based?	All live born?	Hierarchy
Ferencz	1993	USA	81-89	906646	4224	4.7	yes	yes	yes	yes	embryological
Kidd	1993	AUS	81-84	343521	1190	3.5	yes	yes	yes	yes	anatomical
Manetti	1993	ITA	75-84	46895	579	12.3	no	no	yes	yes	none
Cerboni	1993	GLP	88-90	22855	139	6.1	yes	yes	yes	yes	none
Khalil	1994	IND	n/a	10964	43	3.9	yes	no	hosp	yes	none
Bower	1994	AUS	80-89	233502	1787	7.7	no	no	yes	no	anatomical
Andersen	1994	NOR	87-90	14194	145	10.2	no	yes	yes	yes	"leading"
Roy	1994	CAN	66-89	682625	5461	8.0	no	no	yes	yes	"clinical judgement"
Tikanoja	1995	FIN	89-92	12841	139	10.8	no	yes	no	yes	none
Anand	1996	USA	92-93	15949	156	9.8	no	yes	yes	yes	none
Jackson	1996	GBR	79-88	203880	1543	7.6	no	no	yes	yes	physiological
Montana	1996	USA	90-94	194754	1589	8.2	yes	yes	yes	no	embryological
Schoetzau	1997	DEU	84-91	984570	7020	7.1	no	yes	yes	yes	embryological
Robida	1997	QAT	84-94	49887	550	11.1	no	yes	yes	yes	none
Grech	1998	MLT	90-94	26117	231	8.8	yes	yes	yes	yes	physiological
Samanek	1999	CZE	80-90	816569	5030	6.2	no	yes	yes	yes	physiological
Cloarec	1999	FRA	91-94	26082	256	9.8	no	yes	yes	no	"predominant"
Zhang	1999	CHN	?	115836	431	3.7	no	no	yes	yes	none
Bosi	1999	ITA	92-93	341647	1445	4.2	no	?	yes	yes	"complex"
Wren	2000	GBR	85-97	477960	2671	5.6	yes	yes	yes	yes	anatomical
Guitti	2000	BRA	89-98	80262	441	5.5	no	yes	yes	yes	anatomical
Subramanyan	2000	OMN	94-96	139707	992	7.1	no	yes	yes	yes	physiological
Mogyorosy	2000	HUN	94-98	26932	334	12.4	no	yes	yes	no	none
Guía	2000	ESP	78-90	203783	1118	5.5	no	yes	yes	yes	none
Botto	2001	USA	68-97	937195	5656	6.2	yes	no	yes	no	embryological
Bache	2002	DEN	86-95	55750	446	8.0	no	yes	yes	no	as "complex"
Begić	2003	BIH	94-99	39699	243	6.1	no	no	yes	yes	none
Bosi	2003	ITA	80-00	480793	2442	5.1	yes	no	yes	yes	as "miscellaneous"
Putarek	2003	HRV	95-00	276565	2204	8.0	no	yes	yes	yes	embryological
Pradat	2003	FRA	83-92	950000	2749	2.9	yes	n/a	yes	no	as "complex"
"	2003	SWE	81-92	1270000	3171	2.5	yes	yes	yes	no	as "complex"
"	2003	USA	85-92	2200000	7012	3.2	yes	yes	yes	no	as "complex"
Abushaban	2003	KWT	86-89	82531	326	4.0	yes	yes	yes	yes	double counting
"	2003	KWT	92-00	229981	2378	10.3	yes	yes	yes	yes	double counting
Cleves	2003	USA	93-98	213870	1983	9.3	yes	yes	yes	yes	double counting
Garne	2004	DEN	86-98	72519	573	7.9	yes	yes	yes	yes	specific or misc
Bolisetty	2004	AUS	93-00	6156	105	17.1	yes	yes	yes	yes	physiological
Stephensen	2004	ISL	90-99	44013	740	17.0	no	yes	yes	yes	physiological
Arbour	2004	CAN	89-94	2567	77	30.0	yes	yes	yes	no	none
Forrester	2004	USA	86-99	264236	2268	8.6	yes	yes	yes	yes	selected diagnoses
Samson	2004	ARE	01-02	11085	83	7.5	no	yes	hosp	yes	none
Chehab	2004	LBN	99-02	27834	249	8.9	yes	yes	yes	yes	"dominant" or "other"
Meberg	2005	NOR	82-02	49458	553	11.2	no	no	yes	yes	"arbitrary"
Olorón	2005	ESP	89-98	47783	428	9.0	no	yes	yes	yes	none

Other specific inclusions and exclusions varied. Uncommon inclusions were pulmonary artery branch stenosis [Botto 2001], anomalies of systemic veins [Montana 1996], complete atrioventricular block [Montana 1996, Giutti 2000], mitral valve prolapse [Guitti 2000, Roy 1994] and bicuspid aortic valve [Roy 1994, Stephensen 2004]. No mechanism for classification of infants with more than one cardiovascular malformation was mentioned in 41 (48%) papers. The hierarchies employed by others varied widely but the commonest were anatomical, physiological, or embryological (see table 5.4). Other reports listed multiple malformations separately, [Garne 2004] or grouped them as "complex" [Bosi 1999, Bache 2002] or "miscellaneous" [Bosi 2003], or counted them twice [Abushaban 2003, Cleves 2003].

Trends over time – study size

As can be seen from figure 5.3, there is a trend to larger study size over time. The first three reports with denominators of more than 500,000 live births appeared in the 1970s and other reports of that size were mostly published in the 1990s. Fifty-two papers (61%) have a denominator of fewer than 100,000 live births, 22 have 100-500,000 live births and only 11 include more than 500,000 live births.

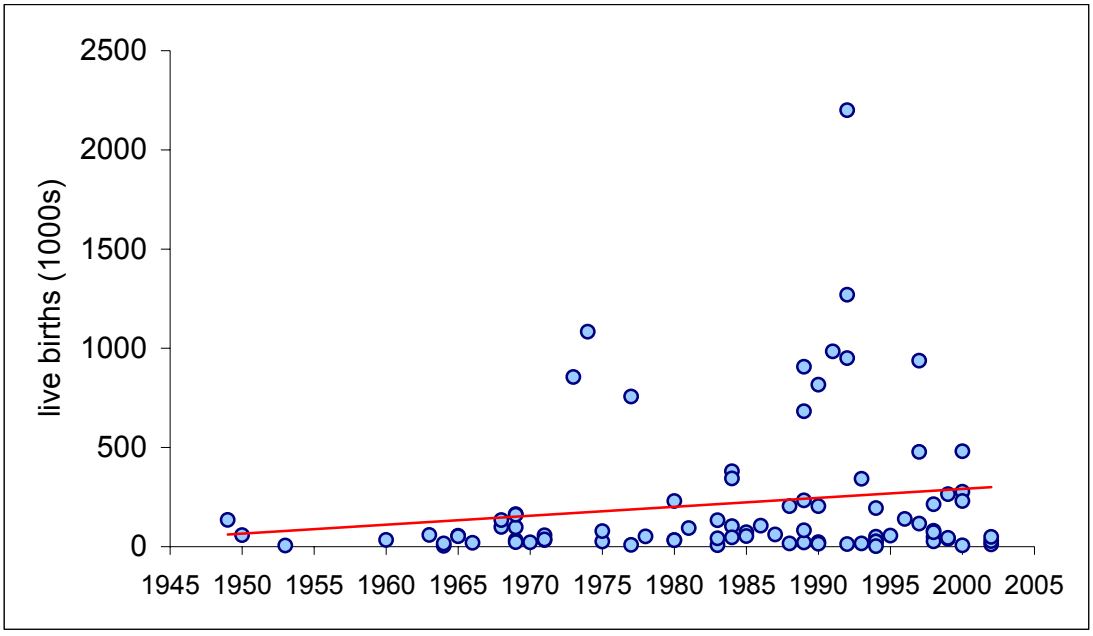

Figure 5.3. The relationship between final year of data collection and study size (denominator live births). Similar results are obtained by plotting middle year of study or year of publication.

Trends over time – prevalence at live birth

The reported live birth prevalence of cardiovascular malformation in the 84 papers varied from 2.1 to 30 per 1000 live births with a mean prevalence of 5.2 per 1000 and a median of 6.7. Figure 5.4 shows the increase in the prevalence at live birth with time – almost certainly from better ascertainment (see discussion below).

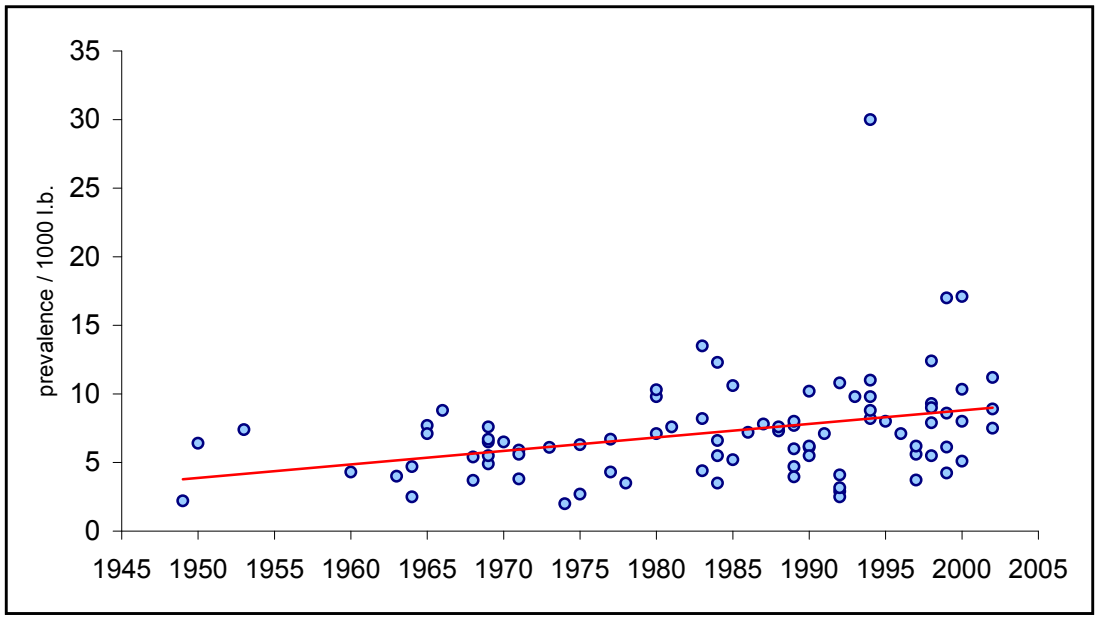

Figure 5.4. The relationship between final year of study and prevalence at live birth of cardiovascular malformations. Similar results are obtained by plotting middle year of study or year of publication.

Relationship between prevalence and study size

Figure 5.5 plots the denominator population size against the prevalence at live birth of cardiovascular malformations. No study with more than 250,000 live births found a prevalence higher than 7 per 1000 whereas 13 smaller studies reported more than 10 per 1000 cardiovascular malformations.

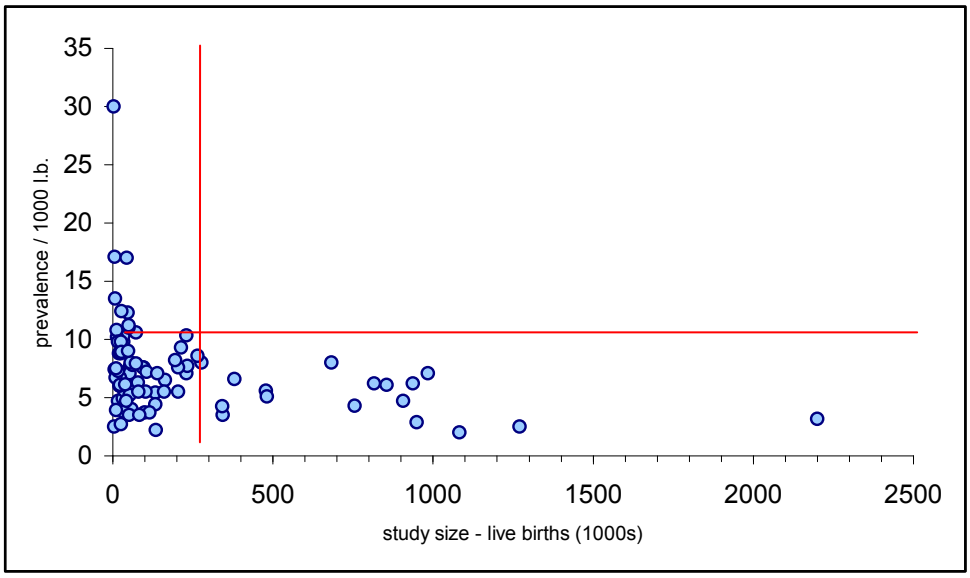

Figure 5.5. The relationship between study size (denominator live births) and prevalence at live birth of cardiovascular malformations. Red lines are drawn at 10 per 1000 live births and 250,000 live births.

Figure 5.6 plots the number of cardiovascular malformations reported against the prevalence. No study with more than 1000 cases of cardiovascular malformation found a prevalence greater than 10 per 1000 whereas 13 smaller studies reported a prevalence of more than 10 per 1000.

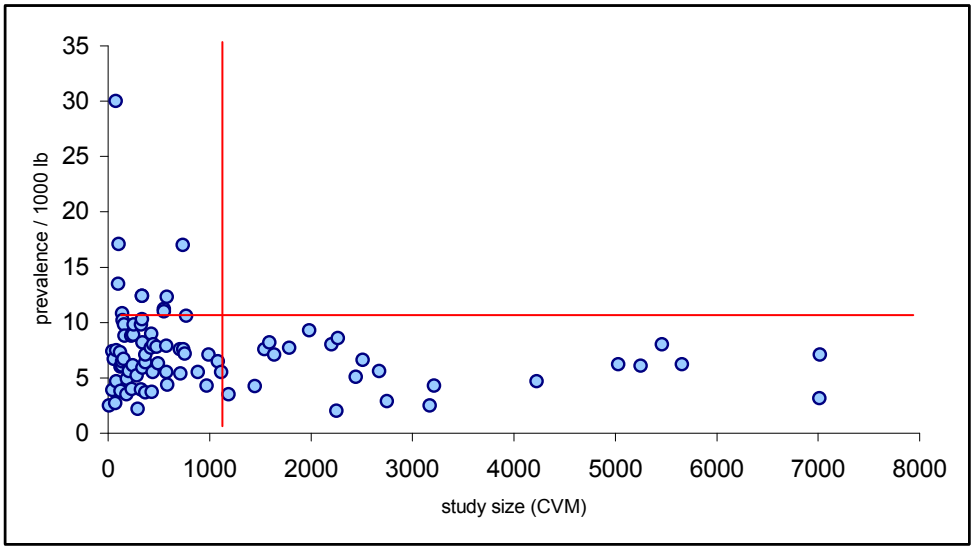

Figure 5.6. The relationship between study size (numerator cases of cardiovascular malformation (CVM)) and prevalence at live birth of cardiovascular malformations. Red lines are drawn at 10 per 1000 live births and 1000 cases of malformation.

Trends over time – reported prevalence of individual malformations

Ventricular septal defect is the most common cardiovascular malformation and is one predicted in table 5.3 to be one of the most susceptible to ascertainment bias. Of the six malformations selected from table 6.3 for more detailed analysis, ventricular septal defect is the only one to show a significant trend to more diagnoses with time (see figure 6.7). This increase is almost certainly from improved diagnosis rather than a true increase in frequency. Several papers have noted the increase, probably mainly due to the ability of colour Doppler echocardiography to confirm diagnoses. [Mayberry 1990, Meberg 1990, Manetti 1993, Tikanoja 1995, Martin 1998].

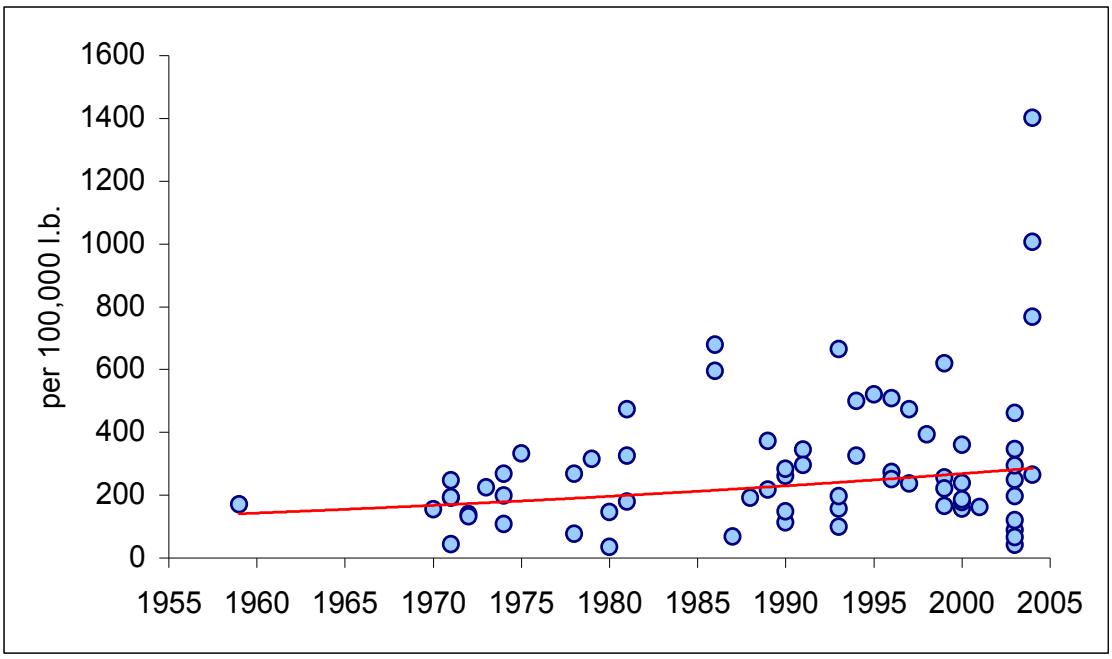

Figure 5.7. The relationship between year of publication and prevalence at live birth of ventricular septal defect.

Colour Doppler echocardiography was widely introduced in the mid-1980s and figure 5.7 shows no report of more than 500 per 10^5 ventricular septal defects before that time but seven reports with more than that later.

In a previous report discussed in section 4.5 we noted an increase in the total number of ventricular septal defects but no change in the number which required surgical closure or were associated with death within the first 12 months of life. [Wren 2000]. In other words, all the increase is from diagnosis of a greater number of small ventricular septal defects. Other reports, of studies involving echocardiography of consecutive neonates, have found tiny ventricular septal

defects in up to 5% of all live births. [Roguin 1995, Sands 1999, Du 1996] Many small ventricular septal defects (up to 85 or 90%) close spontaneously in the first year of life. Thus the prevalence will be higher if the diagnosis is made after systematic examination of neonatal murmurs and early echocardiography. [Du 1998]

Ventricular septal defects relative to other diagnoses

Because ventricular septal defect is by far the most common malformation, any increase in the number of ventricular septal defects will obviously produce an overall increase in the number of malformations. The relationship between the prevalence of ventricular septal defect and the prevalence of all cardiovascular malformations is plotted in figure 5.8. There is an obvious strong association with more ventricular septal defects in papers with more malformations overall. However, the slope of the linear trend line is around 1.7 (y = 1.68x + 246) showing that papers reporting more ventricular septal defects also find more cases of other malformations. This is shown more clearly in figure 5.9 where the prevalence of ventricular septal defect is plotted against the prevalence of all other malformations (excluding ventricular septal defect). The slope (y = 1.69x + 246) shows that on average for every extra 100 ventricular septal defects per 10^5 live births, reports will include another 70 per 10^5 other malformations.

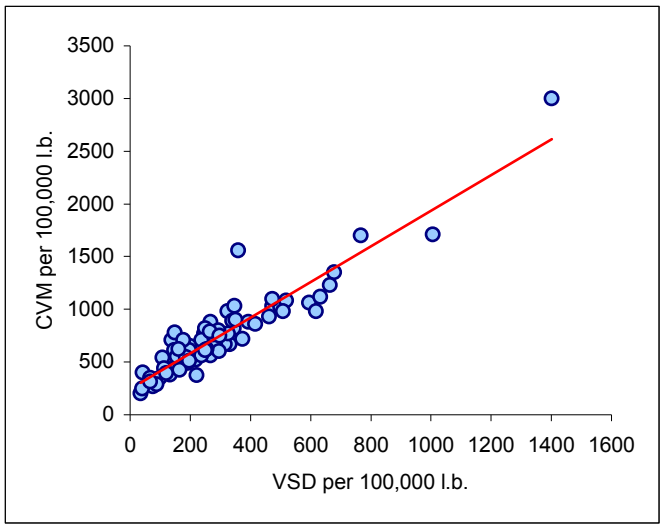

Figure 5.8. The relationship between prevalence at live birth of ventricular septal defect (VSD) and total cardiovascular malformations (CVM). l.b.= live births

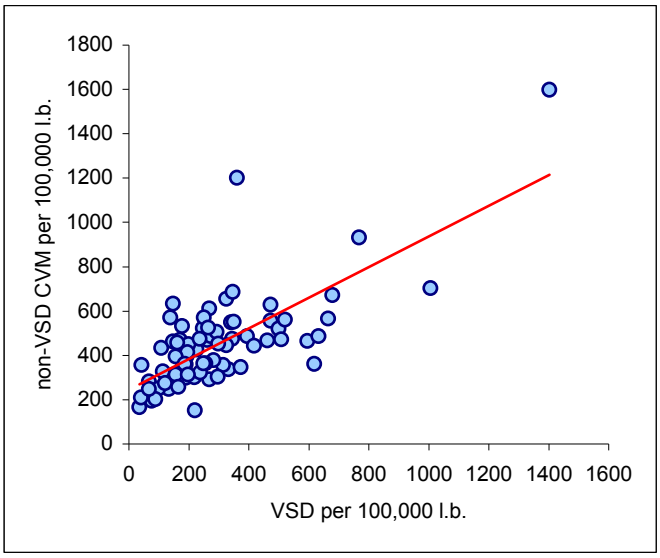

Figure 5.9. The relationship between prevalence at live birth of ventricular septal defect (VSD) and all other cardiovascular malformations (CVM). l.b.= live births

This higher ascertainment is almost certainly due to more recognition of more cases of other minor malformations. Better echocardiography detects more ventricular septal defects but also allows confirmation of the presence of small atrial septal defect, small patent ductus, mild pulmonary stenosis, and mild aortic stenosis.

Confirmation that the higher reported prevalence of ventricular septal defect is not associated with a higher prevalence of significant malformations comes from figure 5.10 which plots the prevalence of ventricular septal defect against the combined prevalence of transposition of the great arteries and tetralogy of Fallot (the two most common types of cyanotic congenital heart disease, predicted in table 5.3 to be the least susceptible to ascertainment bias). As can be seen, there is no association.

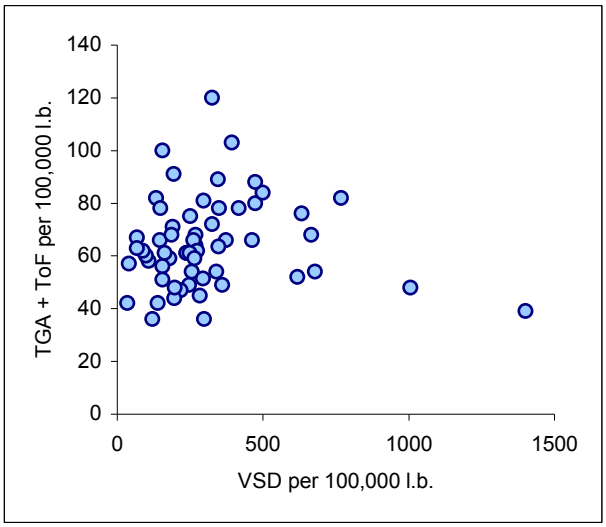

Figure 5.10. Scatter plot of the relationship between prevalence at live birth of ventricular septal defect (VSD) and combined prevalence of transposition of the great arteries (TGA) and tetralogy of Fallot (ToF). l.b.= live births

The same lack of association is seen if birth prevalence of ventricular septal defect is plotted against the combined prevalence of transposition of the great arteries, tetralogy of Fallot, coarctation of the aorta, hypoplastic left heart, and complete atrioventricular septal defect, the other five malformations selected from table 5.3 for more detailed analysis – see figure 5.11.

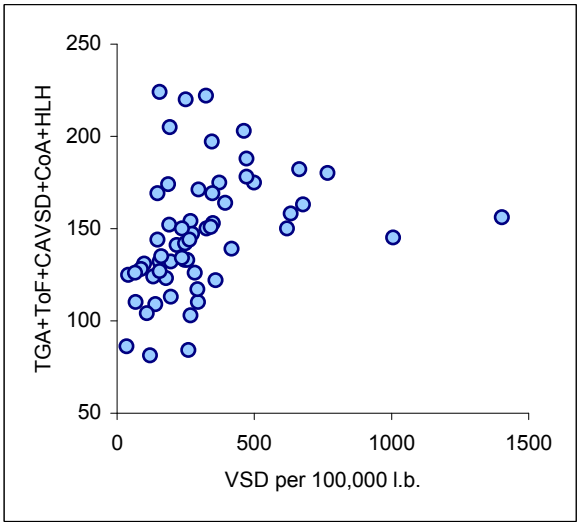

Figure 5.11. Scatter plot of the relationship between prevalence at live birth of ventricular septal defect (VSD) and combined prevalence of transposition of the great arteries (TGA), tetralogy of Fallot (ToF), complete atrioventricular septal defect (CAVSD), coarctation of the aorta (CoA) and hypoplastic left heart (HLH).

Box and whisker plots for analysis of variation in prevalence of specific malformations

Box and whisker plots provide a graphical presentation which is especially useful for comparing two or more data sets with large numbers of observations, especially if the data are skewed and contain outliers. They give a dramatic visual comparison as the median, spread, skew and range are all immediately apparent. First described by Tukey, the box shows the interquartile range and the median. The whiskers extend to the highest and lowest points which are not outliers (i.e. within 1.5 times the interquartile range). Outliers are shown separately.

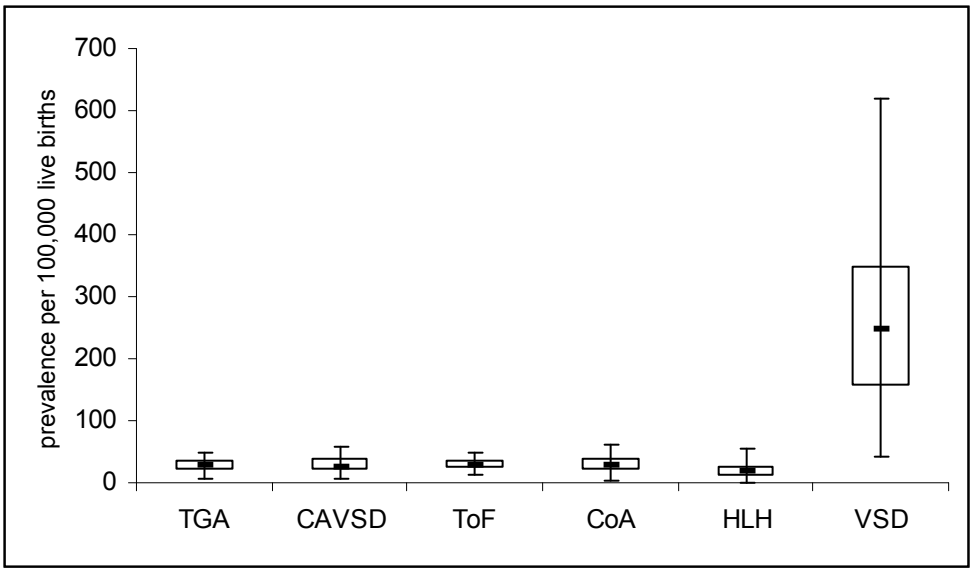

Figure 5.12. Basic box and whisker plot to show variance in reported prevalence of transposition of the great arteries (TGA), tetralogy of Fallot (ToF), complete atrioventricular septal defect (CAVSD), coarctation of the aorta (CoA), hypoplastic left heart (HLH) and ventricular septal defect (VSD).

A basic box and whisker plot of the six selected malformations is shown in figure 5.12. The obvious problem is the wide variation in birth prevalence which means that the first five are dwarfed by the representation of ventricular septal defect. It so happens that the individual rates of transposition of the great arteries, complete atrioventricular septal defect, tetralogy of Fallot and coarctation of the aorta are all very close to 30 per 10^5 while hypoplastic left heart is around 20 per 10^5 and ventricular septal defect around 240 per 10^5. Therefore, if we multiply the data for hypoplastic left heart by 1.5 and divide the data for ventricular septal defect by 8 the data for each malformation will be more easily compared, as in figure 5.13. This figure shows both the median (heavy horizontal line) and the mean (large X) to give some impression of skew. It is easily seen that the least variation is shown for tetralogy of Fallot and transposition of the great arteries with more for the other

malformations, especially ventricular septal defect, as predicted in table 6.3. In figure 5.14, the plots have been augmented by adding the outliers to give the most complete impression of the range, spread and skew.

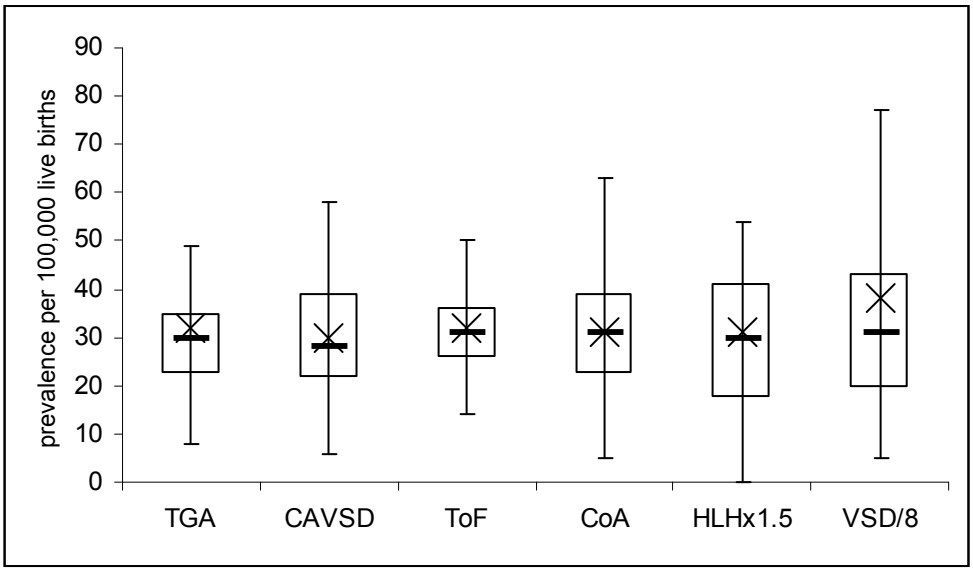

Figure 5.13. Box and whisker plot of the reported prevalence of transposition of the great arteries (TGA), tetralogy of Fallot (ToF), complete atrioventricular septal defect (CAVSD), coarctation of the aorta (CoA), plus 1.5 times the prevalence of hypoplastic left heart (HLH) and 0.125 times the prevalence of ventricular septal defect (VSD).

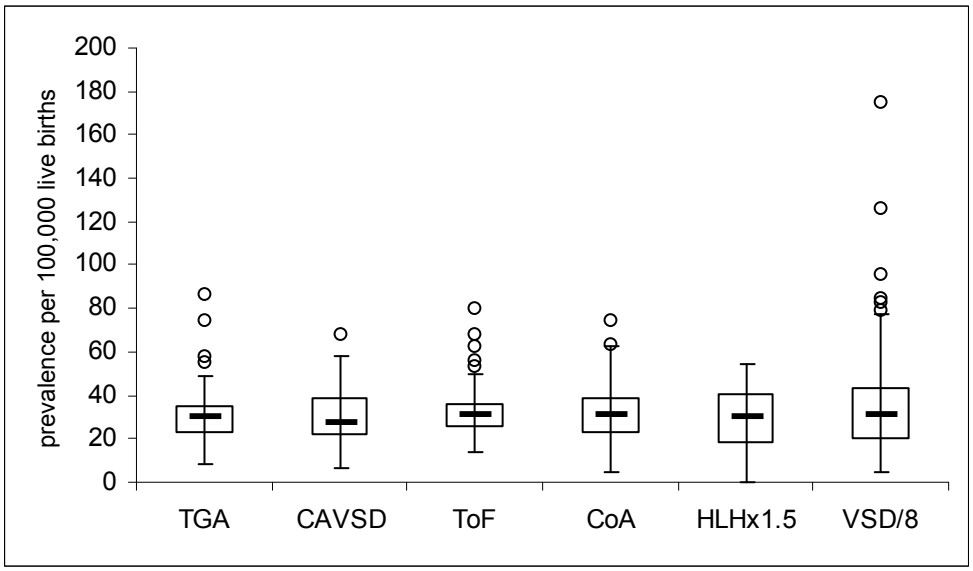

Figure 5.14. Complete box and whisker plot (including outliers) of the reported prevalence of transposition of the great arteries (TGA), tetralogy of Fallot (ToF), complete atrioventricular septal defect (CAVSD), coarctation of the aorta (CoA), plus 1.5 times the prevalence of hypoplastic left heart (HLH) and 0.125 times the prevalence of ventricular septal defect (VSD).

Analysis of variation in reported prevalence of individual malformations

Transposition of the great arteries

Data on 4699 cases of transposition of the great arteries were included in 68 of the 84 papers in table 5.4. The simplest way to analyse variation is to plot the prevalence against study size (denominator live births) as shown in figure 5.15. The mean prevalence was 29 per 10^5 live births and it can be seen that the distribution approximates well to a bell shaped curve. This suggests that there is very little ascertainment bias. There are two possible outliers with high prevalence of transposition but these are both very small studies.

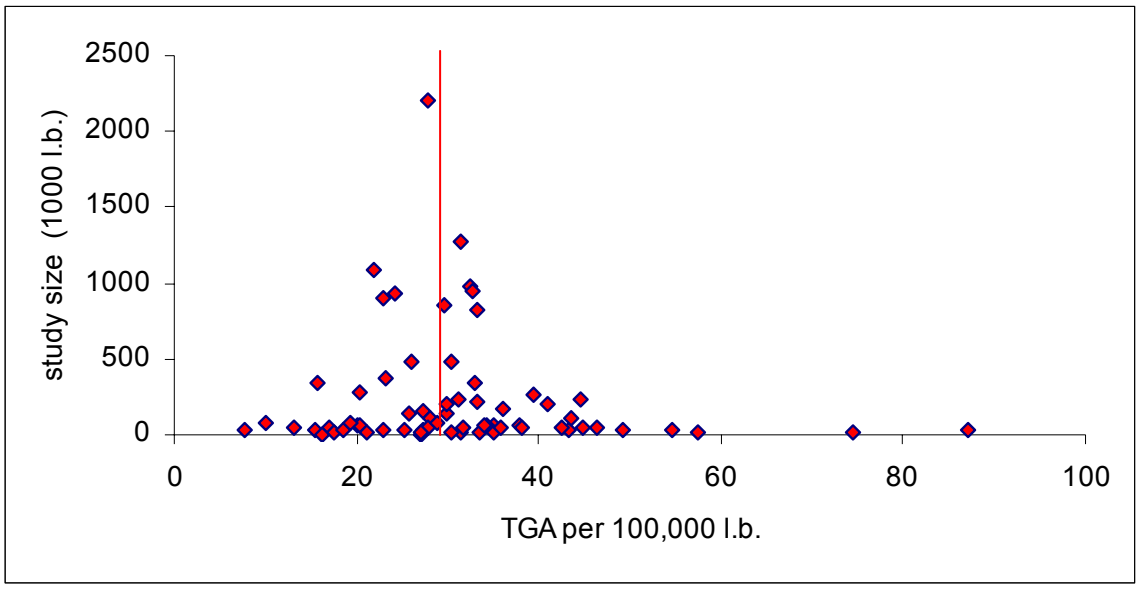

Figure 5.15. The relationship between prevalence at live birth of transposition of the great arteries (TGA), and study size. The red line indicates the mean prevalence of 29 per 10^5 live births (l.b.).

Tetralogy of Fallot

Seventy papers included 4893 cases of tetralogy of Fallot and reported a mean prevalence of 30 per 10^5 live births. The relationship with study size is shown in figure 5.16. Again there is a good approximation to a Gaussian distribution with possible outliers with a high prevalence in very small studies.

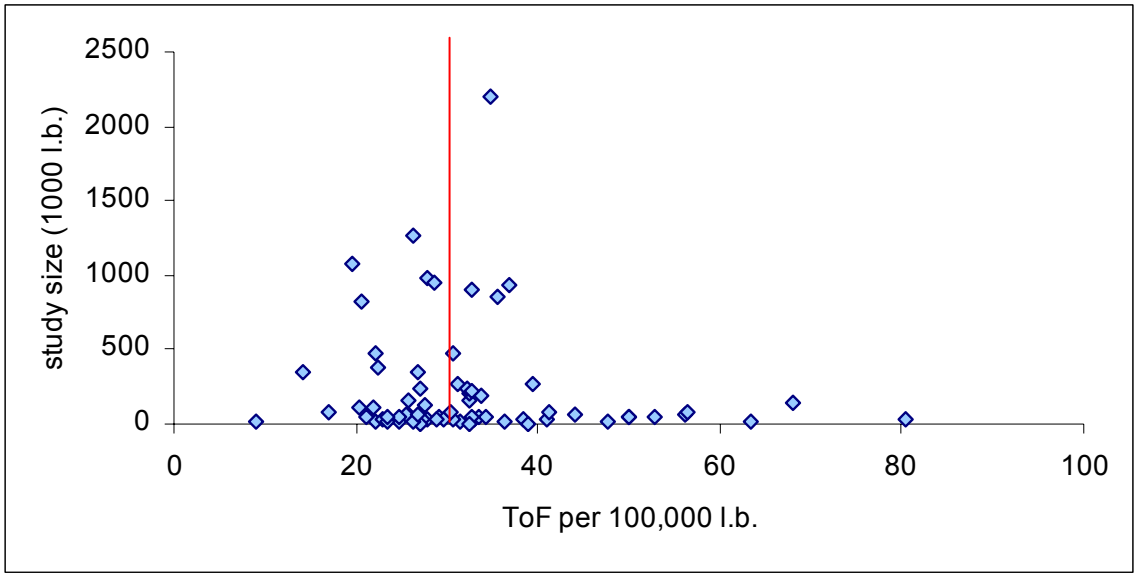

Figure 5.16. The relationship between prevalence at live birth of tetralogy of Fallot (ToF), and study size. The red line indicates the mean prevalence of 30 per 10^5 live births (l.b.).

Complete atrioventricular septal defect

Sixty-five papers included 4345 cases of complete atrioventricular septal defect and reported a mean prevalence at live birth of 27 per 10^5. The relationship to study size is plotted in figure 5.17. There is a good approximation to a bell shaped distribution.

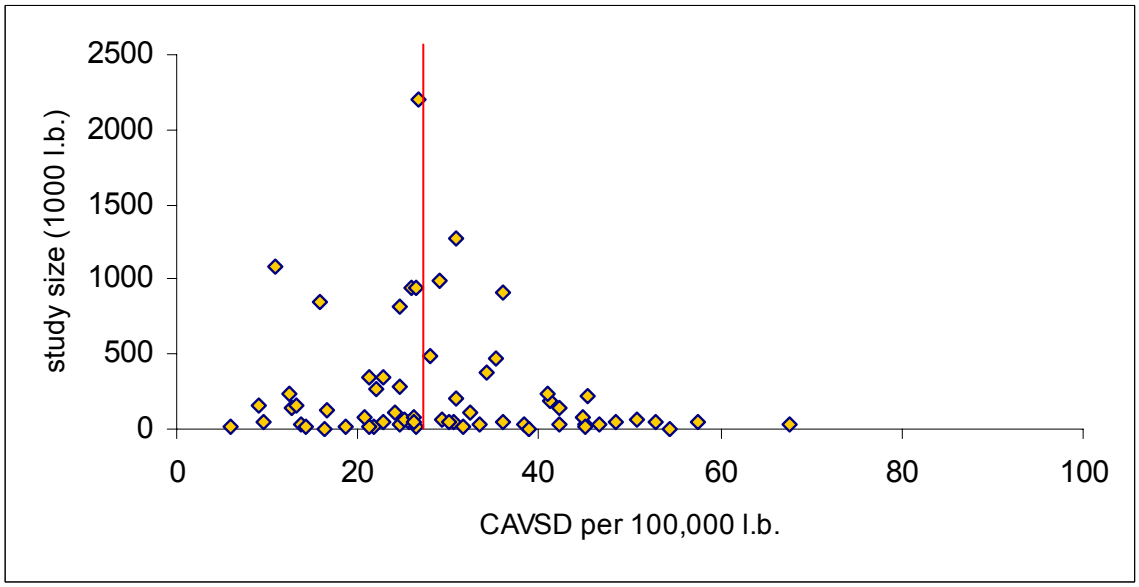

Figure 5.17. The relationship between prevalence at live birth of complete atrioventricular septal defect (CAVSD), and study size. The red line indicates the mean prevalence of 27 per 10^5 live births (l.b.).

Hypoplastic left heart

Sixty-five papers reported 3207 cases of hypoplastic left heart with a mean prevalence at live birth of 21 per 10^5. Figure 5.18 plots the prevalence against study size. There is symmetrical distribution around the mean.

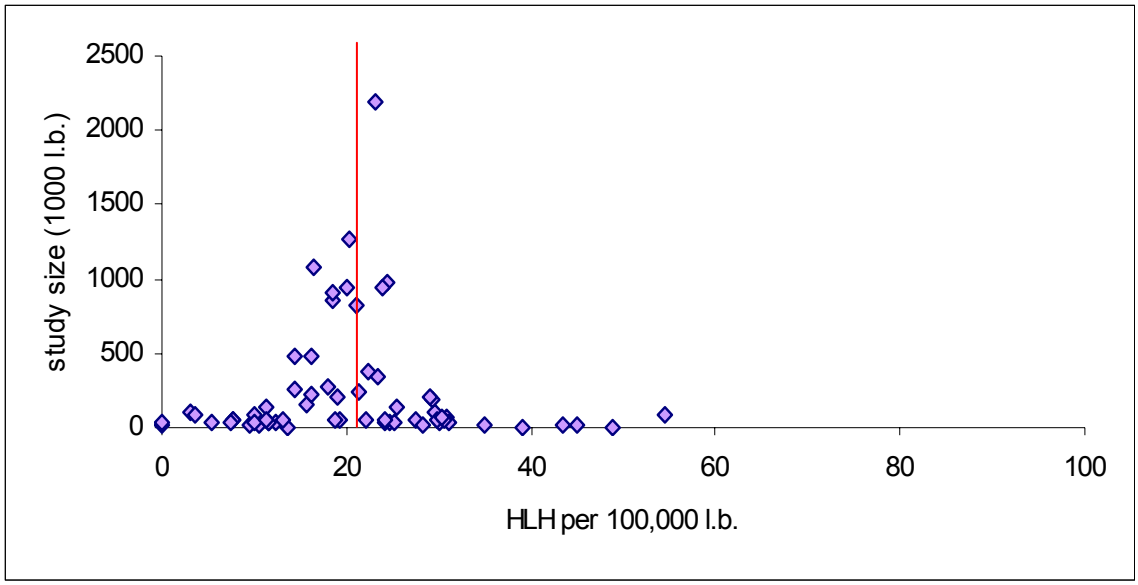

Figure 5.18. The relationship between prevalence at live birth of hypoplastic left heart (HLH), and study size. The red line indicates the mean prevalence of 21 per 10^5 live births (l.b.).

All four malformations discussed above were predicted in table 5.3 to be relatively unaffected by ascertainment bias and all show a fairly symmetrical distribution around the mean, suggesting that they are little affected by ascertainment bias (or other types of bias).

Coarctation of the aorta

Data on coarctation of the aorta were included in 66 of 84 papers. They reported 4175 cases with a mean prevalence at live birth of 26 per 10^5. Figure 5.19 shows a much wider distribution in relation to study size. There is less symmetry and an apparent skew. It seems likely that this is evidence of bias – most probably ascertainment bias. Coarctation was predicted in table 5.3 to be significantly affected by two types of ascertainment bias. Coarctation will be under reported if an anatomical rather than physiological hierarchy is used (as discussed in section 2.6). In a previous report we found 64% more cases of coarctation using a physiological hierarchy compared with an anatomical hierarchy. [Wren 2000] Open-ended ascertainment (as opposed to ascertainment limited to infancy) gives the opportunity for a higher prevalence. In a further previous report we found that 31% of all cases of coarctation diagnosed in children first came to notice after infancy. [Wren 2001]

The data in figure 5.19 show a skew to a lower prevalence in larger studies. Studies based on smaller populations are likely to have open-ended recruitment to increase the numbers. Analysis of data in table 5.4 shows that the mean number of live births in the denominator population in studies which limited ascertainment to infancy was 279,312 whereas in others it was 156,787 – confirming the potential for recruitment bias.

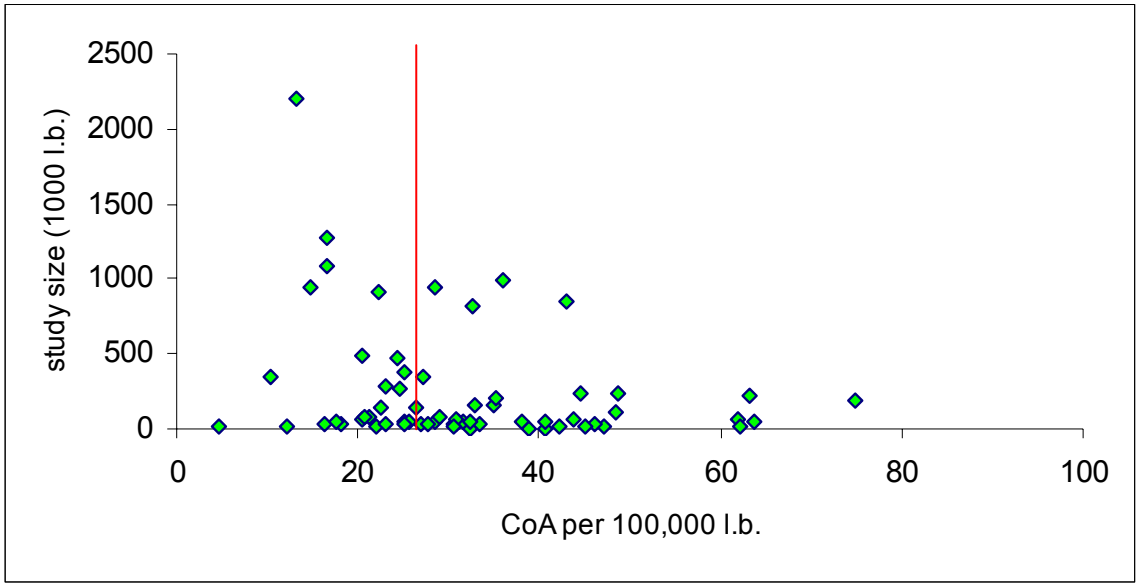

Figure 5.19. The relationship between prevalence at live birth of coarctation of the aorta (CoA), and study size. The red line indicates the mean prevalence of 26 per 10^5 live births (l.b.).

Ventricular septal defect

Data on ventricular septal defect were included in 74 of 84 papers. They reported 28,586 cases with a mean prevalence at live birth of 174 per 10^5. The relationship with study size is shown in figure 5.20. Again the data are very asymmetrical and skewed to lower prevalence in larger studies. Ventricular septal defect is predicted to be susceptible to various types of ascertainment bias as discussed in section 5.4 and table 5.3.

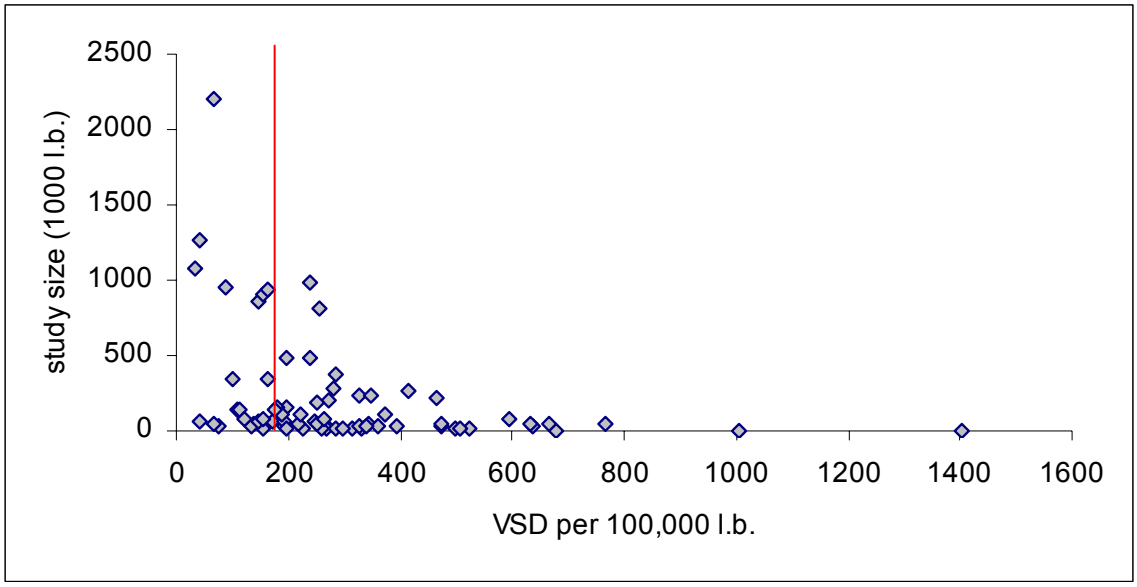

Figure 5.20. The relationship between prevalence at live birth of ventricular septal defect (VSD), and study size. The red line indicates the mean prevalence of 174 per 10^5 live births (l.b.).

Assessment of skew for analysis of ascertainment bias

Bias is strongly suggested by asymmetry or skew in the distribution of the data points. Detailed analysis of skew is very complicated and requires a regression analysis programme. However, a good approximation can be obtained by plotting data on a log scale with a linear regression line (D Spiegelhalter, personal communication). Two examples are given below using data from hypoplastic left heart which is symmetrical, and ventricular septal defect, which is asymmetrical.

Figure 5.21 plots the same data for hypoplastic left heart as shown in figure 5.18 but the X and Y axes are reversed. The appearance of symmetry is confirmed.

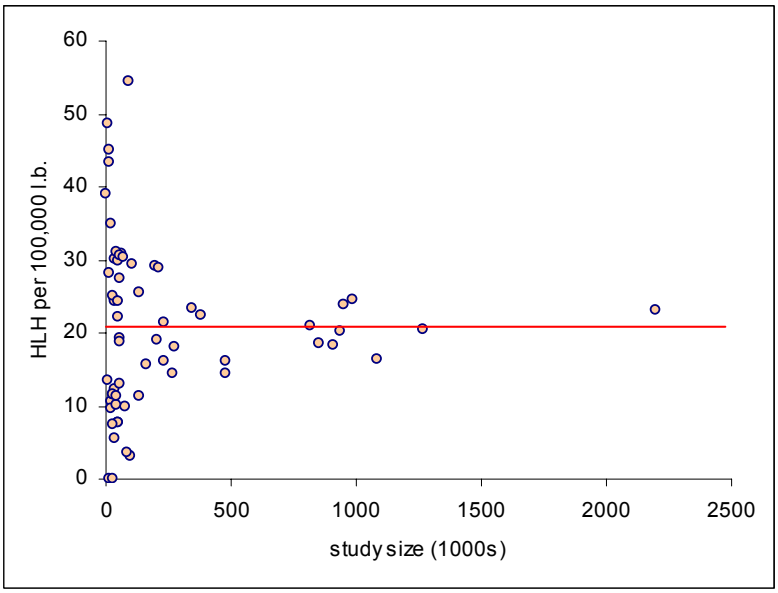

Figure 5.21. The relationship between prevalence at live birth of hypoplastic left heart (HLH), and study size. These are the same data as shown in fig 5.18 with the X and Y axes reversed.

Figure 5.22 plots the birth prevalence on a log scale and a linear regression line is also shown. There is very little separation between the regression line and the mean, confirming absence of skew.

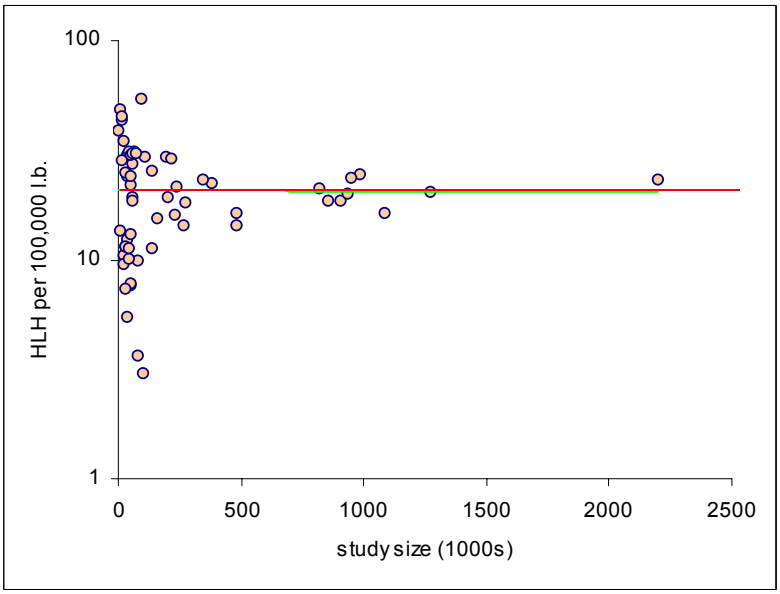

Figure 5.22. The relationship between prevalence at live birth of hypoplastic left heart (HLH), and study size, plotted with a log scale on the Y axis. The red line indicates the mean prevalence of 21 per 10^5 live births; the green line is the linear regression line (see text).

Figure 5.23 plots the data for ventricular septal defect from figure 5.20 with the X and Y axes reversed. The appearance of asymmetry is confirmed with lower prevalence in larger studies.

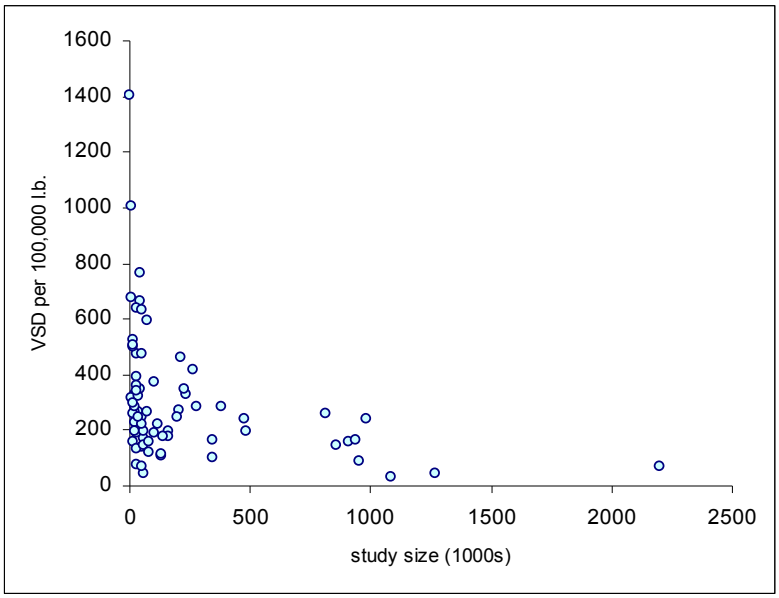

Figure 5.23. The relationship between prevalence at live birth of ventricular septal defect (VSD), and study size. These are the same data as shown in fig 5.20 with the X and Y axes reversed.

Figure 5.24 plots the same data on a log scale with a linear regression line. The wide separation between the regression line and the mean confirms the skew in the data.

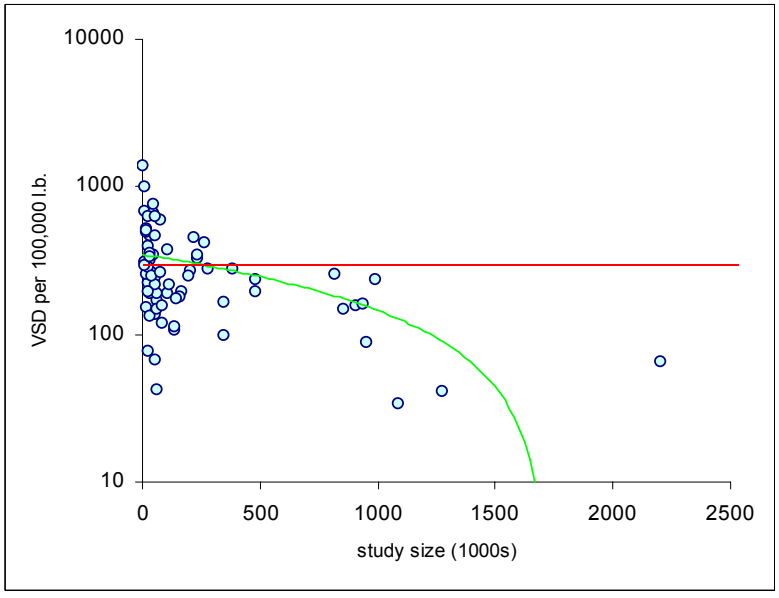

Figure 5.24. The relationship between prevalence at live birth of ventricular septal defect (VSD), and study size, plotted with a log scale on the Y axis. The red line indicates the mean prevalence of 21 per 10^5 live births; the green line is the linear regression line (see text).

Funnel plots for analysis of ascertainment bias

The graphs in figures 5.15-5.20 are in effect a type of funnel plot. A true funnel plot extends the analysis by applying a mean and lines showing the limits of two and three standard deviations. Funnel plots for all six malformations are shown in figures 5.25-5.30. 95% of data points should lie within two standard deviations of the mean and 99.73% within 3 standard deviations. The data points are most tightly distributed in plots of transposition of the great arteries (figure 5.25) and hypoplastic left heart (figure 5.26), supporting the suggestion that they are minimally affected by ascertainment bias..

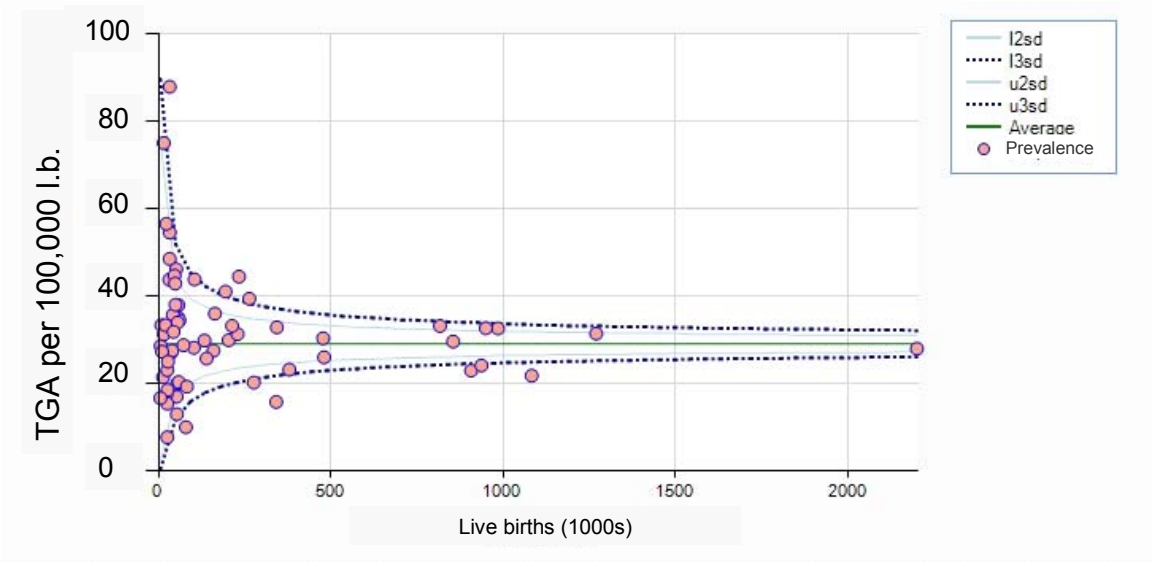

Figure 5.25. Funnel plot of the relationship between prevalence at live birth of transposition of the great arteries (TGA), and denominator live births (l.b.).

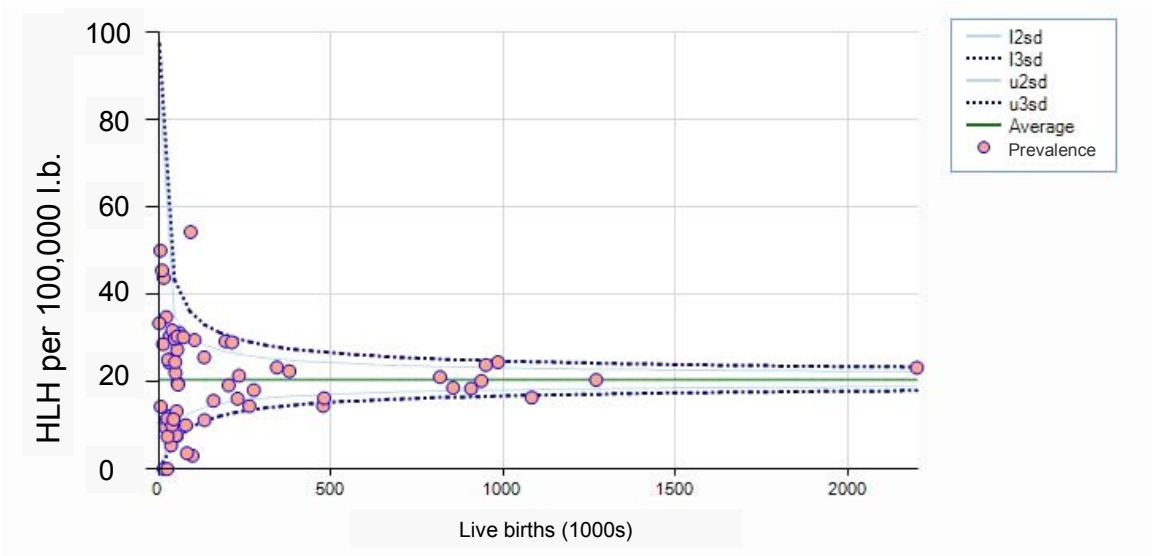

Figure 5.26. Funnel plot of the relationship between prevalence at live birth of hypoplastic left heart (HLH), and denominator live births (l.b.).

The distribution is also fairly symmetrical for tetralogy of Fallot (figure 5.27) and complete atrioventricular septal defect (figure 5.28).

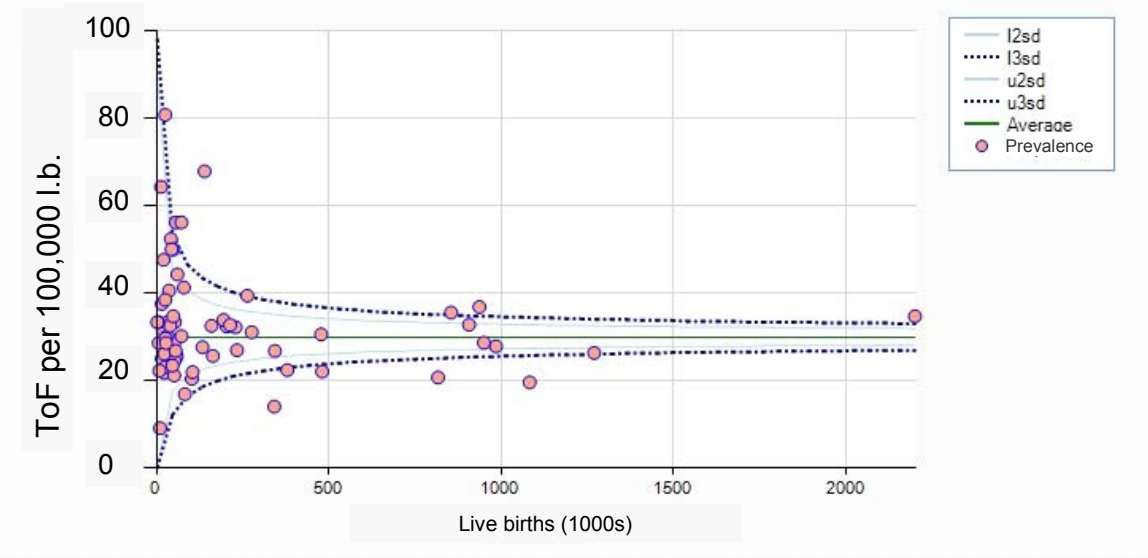

Figure 5.27. Funnel plot of the relationship between prevalence at live birth of tetralogy of Fallot arteries (ToF), and denominator live births (l.b.).

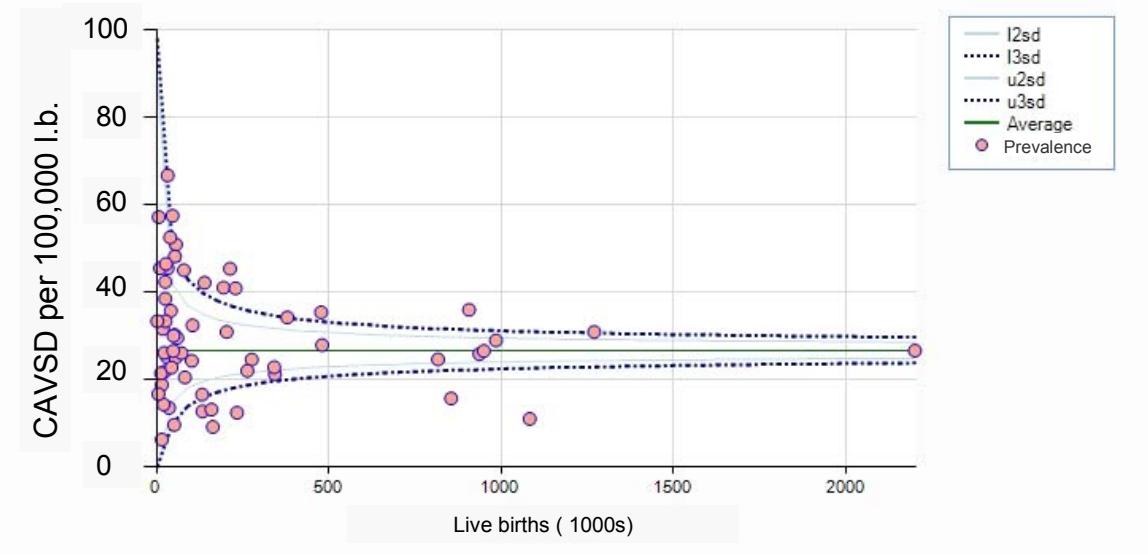

Figure 5.28. Funnel plot of the relationship between prevalence at live birth of complete atrioventricular septal defect (CAVSD), and denominator live births (l.b.).

The asymmetry, skew, and wide variation in the reported prevalence of coarctation (figure 5.29) and ventricular septal defect (figure 5.30) are confirmed. This is consistent with the prediction in table 5.3 that these malformations will be prone to ascertainment bias.

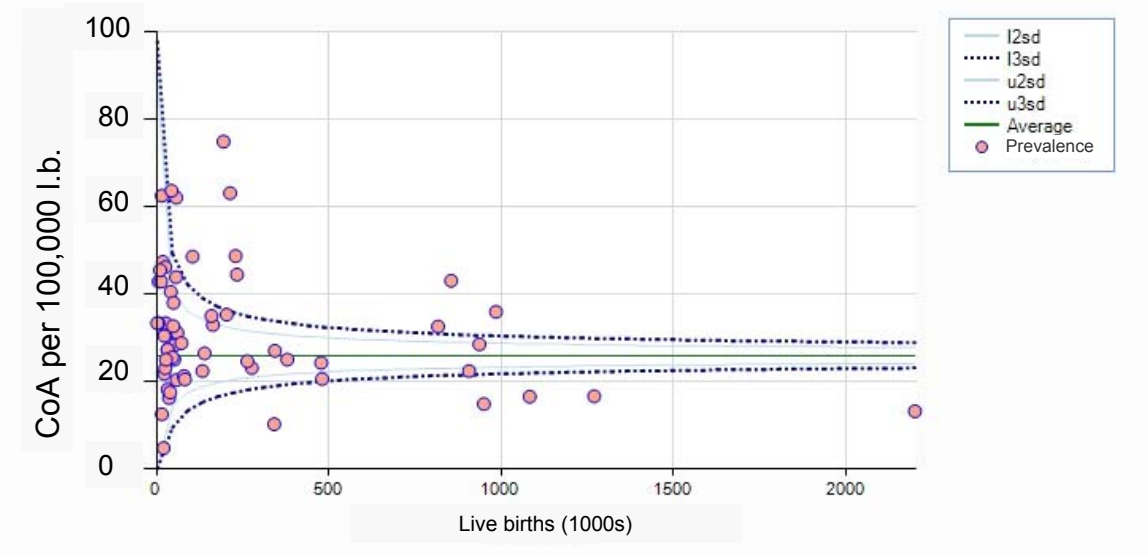

Figure 5.29. Funnel plot of the relationship between prevalence at live birth of coarctation of the aorta (CoA), and denominator live births (l.b.).

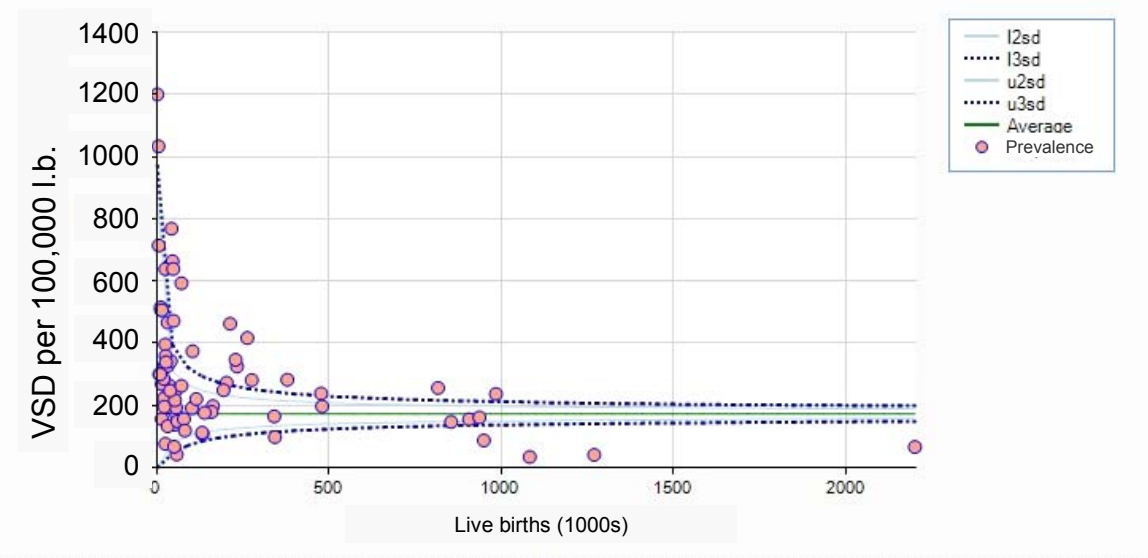

Figure 5.30. Funnel plot of the relationship between prevalence at live birth of ventricular septal defect (VSD), and denominator live births (l.b.).

5.7 FURTHER ANALYSIS OF PAPERS WITH A COMMON METHOD

The 15 papers that included only live births, limited ascertainment to infancy, excluded clinical diagnoses, and had a population base to permit calculation of birth prevalence are listed in Table 5.5. Their denominator populations range from just over 6,000 to >900,000 but only five papers have >250,000 live births. The 15 papers include 2,875,384 denominator live births and 17,836 cardiovascular malformations. The reported prevalence at live birth ranges from 346 to 1706 per 10^5 live births with a mean of 620 per 10^5.

All 15 papers give details of prevalence of the most common individual diagnoses although other diagnoses that are included vary between reports. The method of classifying cases with more than one cardiovascular malformation also varies considerably. Two papers have a physiological hierarchy, two an anatomical hierarchy, two an embryological or mechanistic hierarchy, and two double-count multiple malformations. Five papers make no mention of how cases with multiple malformations were classified. One included only selected diagnoses and one used specific sub categories. The papers also differed in the method of classifying pulmonary atresia, double outlet right ventricle, and other less common diagnoses.

All 15 papers find that ventricular septal defect is the most common diagnosis with a prevalence ranging from 86-1007 per 10^5 live births, being greater in later series. The prevalence of diagnoses that are rare, or subject to variability of definition or ascertainment, varies the most. Only one of the papers defines pulmonary valve stenosis [Chehab 2004] and the reported prevalence of this malformation varies from 19-165 per 10^5 live births. The prevalence of diagnoses likely to have a constant definition and more or less full ascertainment is fairly constant, e.g. coarctation of the aorta (23-32 per 10^5 live births), complete atrioventricular septal defect (16-38 per 10^5 live births), transposition of the great arteries (16-30 per 10^5 live births), and total anomalous pulmonary venous connection (7-16 per 10^5 live births). Rare diagnoses are known to be subject to more variability because of the small numbers. [Wren 2000]

1st Author	Grabitz	Sung	Ferencz	Kidd	Cerboni	Robida	Grech	Wren	Mogyorosy	Abushaban	Bolisetty	Cleves	Garne	Forrester	Chehab	Hoffman & Kaplan		
Year	1988	1991	1993	1993	1993	1997	1998	2000	2000	2003	2004	2003	2004	2004	2004			
Era	81-84	87-89	81-89	81-84	88-90	84-94	90-94	85-97	94-98	86-00	93-00	93-98	86-98	86-99	99-02			
Origin	CAN	CHN	USA	AUS	GLP	QAT	MLT	GBR	HUN	KWT	AUS	USA	DEN	USA	LBN			
Livebirths	103411	20928	906646	343521	22855	49887	26117	477960	26932	312512	6156	213870	72519	264236	27834			
																lower Q	median	upper Q
Prevalence	554	597	468	346	608	1108	884	559	1240	1429	1706	927	676	858	849	534	767	1382
VSD	191	296	156	99	196	473	394	238	360	287	1007	463	265	417	341	176	283	448
PDA	25	62	11	12	39	62	19	23	100	165	130	excluded	25		36	32	57	78
ASD	58	24	38	12	74	86	42	28	434	84	179	382	88	206	68	37	56	106
CAVSD	24	14	36	21	22	30	38	35	41	36	16	45	26	22	47	24	34	40
PS		76	44	23	22	102	165	44	74	66	32	108	41	33	86	36	53	84
AS			14	10	9	16	8	20	59	18	16	49	25	12	50	16	26	39
CoA		5	22	27	31	38	23	24	33	41	32	63	29	25	25	29	36	49
ToF	20	48	33	27	26	50	80	31	30	28	32	33	30	39	29	29	36	58
TGA	28	33	23	33	18	38	23	30	19	28	16	33	29	39	25	23	30	39
HLH		10	18	23	35	22	0	14	7	13	49	29	30	14		15	23	28

Table 5.5. The prevalence of the ten most common cardiovascular malformations in the 15 papers with common basic methods selected for further analysis. Data from the review by Hoffman and Kaplan are presented for comparison. Q = quartile. Prevalence is per 10^5 live births. The country abbreviations are taken from the standard United Nations abbreviations, details of which can be found at: http://unstats.un.org/unsd/methods/m49/m49alpha.htm. Other abbreviations are as in table 5.3.

As with the 84 papers in table 5.4, the reported birth prevalence of cardiovascular malformations increased over time (fig 5.31) and was inversely related to study size (fig 5.32).

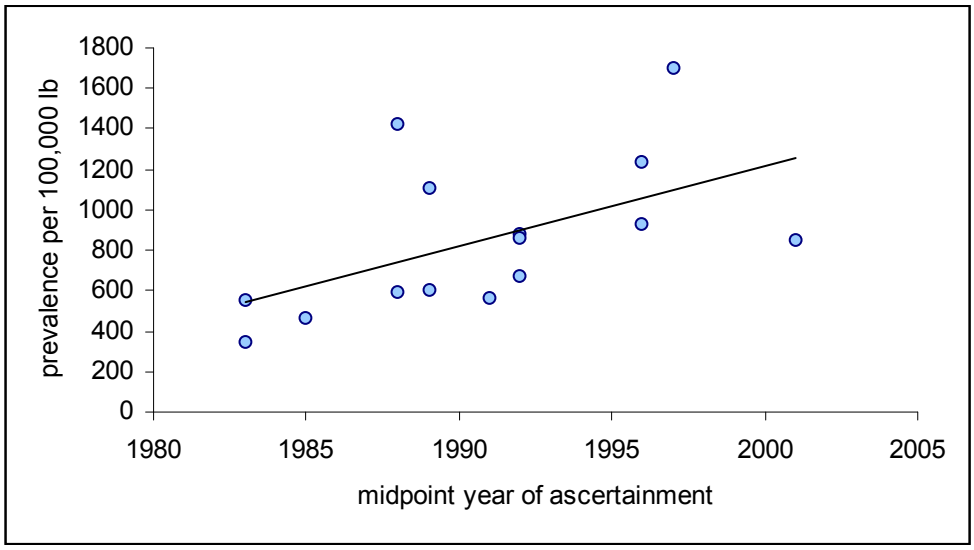

Figure 5.31. The relationship between midpoint year of ascertainment and prevalence at live birth of cardiovascular malformations in the 15 papers in table 5.5. Similar results are obtained by plotting prevalence against year of publication.

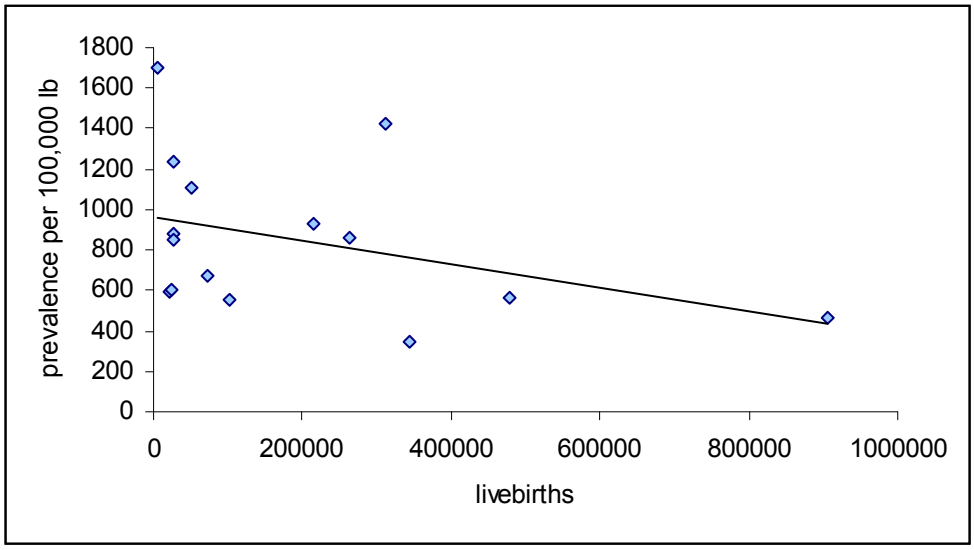

Figure 5.32. The relationship between study size (denominator live births) and prevalence at live birth of cardiovascular malformations in the 15 papers in table 5.5.

Table 5.5 also compares the prevalence at live birth of the 10 most common malformations in the 15 papers with the findings of a review by Hoffman and Kaplan. [Hoffman 2002] Published in 2002, this was a seminal review entitled "The incidence of congenital heart disease". As discussed in section 1.4 in chapter 1, Hoffman and Kaplan are in the minority who prefer the term incidence to describe

what is known in this review as the prevalence at live birth of cardiovascular malformations. Although it is comprehensive, a limitation of their review is that it has no inclusion or exclusion criteria but simply includes all published reports and gives them equal weight in the analysis. Thus papers limited to symptomatic neonates or diagnoses made before first discharge from hospital are included alongside those with ascertainment which includes termination of pregnancy and stillbirth to the whole of childhood.

Figure 5.33 is derived from the data in table 5.5 and compares the median prevalence and interquartile range of individual malformations in the 15 papers selected for secondary analysis with the findings of Hoffman's review. The greater homogeneity and selectivity of the 15 papers, and the fact that they are more recent, leads to differences in the reported prevalence rates.

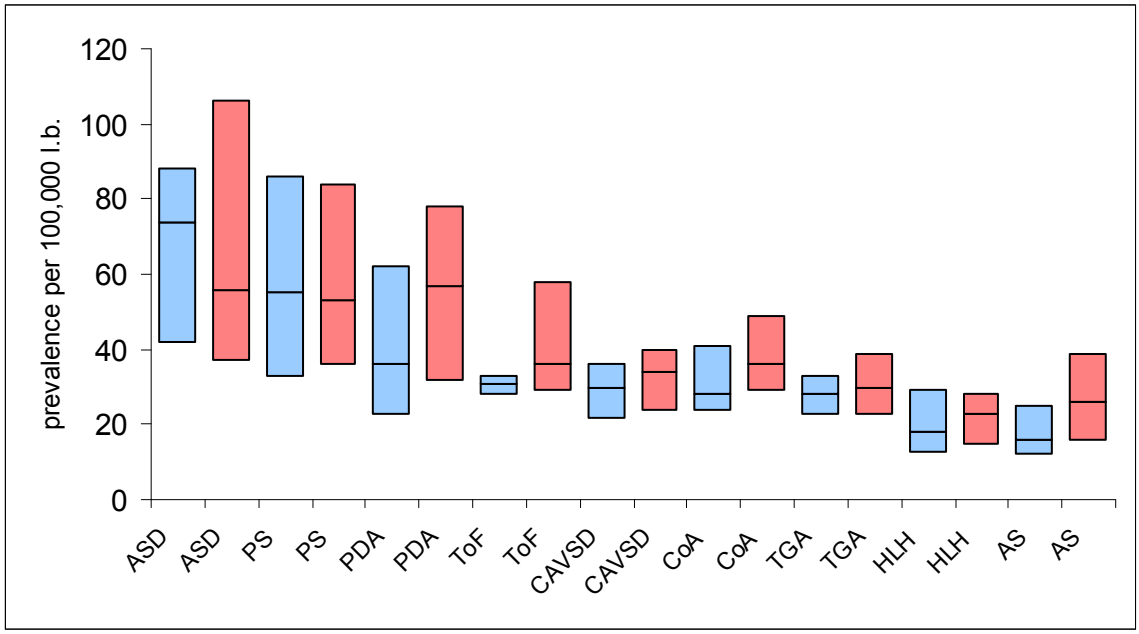

Figure 5.33. Comparison of reported median prevalence and interquartile range in the 15 papers with common methodology in table 5.5 (blue bars) and the Hoffman review (orange bars) of: atrial septal defect (ASD), pulmonary valve stenosis (PS), patent ductus arteriosus (PDA), tetralogy of Fallot (ToF), complete atrioventricular septal defect (CAVSD), coarctation of the aorta (CoA), transposition of the great arteries (TGA), hypoplastic left heart (HLH), and aortic valve stenosis (AS). The reported prevalence of ventricular septal defect (VSD) was similar in the two series but is omitted so as not to distort the scale. Malformations are ranked according to median prevalence in the 15 papers in table 5.5.

The 15 papers have roughly the same median prevalence as Hoffman for malformations where ascertainment is expected to be complete or more or less complete in infancy (eg transposition of the great arteries, tetralogy of Fallot, hypoplastic left heart and complete atrioventricular septal defect) but have a narrower interquartile range for some – particularly tetralogy of Fallot and transposition of the great arteries. They find fewer than Hoffman of the

malformations predicted in table 5.3 to be more affected by open-ended ascertainment (eg patent ductus arteriosus, coarctation of the aorta, and aortic valve stenosis). The interquartile ranges for these diagnoses are notably wider. Interestingly, the 15 papers find more atrial septal defects than Hoffman's review, probably a reflection of the fact that all were written in the echocardiographic era and were, therefore, subject to overdiagnosis of small and clinically unimportant atrial septal defects early in life. [Sands 2002]

Summary of findings

Even when analysis is confined to the papers in table 5.5 there are still significant differences between them. Despite a common basic method - being population-based, confined to live births, and including only confirmed diagnoses in infancy - there is marked variation in the detailed methods of these 15 papers.

The 15 papers also use different diagnostic hierarchies so infants with more than one malformation (such as coarctation of the aorta and ventricular septal defect or truncus arteriosus with interruption of the aortic arch) are classified differently in different studies. The threshold for diagnosis probably varies as well. For instance what is the definition of pulmonary valve stenosis? Only one of the 15 defines it.

They find a prevalence at live birth of around 30 per 10^5 transposition of the great arteries, tetralogy of Fallot, complete atrioventricular septal defect, and coarctation of the aorta, around 20 per 10^5 for hypoplastic left heart and around 300 per 10^5 for ventricular septal defect. Interquartile ranges are narrow in comparison with findings of the unselective approach of Hoffman's review, despite their small number and generally small size.

5.8 DISCUSSION

Comparisons between reports in different populations or different countries are potentially of great interest. The papers analysed for this study show wide variation in the prevalence at live birth of cardiovascular malformations. Before comparisons can be made it is important to analyse the study methods in detail. There are a number of potential explanations for the differences in reported prevalence of congenital cardiovascular malformations. Only when all of these have been excluded can we conclude that there is a real difference between the findings in different populations.

Ascertainment bias and selection bias

Some of the largest studies have a low prevalence of cardiovascular malformations, presumably because of low ascertainment. [Fyler 1980, Ferencz 2003] Some of those with the highest reported prevalence are from very small study populations, where resources probably permit much more careful evaluation and ascertainment is likely to be fairly complete. [Arbour 2004, Bolisetty 2004] There are obvious potential problems with ascertainment in multicentre studies, especially those performed over several years. [Fyler 1980, Ferencz 2003] All specialist centres rely on referrals from other primary, secondary or tertiary providers of health care and none of the papers has defined the referral pattern or threshold for referral. Mild disease (such as small ventricular septal defect or mild pulmonary valve stenosis) may not be referred and very severe malformations may cause early death before diagnosis. [Abu-Harb 1994] Infants with severe non-cardiac malformations (such as lethal trisomy) may not be referred for investigation if there is already no prospect of survival. [Wyllie 1994, Embleton 1996] Ascertainment may also be limited by the availability of paediatricians or paediatric cardiologists in countries with less well developed health care systems.

The prevalence of cardiovascular malformations is generally lower in earlier studies, due in part to the later wide availability of colour Doppler echocardiography. Hoffman drew attention to the influence of the ascertainment of small ventricular septal defects on the overall prevalence, also discussed above. [Hoffman 2002] In several studies demonstrating an apparent increase in prevalence of cardiovascular malformations over time this was almost entirely due to increased recognition of minor defects, principally small ventricular septal defects. [Wren 2000]

Most cardiovascular malformations, especially the more serious, are diagnosed in the first year of life. However, 26% of cardiovascular malformations in children are first diagnosed beyond infancy so studies which continue ascertainment beyond infancy are likely to report a higher overall prevalence. [Wren 2001]

Inheritability of cardiovascular malformations

Although there is no evidence of a true increase in the prevalence of cardiovascular malformation with time, other effects on birth prevalence have been identified. There is known to be an increased risk to offspring of parents who had malformations themselves. The risk is around 5% (roughly a fivefold increase) for affected mothers and 2% for affected fathers. [Whittemore 1994, Burn 1998] More

and more children with congenital heart disease are surviving to adult life and are likely to have their own children. [Taussig 1979, Wren 2001] All other things being equal, these effects will lead to an increase in prevalence at live birth of cardiovascular malformations in the population. Carter estimated that the birth prevalence of malformations would double in seven generations. [Carter 1974]

Other genetic factors

The influence of parental consanguinity on the prevalence at live birth of cardiovascular malformations is intriguing but has proved difficult to investigate – mainly because of the problem of identifying consanguinity in denominator populations. [Sadiq 1995, Robida 1997, Becker 2001] In a recent report, Chehab et al compared rates of consanguinity in Beirut in the parents of 1585 children with cardiovascular malformation with parents of 1979 children with normal hearts. [Chehab 2007] Another reference group was provided by data from 1625 children investigated by UNICEF in Lebanon. First-cousin consanguinity was found in 19.4% of the study sample compared with 14.4% of the control group ($p<0.001$). The small numbers of individual malformations precluded detailed analysis but consanguinity was more common in cases of atrial septal defect, aortic valve stenosis and tetralogy of Fallot. Outside the Middle East and a few other populations, consanguinity is uncommon or rare and will have little influence on the prevalence of cardiovascular malformation.

Antenatal diagnosis and termination of pregnancy

Termination of pregnancy after antenatal diagnosis is an increasing influence on the live birth prevalence of cardiovascular malformations in many populations. It has yet to be shown that termination of pregnancy has a major influence on the overall prevalence at live birth of cardiovascular malformations although it may do so in future. [Montana 1996, Allan 2000, Gardiner 2001] It is likely that the effect of termination will be greatest on the most severe and most easily recognised malformations and those with the worst prospect of survival. Thus the prevalence at live birth of those diagnoses most amenable to antenatal diagnosis and therefore likely to undergo termination of pregnancy (such as hypoplastic left heart, pulmonary atresia with intact septum), are likely to show the effect soonest. The overall effect on the prevalence at live birth of malformations is likely to be limited. [Abu-Harb 1995, Acharya 2004]

We cannot easily correct for the epidemiological effects of termination of pregnancy. We lack precise knowledge of the natural history in utero of defects selected for termination, selected to continue pregnancy or not diagnosed before birth. Another problem is that termination of pregnancy may follow detection of a non-cardiac malformation (such as neural tube defect) or chromosomal abnormality (such as fatal trisomy) before assessment for co-existent cardiac abnormalities. Inclusion of cases ending in stillbirth or termination distorts epidemiological assessment of prevalence of malformation but exclusion of cases which may well have been live born does likewise.

Bull reported results from a UK wide study of births in 1993-1995. [Bull 1999] She found that the pregnancy termination rate was strongly influenced by the specific type of cardiovascular malformation, ranging from 47% in hypoplastic left heart to 3% in tetralogy of Fallot. The termination rate was also related to the gestational age at diagnosis, being 70% with diagnoses before 19 weeks, 61% for a diagnoses before 23 weeks and 50% overall. Diagnoses were strongly skewed towards those producing more obvious abnormalities on the fetal scan. Hypoplastic left heart was the commonest, accounting for 20% of all antenatal diagnoses whereas it accounts for only 3.9% of malformations in the 84 papers analysed in table 5.4. By contrast, transposition of the great arteries accounts for 5.5% of all live born cardiovascular malformations but represented only 0.01% of antenatal diagnoses in the UK study.

Bull also provided valuable data on the fetal mortality by individual diagnosis. [Bull 1999] Excluding terminations, the fetal mortality in continuing pregnancies was 16% for tetralogy of Fallot, 13% for complete atrioventricular septal defect, 12% for hypoplastic left heart, 10% for transposition, and 12% overall. A study from Italy reported similar findings with a 12% in utero mortality in pregnancies continuing after diagnosis of a cardiovascular malformation. [Fesslova 1999]

Thus, depending on the diagnosis, inclusion or exclusion of cases resulting in termination of pregnancy may have a substantial impact on the reported prevalence of cardiovascular malformations. The ideal solution is probably to report data separately for terminations, stillbirths and live births from the same population.

Inclusion of data for termination of pregnancy in the numerator for all cardiovascular malformations is problematic as the antenatal diagnosis rate varies widely between studies (and was zero in earlier reports) especially as the spontaneous mortality in

continuing pregnancies may be up to 16%. The converse is also true. Cragan and Khoury examined the effect of prenatal diagnosis on epidemiological studies of birth defects, using case control studies of the aetiology of neural tube defects as a model. [Cragan 2000] Prenatal diagnosis and termination of pregnancy are much more common in neural tube defects than in cardiovascular malformations. Cragan and Khoury showed that exclusion of pregnancies electively terminated after prenatal diagnosis of neural tube defects may have a substantial effect on the results of epidemiological studies of these defects. Study precision may be reduced or results may be biased (towards or away from the null) depending on how the risk factor of being studied is related to the likelihood of diagnosis or termination.

Another factor to be taken into account is that prenatal diagnostic techniques may lead to increased rates of diagnosis of some malformation in continuing pregnancies. This effect is likely to be limited in cardiovascular malformations but it is probable that small muscular ventricular septal defects are even more common in utero than they are after live birth. Although they are not easy to see with current imaging, more and more are being recognised and yet may well undergo spontaneous closure even before birth.

Cardiovascular malformations in stillbirths

Hoffman has highlighted the greatly increased prevalence of cardiovascular malformations in spontaneous abortions and stillbirths compared with live births. [Hoffman 1995] There are significant and obvious difficulties with ascertainment of cardiovascular malformations in stillbirths and the reported prevalence varies very widely from 0.5 to 39.5% with a median of 7.9%. Ascertainment varies with gestational age and with many other factors. Exclusion of cardiovascular malformations in stillbirths underestimates their true “incidence” but variable inclusion precludes comparison between studies.

Hoffman estimates that 25-30% of pregnancies of at least four weeks duration end in spontaneous abortion or stillbirth. Early fetal losses have a very high proportion of chromosomal defects - around 40% before 28 weeks compared with 0.7% in live births. Beyond 28 weeks, the percentage of chromosomal defects in stillbirths is lower, being around 7-16%. [Hoffman 1995] These findings have significant implications for our understanding of the true prevalence or incidence of cardiovascular malformations. Chromosomal defects are present in about 5% of live births with cardiovascular malformations but the overall prevalence of cardiovascular

malformations in all chromosomal abnormalities is over 30%. [Pierpont 2007] However, it ranges from around 25% in Turner's syndrome (monosomy X) to almost 100% in trisomy 18 (Edward's syndrome). [Pierpont 2007] Thus exclusion of stillbirths will significantly underestimate the true incidence of cardiovascular malformations.

The true prevalence of cardiovascular malformations in stillbirths is difficult to ascertain, partly because of problems with morphological and pathological examination which are likely to produce a bias towards more recognition of more major malformations. Stillbirths have an increased prevalence of coarctation of the aorta and or more complex abnormalities such as double inlet left ventricle, hypoplastic left heart, truncus arteriosus, and atrioventricular septal defect. [Hoffman 1995] Hoffman has calculated the influence of stillbirths on the true incidence of cardiovascular malformations. Modifying his calculations a little, in 100,000 pregnancies of four weeks duration or more one might expect 25,000 early spontaneous abortions, 2000 still births, and 73,000 live births. If the prevalence of cardiovascular malformations is 20%, 10% and 1% respectively, the true number of cardiovascular malformations is 5000 + 200 + 730 = 5930 or 6%. It follows from this that only about 10 or 15% of all cardiovascular malformations reach live birth with the majority ending in death in early pregnancy, often associated with fatal chromosomal defects. The implication of this that any study that includes a significantly high ascertainment of stillbirths will increase the number and skew the spectrum of reported cardiovascular malformations. If cardiovascular malformations in spontaneous abortions and stillbirths are ignored, however, the significance of genetic, chromosomal and environmental influences will be greatly underestimated.

Implications for future studies

How is it best to deal with the data to get around these problems? Future epidemiological studies should use a standard basic method: this should define a birth cohort; exclude or list separately stillbirths and terminations; exclude unconfirmed diagnoses; and define ascertainment, hierarchy, and diagnostic classification. Findings in live births, stillbirths and terminations should be listed separately if available in the same study population. Analysis of studies could group diagnoses into categories such as mild, moderate, and severe to increase numbers – although this obviously limits the detail available. Comparison between studies might be best limited to analysis of marker malformations, i.e. those which cause no diagnostic confusion, are usually isolated (to avoid problems with hierarchy), and

which are likely to survive to diagnosis. The disadvantage of such a limitation is that one then cannot analyse any effects on the total number and spectrum of malformations. It seems likely that genetic or environmental influences will affect specific malformations rather than the overall prevalence [Mone 2004, Jenkins 2007].

5.9 CONCLUSIONS

There is wide variation in the reported prevalence at live birth of all congenital cardiovascular malformations (2.0-30.0 per 1000 live births) and of individual malformations. Comparisons between studies take little account of potential sources of bias – mostly ascertainment bias. Specific malformations predicted to show least susceptibility to ascertainment bias show least variation in reported prevalence. There is no good evidence of real differences in the prevalence of all or of individual malformations in different populations. Future investigations should use a common method to allow comparisons between studies.

CHAPTER 6: FUTURE DIRECTIONS FOR EPIDEMIOLOGY STUDIES OF CARDIOVASCULAR MALFORMATIONS

6.1 INTRODUCTION

Epidemiological studies of cardiovascular malformations have many roles other than being simply descriptive, as discussed at length in section 1.2. Measurement of the amount of disease in the population can be extended to measure the disease burden, such as the contribution to mortality, the demand for surgical and other treatments, and the implications for workforce planning. Studies of survival rates can yield important information about predictions of survival into adult life and have predicted the linear growth of demand for adult congenital heart disease services.

Changes likely to occur in the next few years will have an impact on the occurrence of cardiovascular malformations. For example, the trend of increasing maternal age in the population is likely to increase the incidence of certain chromosomal anomalies (particularly Down syndrome) and their associated heart defects. As discussed in section 5.8, increased prenatal detection followed by termination of pregnancy will reduce the apparent, though not the real incidence of cardiovascular malformations.

Advances in our understanding of the causes of cardiac malformations have been limited to so far but identification of the genetic contribution to these malformations is likely to make significant progress in coming years. Although environmental causes amenable to manipulation for primary prevention are likely to be few, there are intriguing results from some investigations of folic acid supplementation. The contribution of epidemiological investigations to the study of cardiovascular malformations is discussed further below.

6.2 THE IMPACT OF CARDIOVASCULAR MALFORMATIONS – THE DISEASE BURDEN

Population prevalence of cardiovascular malformations

The relative merits of the various terms used to measure the frequency of disease in a population were discussed in section 1.4. Prevalence at live birth was preferred to describe the identification of new cases of malformation detected in infancy. The simple term “prevalence” measures the total disease burden in a population at any given time. Hoffman *et al* estimated the total prevalence of cardiovascular malformations by modelling the possible survival of individual malformations with

and without treatment over the period 1940-2002. [Hoffman 2004] They thus produced high and low estimates and predicted the range of malformations to be found within the total population. Rosamond *et al*, in the 2007 update of US Heart Disease and Stroke Statistics, assumed that the true prevalence is two thirds of the way between Hoffman's estimated high and low ranges. [Rosamond 2007] This leads to predictions that the total population prevalence of all cardiovascular malformations is 3.9‰ and of severe malformations 0.46‰. These estimates exclude isolated bicuspid aortic valves, which alone are thought to affect 2% of the population (20‰).

In a different prediction of disease prevalence, Marelli used a health care administration database in Montreal to determine the population prevalence of severe and other cardiovascular malformations in 1985, 1990, 1995 and 2000 in Quebec. [Marelli 2007] The prevalence was 4.1‰ adults for all malformations and 0.38‰ for severe malformations. The prevalence increased over the time of the study and they found that 49% of all the malformations in the population were in adults by the year 2000. Extrapolating this predication means that by now there are more adults than children with cardiovascular malformations.

Table 6.1 summarises these findings and applies them to the UK, EU and US populations.

Table 6.1: Estimates of population prevalence of cardiovascular malformations.

			UK	EU	US
2005 population			60,266,000	491,875,000	281,422,000
2005 birth rate (per 1000 population)			12.0	10.4	14.1
2005 births			723,000	5,134,000	3,940,000
New cases of CVM (at 10 per 1000 l.b.)			7,000	51,000	39,000
Hoffman	all CVM	3.9	235,000	1,919,000	1,110,000
	severe CVM	0.46	28,000	226,000	129,000
Marelli	all CVM	4.1	247,000	2,017,000	1,154,000
	severe CVM	0.38	23,000	187,000	107,000

CVM= cardiovascular malformation. l.b. = live births

As can be seen, it is predicted that around 240,000 people are living in the UK with a cardiovascular malformation of some sort and 23-28,000 have a severe malformation. Similar figures for the European Union predict that about 2,000,000 people have a malformation and 200,000 of these a severe malformation.

In our 2001 paper on the predicted need for adult follow up, we documented an 82% one year survival of all cardiovascular malformations in 1985-1994 and estimated a total survival to adult life from birth of 78% for diagnoses made in infancy. [Wren 2001] Adding post infant ascertainment (cases which, by definition, have survived infancy) there is an overall 84% survival to adult life. Improvements in diagnosis and treatment since the late 1980s mean that survival to adult life for cardiovascular malformations overall is now probably nearer 90%. Our 2001 paper also predicted that just over 2 patients per 1000 total population per year would graduate from the paediatric cardiology clinic to the adult congenital heart clinic needing specialist follow up. These numbers are consistent with predictions made by Hoffman and Marelli as discussed above.

The increasing number of children with heart defects who now survive into adolescence and adulthood underscores the need for the health care community to prepare for the challenging and often complex needs of adults with congenital heart defects. The predicted number of patients graduating to adult follow up each year is relatively small compared with the number of adults with heart disease. However, these patients, their families, and their cardiologists and surgeons have already invested greatly in time, effort, and resources. Rapid recent advances have led to the emergence of adult congenital heart disease as a distinct subspecialty and it is important to be able to predict its future growth to ensure appropriate provision of medical manpower, facilities, and resources for the care of adults with congenital heart disease.

Predicting and measuring surgical workload

The US Heart Disease and Stroke Statistic 2007 Update by Rosamond *et al* used predictions from Moller to suggest that cardiovascular malformations needing surgery within the first year of life or causing death within the first year of life occur in 2.3 per 1000 live births. [Rosamond 2007] [Moller 1998] United Kingdom Central Cardiac Audit Database (UKCCAD) data for 2005-2006 showed that 2372 operations were performed in infancy – 3.3 per 1000 live births (another 1612 operations were done in childhood). [UKCCAD 2005] These data are for surgical

operations and another 628 catheter interventions were performed in infancy. Thus there were 3000 procedures in infancy in total (4.2 per 1000 live births). There will have been more than one surgical or catheter intervention per patient in infancy (for instance, most babies with transposition of the great arteries will have a balloon atrial septostomy followed by an arterial switch operation) so the number of patients requiring cardiac intervention in the first year is probably around 3-3.5 per 1000 live births. These data can be used to predict the surgical workload and show that around 2,200-2,500 infants per year will require intervention in the UK and 15,000-18,000 within the EU. The prediction for the US of 12,000-14,000 procedures is close to measured activity. [Rosamond 2007]

6.3 MEASUREMENT OF OUTCOME

Measurement of mortality

As shown below there have been enormous improvements in outcome after cardiac surgery over the past 20 years. Despite this mortality rates rather than survival rates are still used to assess outcome. [Ma 2007] It is generally thought that a lower "operative" mortality is an indicator of better performance but this is not necessarily the case. Comparison of variations in risk of paediatric cardiac surgery between institutions is complicated by the diverse nature and rarity of individual cardiovascular malformations, differing case-mix, and the current low operative risk. Analysis of results will be affected by data quality, different case-mix and chance. Data quality is dependent on dedicated personnel who must achieve and maintain data integrity, and the use of standard nomenclature and definitions. [Mavroudis 2000] Verification of data completeness is crucial because it has been previously shown that patients not included in medical audit have worse outcomes than those included. [Elfstrom 1996]

As Williams has pointed out, the long term mortality after any cardiac surgery is 100% - it is only the timing of death which is variable. [Williams 2005] The traditional measurement of mortality has been either mortality within 30 days from a procedure, or mortality during the same hospital stay. Both have been used to measure surgical mortality, even in contemporaneous reports from the same surgical centre. [Bull 2000, van Doorn 2000, de Leval 2000, Stark 2001] The situation becomes complicated in patients undergoing multiple procedures or those transferred between hospitals. New guidelines have recently been published by an international taskforce [Jacobs 2006] and reviewed by Bill Williams from Toronto

[Williams 2006]. Whatever the guidelines and the definitions involved, nothing can detract from the importance of the accuracy, validity and completeness of the data.

The first 30 postoperative days or the same hospital admission have been used as points at which to measure mortality mainly for convenience. However, the risk of death continues beyond these points, even though it is then lower. In the UK every child's record in the Central Cardiac Audit Database (UKCCAD) is linked to the Office for National Statistics to provide an outcome (alive or dead) one year after the operation. Access to central tracking of mortality identified errors in institutional data and provided a more complete assessment of institutional performance without the limits imposed by the arbitrary 30-day or in-hospital limit. [Gibbs 2004] Central tracking of 5494 paediatric cardiac procedures in the UK identified 469 deaths within one year, including 194 within the first 30 days. Contributing hospitals had identified only 78% of the deaths within 30 days. Furthermore, institutional records for 30 day mortality accounted for only 32% of all deaths within 1 year. These data further support the concept that the early hazard of death extends well beyond the initial 30 day period. It is also worth pointing out that mortality may be nothing to do with the operation and the later the death, the lower the chance that it is related to the surgery or even to the heart problem. One of the operations with the highest late mortality in the UKCCAD data was ligation of patent ductus in prematurity – a relatively minor procedure. Late mortality here almost certainly reflects the risk of preterm birth rather than the risk of surgery.

Trends in mortality

Mortality associated with cardiovascular malformations has been assessed in several studies although most concentrate only on surgical or postoperative mortality. [Ma 2007] Boneva analysed death certificate data to investigate trends in mortality associated with cardiovascular malformations in the United States in 1979-1997. [Boneva 2001] During that time mortality decreased from 2.5 to 1.5 per 100,000 persons in the whole population. Mortality in infancy declined by 39% although in 1995-1997, 51% of all deaths still occurred in infancy. The median age at death increased from 6 to 12 months during the study period, suggesting an overall increase in survival. In Western populations it is estimated that 44% of all deaths from malformations are due to cardiovascular malformations [Botto 2003a] and that cardiovascular malformations cause around 10% of all infant deaths [Rosano 2000].

Figure 6.1 shows the 30-day postoperative mortality data from our own unit in Newcastle upon Tyne. Outcome data have been collected and validated since 1989. Validated national data have been collected since 2000 but so far have been published in a format to allow comparison with our own only for 2000 and 2001. The figure shows that mortality fell by 80% over 16 years.

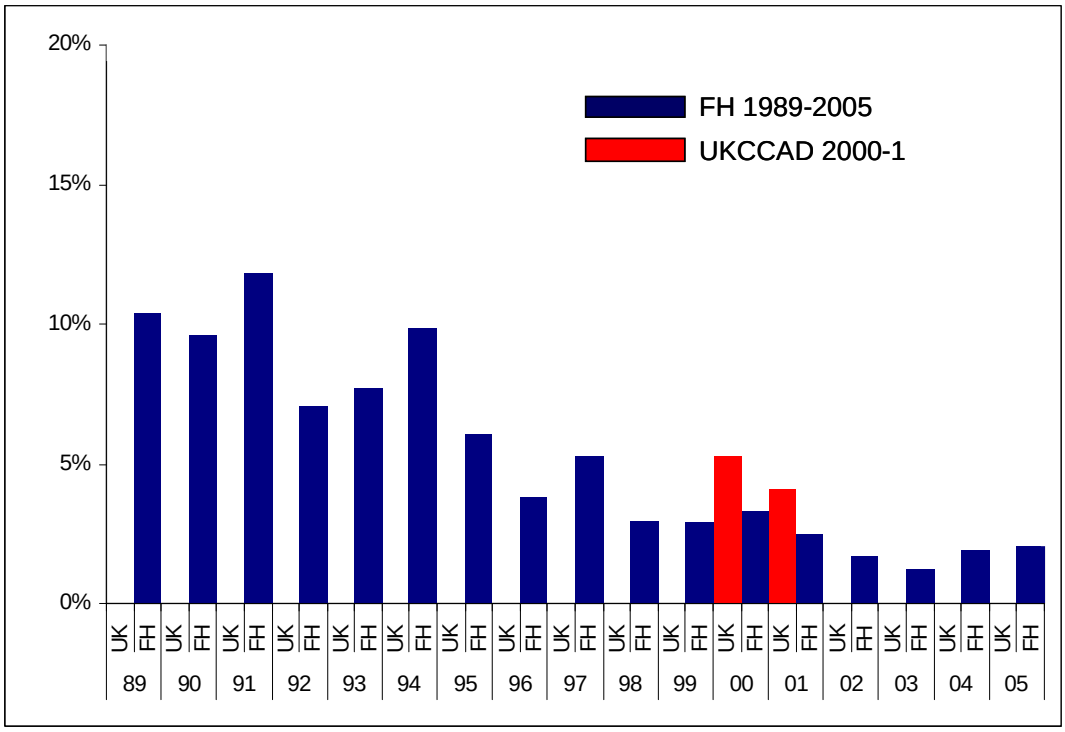

Figure 6.1. Trends in postoperative mortality in Freeman Hospital, Newcastle upon Tyne (FH) for 1985-2005 compared with data from the United Kingdom Central Cardiac Audit Database (UKCCAD) for 2000-2001, the only two years for which validated outcomes are available.

The contribution of individual malformations to total mortality can be derived from published data. [Boneva 2001] Figure 6.2, adapted from Botto [2003a], shows that in the United States hypoplastic left heart made the highest individual contribution to mortality, ahead of transposition of the great arteries and other malformations.

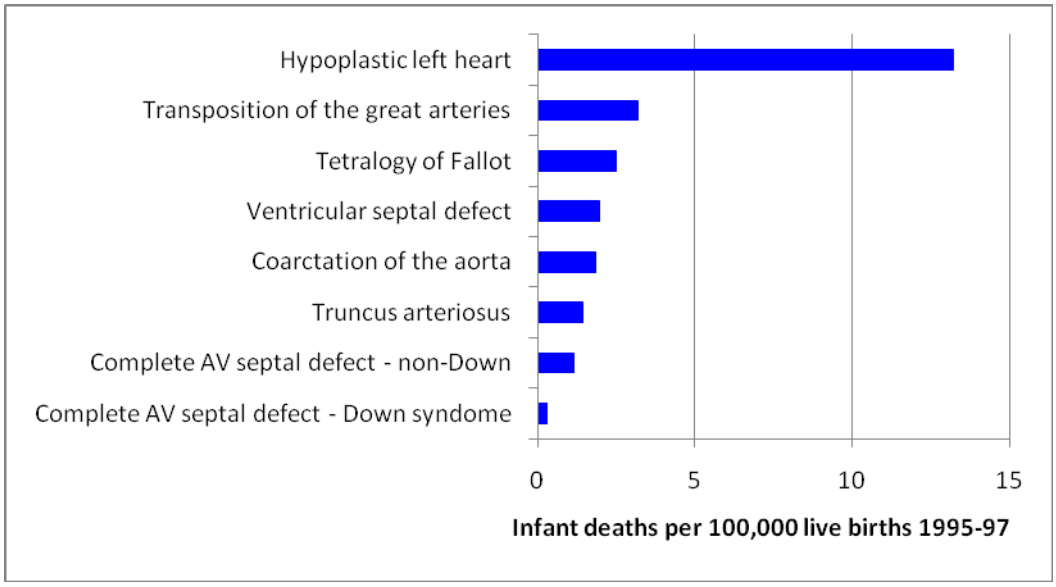

Figure 6.2. The contribution of individual diagnoses to infant mortality. Redrawn from data in Boneva 2001. AV = atrioventricular

Figure 6.3 shows our own data, calculated from infant survival in our study of predictions of the need for adult congenital heart disease follow up. [Wren 2001]

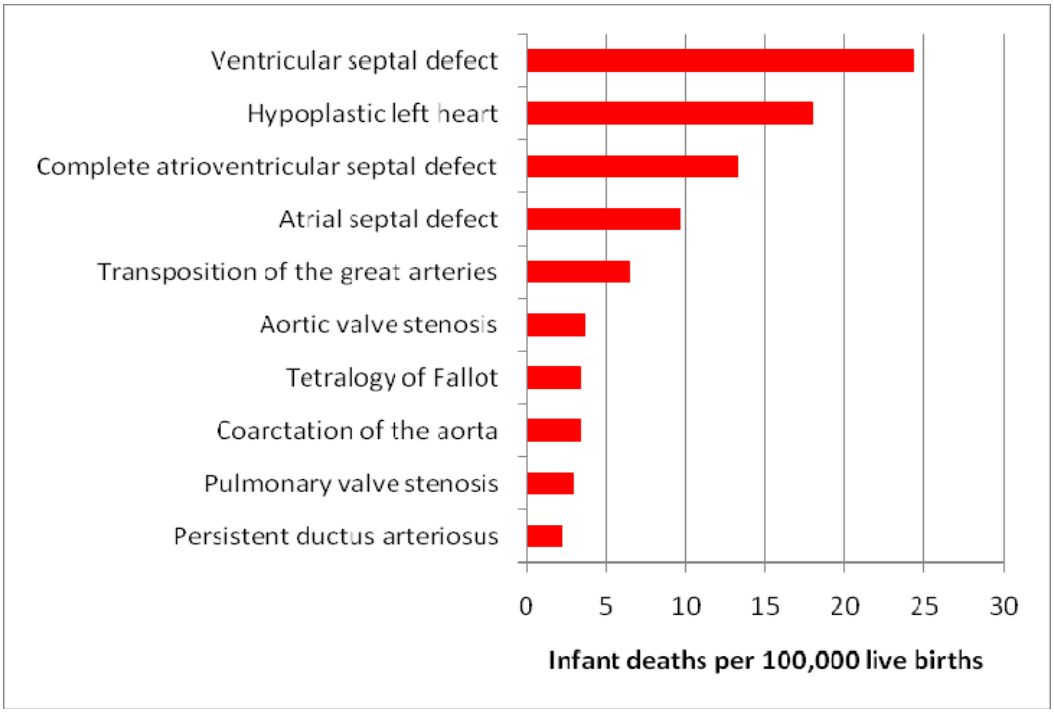

Figure 6.3. The contribution of individual diagnoses to infant mortality. Calculated from data in Wren 2001.

A different picture emerges, with ventricular septal defect making the largest contribution to infant deaths. The discrepancy between these two findings is explained by the fact that the American study investigated the *cause* of death whereas we looked at death or survival in infants *with* a malformation. Most of the

deaths in infants *with* ventricular septal defects were not *caused by* the malformation but represent the total mortality in patients who have associated severe non-cardiac malformations or chromosomal and genetic problems such as fatal trisomy. This also explains the high mortality associated with (but not caused by) atrial septal defect in our data. Data from Boneva show that at least 24% of deaths in persons *with* a cardiovascular malformation are not *caused by* the malformation and this proportion is very probably higher in infancy. [Boneva 2001]

Our own data were collected in 1985-1994. [Wren 2001] The perioperative mortality has declined very significantly since then although we have not yet analysed up to date data on total mortality. As seen in section 4.11, our study of life-threatening cardiovascular malformations showed a fall in mortality from around 50% to around 20% in the years 1985-2004. [Wren 2008] Most of the decline in mortality will have come in improved treatment of common malformations such as transposition of the great arteries, tetralogy of Fallot, and atrioventricular septal defect, all of which currently have a surgical mortality of around 1%. This means that hypoplastic left heart and other severe malformations now make a more significant proportional contribution to total mortality than that shown in figures 6.1 and 6.2.

Remaining surgical challenges

The perioperative mortality for many cardiovascular malformations is now so low that survival is expected in all. The mortality risk of correction of common major malformations such as ventricular septal defect, transposition of the great arteries, tetralogy of Fallot, coarctation of the aorta and complete atrioventricular septal defect, most of which were universally fatal in the pre-surgical era, is now <2%. The cumulative surgical mortality of staged surgical procedures for complex malformations with “single ventricle” physiology, such as tricuspid atresia, double inlet left ventricle etc, is well under 10%. Because of this increasing surgical success, attention is switching to areas that continue to present a challenge, particularly management of hypoplastic left heart, complex pulmonary atresia, and failing ventricular function late after previous palliation. More resources will need to be devoted to medical and surgical management of adolescents and young adults requiring repeat surgery or, in some cases, transplantation. Accurate validated data relating to the occurrence of, survival with, and results of, surgical repair of cardiovascular malformations are vital if improvements in management are to be maintained and the validity of developments in management strategies is to be proven.

Measuring morbidity and disability

If defining and measuring mortality are difficult, the challenges in assessing morbidity are even greater and have so far proved insuperable. The UKCCAD has recently been considering how to tackle the problem but no proposals for collecting and validating data have yet been agreed. Cardiac surgery and interventional cardiac catheterisation procedures are very invasive and have the potential to do harm. They are often performed in ill patients with multiple other problems and any late effects may be subtle – such as the potential influence on IQ or development and behaviour. The complexities of these problems are beyond the scope of this discussion but have been reviewed in detail. [Brown 2005, Schultz 2005, Wernovsky 2005]

Performance assessment

Reports of high mortality from paediatric cardiac surgery at Bristol Royal Infirmary led to the establishment of an independent public inquiry. [Bristol Royal Infirmary Inquiry 2001] One of the key terms of reference was whether or not the mortality of children receiving complex cardiac surgical services at the Bristol Royal Infirmary was unusual compared with other specialist centres.

A retrospective comparison of UK paediatric cardiac surgical performance was reported by the team which had analysed the data for the Bristol Inquiry. [Aylin 2001] The report concluded that:

> "Bristol was an outlier, and we do not believe that statistical variation, systematic bias in data collection, case-mix, or data quality can explain a divergence in performance of this size."

Amongst the Bristol Inquiry's conclusions was the following:

> "Bristol was awash with data. There was enough information from the late 1980s onwards to cause questions about mortality rates to be raised both in Bristol and elsewhere had the mindset to do so existed. Little, if any, of this information was available to the parents or to the public. Such information as was given to parents was often partial, confusing and unclear. For the future, there must be openness about clinical performance. Patients should be able to gain access to information about the relative performance of a hospital, or a particular service or consultant unit."

Subsequent analysis based on hospital episode statistics confirmed the interpretation of the data relating to Bristol, showed that performance had improved after changes in management and personnel, and highlighted concern about performance in Oxford. [Aylin 2004] Analysis of hospital episode statistics may be misleading [Singleton 2007] and a further analysis of data from Oxford in the UK Central Cardiac Audit Database (UKCCAD) has reached different conclusions [Westaby 2007]. Earlier allegations of problems at Harefield Hospital and Brompton Hospital were also the subject of an investigation which found that in some areas mortality was higher than average. [Wise 2001] For example, in 1991-1995 there was strong evidence of excess mortality for open heart surgery in children aged over 1 year. Fontan procedures were associated with a high mortality and there was another run of poor performance in 1995-1999, when there were identifiable areas of higher mortality in infants, particularly for repair of tetralogy of Fallot. The report concluded:

> "… the two available national sources on clinical outcomes - hospital episodes statistics and the cardiac surgical register - are inadequate in providing accurate, reliable, verified, comparative data that are understandable and usable".

All these problems mean that the importance of collecting complete and accurate data and subjecting them to appropriate analysis to enable publication of appropriate indicators of performance assessment is now widely recognised. For many reasons it would be helpful to compare the performance of individual units and of individual surgeons doing individual operations. This would provide choice for cardiologists and parents and would also identify substandard results to allow an early corrective process such as retraining, reallocation etc. However, there are many pitfalls. The first, and perhaps the most important, is concern over the integrity, validity and completeness of data. This depends fundamentally on the accuracy of coding of diagnoses, operation and risk factors. The second difficulty is in measuring outcome. As discussed above, even mortality can be difficult to define and assessment of morbidity (which may be more important now that mortality is so low) is very difficult. Another major problem is accounting for variations in case-mix. A surgeon who limits himself to simpler "lower risk" operations would be expected to have better results. If no allocation is made for case-mix, publication of unadjusted results may deter surgeons from taking on more complex or more difficult cases.

Two risk-adjustment systems have been introduced in an attempt to measure performance in paediatric cardiac surgery. The first, the Risk Adjustment In Congenital Heart Surgery (RACHS-1) system, was developed in Boston. [Jenkins 2002] RACHS-1 was developed in 1993-1995 and stratified congenital cardiac operations into one of six categories developed by consensus by a panel of experts. The risk category of some procedures also varied with patient age. RACHS-1 has been validated and found to have good predictive value. [Boethig 2004, Larsen 2005]. The other system, the Aristotle Basic Complexity score was devised by a panel of experts from fifty centres in 23 countries. [Lacour-Gayet 2004] It allocated up to five points each for the potential for mortality, potential for morbidity, and technical difficulty to devise a continuous score with a range of 1.5 – 15. The score then grouped procedures into four levels, depending on complexity. The Aristotle System also defined complexity as the sum of mortality, morbidity and technical difficulty and performance as the product of complexity and survival.

Two attempts have been made to compare these two systems. Al-Radi *et al*, in a combined report from Toronto, Tennessee and Florida found that 96% of operations could be given an Aristotle Score and 84% a RACHS-1 score. [Al-Radi 2007] They concluded that both systems are useful but that the RACHS-1 gave a better prediction of mortality and length of hospital stay. Kang *et al* also compared the two systems in a retrospective analysis of 1058 operations at Great Ormond Street Hospital. [Kang 2006] They found that 99.4% of operations could be scored using the Aristotle Basic score and 92% using RACHS-1. They concluded that the Aristotle score was only weakly associated with postoperative mortality whereas RACHS-1 was a powerful predictor of mortality. They speculated that their analysis might have been affected by the relatively high overall complexity in their practice. There are efforts being made to combine the two systems to produce an improved mortality score based on outcome data from the European Association of Cardiothoracic Surgeons (EACTS) and the US Society of Thoracic Surgeons (STS) databases. [Lacour-Gayet 2006].

In a comment on the Al-Radi report, Marc de Leval said that if the aim is to be able to compare performance of individuals or institutions it is important that patient-specific and procedure-specific factors should not overwhelm potential institution-specific or surgeon-specific factors. [Al-Radi 2007] He went on to say it would be better to try to understand the reasons for variability between institutions which would not be explained by minutely detailed analysis of case-mix. Dr de Leval had

previously encountered a problem with his own performance of arterial switch operations at Great Ormond Street. [de Leval 1997] The run of poor performance was eventually recognised and remedial action was taken but not before there had been an excess number of deaths. de Leval and his team developed the concept of analysis of “near-misses” and “human factors” to improve the sensitivity of early warning analysis of surgical and institutional performance. [de Leval 2000]

A further problem with performance analysis is that some operations, for example the arterial switch operation, are very operator-specific, whereas others, such as repair of complete atrioventricular defect, are more dependent on the performance of the whole team which includes cardiac anaesthetists, intensivists etc.

Performance analysis is here to stay. The ideal method of data collection, data validation, and data interpretation has not been developed. Similarly the ideal method of publishing and displaying information derived from analysis is yet to be defined. What is clear is that collection of accurate data and continuing analysis of performance is now an accepted part of routine clinical practice. [Keogh 2005]

6.4 AETIOLOGY OF CARDIOVASCULAR MALFORMATIONS

Every malformation presumably has a cause although most have not yet been identified. Even when a “cause” seems obvious, for instance in atrioventricular septal defect or other malformation in Down’s syndrome, the precise mechanism usually remains obscure. Over the past few years, there have been major developments in our understanding of inherited causes of congenital cardiovascular malformations, including the identification of specific genetic abnormalities for some types of malformations. Although relatively less information has been available on non-inherited modifiable factors that may have an adverse effect on the fetal heart, there is a growing body of epidemiological literature on this topic.

Environmental causes and opportunities for prevention

Although the expression ‘‘environmental cause’’ suggests toxic pollution from a landfill site or traffic, it refers more broadly to any factor which is not genetic. Most of the environmental causes of cardiovascular malformations occur within the fetal-placental-maternal ‘‘environment.’’

Jenkins *et al* recently published an extensive review of evidence of non-inherited risk factors which may affect the occurrence of cardiovascular malformations.

[Jenkins 2007] Factors associated with increase risk include maternal illness and infection, maternal nutritional excesses and deficiencies, maternal drug exposure, and other environmental exposure and are summarised in table 7.2. Avoidance of such factors may reduce the risk. Progress in prevention of cardiovascular malformations has been hampered by a lack of information about modifiable risk factors for abnormalities in cardiac development. The proportion of cases that are potentially preventable through changes in the fetal environment is unknown. One study suggests that the fraction of cases attributable to identifiable and potentially modifiable factors may be as high as 30% for some types of defects. [Wilson 1998]

Table 6.2 Exposures associated with definite or possible increased risk of offspring with cardiovascular malformations.

Maternal illness / infection	Diabetes Epilepsy Influenza/febrile illness Phenylketonuria Rubella
Maternal drug exposure	Alcohol Anticonvulsants Ibuprofen Marijuana Thalidomide
Maternal environmental exposure	Organic solvents
Maternal nutritional excess / deficiency	Folic acid

Although a case-control study is an appropriate model for investigation of associations between multiple risk factors, it is open to many types of bias. To give only a few examples, the Baltimore Washington Infant Study reported significant associations between transposition of the great arteries and paternal marijuana use or maternal influenza; between tetralogy of Fallot and paternal anaesthesia; between atrioventricular septal defect in Down's syndrome and paternal welding or ibuprofen; and between hypoplastic left heart and paternal exposure to degreasing agents etc. [Ferencz 1993] To some observers it may not be biologically plausible that there is such a wide variety of "causative" associations. It is possible, however, that there is variable genetic susceptibility to environmental influences. Unfortunately other investigations of possible environmental "causes" or associations come up with different findings. [Jenkins 2007].

Folic acid supplementation

There is good evidence that maternal use of multivitamin supplements containing folic acid, or folic acid alone, is associated with a reduction in occurrence of neural tube defects. Factors known to, or suspected of being able to reduce the occurrence of cardiovascular malformations are few. One intriguing recent discovery is the possibility that periconceptional intake of multivitamin supplements containing folic acid might reduce the risk of cardiovascular malformations in offspring, similar to the proven risk reduction for neural tube defects. This first came to light after analysis of data from a Hungarian randomized trial on birth defects. [Czeizel 1998] Findings from subsequent case-control studies offer some support to the findings but are certainly not conclusive [Scanlon 1998], while others have failed to show any benefit [Werler 1999, Botto 2004].

In addition to these reports investigating the association between multivitamin use and risk reduction for cardiovascular malformations, other studies have shown that women who took folic acid antagonist medications, such as dihydrofolate reductase inhibitors (eg trimethoprim) or antiepileptic drugs, had an increased risk of offspring with cardiovascular malformations. In the same studies this risk was reduced for women who also took multivitamin supplements containing folic acid. [Hernandez-Diaz 2000, Czeizel 2001]

The findings of a possible protective effect for cardiovascular malformations from multivitamin supplements containing folic acid are interesting but inconclusive. Associations between environmental factors and cardiovascular malformations may be causal, but they may also be a result of chance, bias, or confounding. An exploratory study can produce an association as a result of multiple comparisons. Confounding is also a concern in that the apparent protective effect of multivitamin supplement use might be due not to the use itself but to the behaviour of the user. Given the large number of studies of folic acid supplementation related to risk reduction for neural tube defects, it is surprising that, if the association were real, more evidence has not come to light before now. Additional studies may be warranted to determine whether the association of specific phenotypes with multivitamins can be corroborated. Large population-based studies would be needed in which multivitamin intake can be validated, potential confounders such as maternal age and diabetes can be taken into account, and the components of the supplements responsible for the association can be identified.

Genetic causes of cardiovascular malformations

Previous investigations have shown that cardiovascular malformations are associated with non-cardiac malformations in about 25% of individuals, about one third of whom have a recognizable syndrome. [Ferencz 1993, Pierpont 2007] In one report on patients undergoing an interventional procedure or cardiac surgery, a syndrome was identified in 39% [Rope 2004]. Population-based studies have reported chromosome abnormalities in approximately 13% of newborns with cardiovascular malformations. [Ferencz 1993] The autosomal trisomies (of chromosomes 21, 18, and 13) have long been recognized as having a causative association with cardiovascular malformations. More recently chromosome 22q11 microdeletion has also been identified as a chromosome cause of cardiovascular malformation. [Botto 2003b]

Nora first proposed the “multifactorial” model in 1968 to explain the aetiology of isolated cardiovascular malformations in which several genetic loci interact together, with or without environmental factors. [Nora 1968] The overall recurrence risk was quoted as 2-4%. Since then, however, many studies have produced data that do not seem to fit a polygenic or multifactorial model. [Burn 1987]

Further support for the more widespread influence of genetic factors in the aetiology of cardiovascular malformations comes from studies of recurrence risk. The occurrence of malformations among first-degree relatives of a proband with a cardiovascular malformation varies depending on the relationship. John Burn, professor of clinical genetics at Newcastle University, with colleagues from around the UK, studied the offspring of adults who survived surgery for selected major cardiovascular malformations – abnormalities of situs, abnormalities of atrioventricular or ventriculoarterial connection, anomalous pulmonary venous connection, atrioventricular septal defect, or tetralogy of Fallot. [Burn 1998] He found that recurrence among offspring (4.1%) was significantly greater than among siblings (2.1%) and that recurrence in the offspring of affected mothers (5.7%) was higher than in those with affected fathers (2.2%). The reasons for this maternal excess are not clear although several theories have been proposed. [Burn 1998]

A study from Guy’s Hospital, the United Kingdom’s largest fetal cardiology unit, examined the recurrence risk of cardiovascular malformations using fetal echocardiography in 6640 consecutive pregnancies where a first-degree relative had a cardiovascular malformation. [Gill 2003] The recurrence rate for

cardiovascular malformations overall was 2.7%, with a high concordance for the specific type of malformation (37%), or for malformation of the same group (44%). In families with two or more recurrences, the concordance rate was higher still (55%). While the concordance rates of the various cardiovascular malformations varied, two specific types of malformations, isolated atrioventricular septal defect and laterality defects, showed the highest concordance at 80% and 64%, respectively.

The Baltimore-Washington Infant Study also provided information on the heritability of cardiovascular malformations, weakening support for the multifactorial model and suggesting a substantial genetic component in the aetiology of some groups of cardiovascular malformations. [Boughman 1987] As an example, although the overall frequency of having a previous sibling with a cardiovascular malformation (precurrence risk) was 3.1%, the rate was higher when the proband had either hypoplastic left heart (8.0%) or coarctation of the aorta (6.3%). The familial aggregation of obstructive left-sided malformations has been examined in studies including echocardiograms on first-degree relatives. [Loffredo 2004]

Recent research has shown that variations or alterations in genes contribute to the origin of cardiovascular malformations to a greater degree than was previously suspected. Further developments are likely to lead to greater understanding of the causes and implications of these defects.

6.5 CONCLUSIONS

Cardiovascular malformations are the commonest congenital malformations and are important because of their frequency and severity and because of the burden they impose on medical resources and on families. From the epidemiological point of view, research priorities include monitoring of the prevalence at live birth to detect trends which might indicate changes in, or introduction of, risk factors in the population. Monitoring of outcome, including measurement of mortality and morbidity, is equally important to predict requirements for medical and surgical care and the wider effects on malformations in the population. If confirmed, newer evidence, including the increasing evidence of a possible protective effect of maternal multivitamin supplements containing folic acid may lead to opportunities for primary prevention.

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APPENDIX A. PROPOSALS FOR META-ANALYSIS OF OBSERVATIONAL STUDIES IN EPIDEMIOLOGY

Table. A Proposed Reporting Checklist for Authors, Editors, and Reviewers of Meta-analyses of Observational Studies

Reporting of background should include
Problem definition
Hypothesis statement
Description of study outcome(s)
Type of exposure or intervention used
Type of study designs used
Study population
Reporting of search strategy should include
Qualifications of searchers (eg, librarians and investigators)
Search strategy, including time period included in the synthesis and keywords
Effort to include all available studies, including contact with authors
Databases and registries searched
Search software used, name and version, including special features used (eg, explosion)
Use of hand searching (eg, reference lists of obtained articles)
List of citations located and those excluded, including justification
Method of addressing articles published in languages other than English
Method of handling abstracts and unpublished studies
Description of any contact with authors
Reporting of methods should include
Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested
Rationale for the selection and coding of data (eg, sound clinical principles or convenience)
Documentation of how data were classified and coded (eg, multiple raters, blinding, and interrater reliability)
Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)
Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results
Assessment of heterogeneity
Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated
Provision of appropriate tables and graphics
Reporting of results should include
Graphic summarizing individual study estimates and overall estimate
Table giving descriptive information for each study included
Results of sensitivity testing (eg, subgroup analysis)
Indication of statistical uncertainty of findings
Reporting of discussion should include
Quantitative assessment of bias (eg, publication bias)
Justification for exclusion (eg, exclusion of non–English-language citations)
Assessment of quality of included studies
Reporting of conclusions should include
Consideration of alternative explanations for observed results
Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)
Guidelines for future research
Disclosure of funding source

APPENDIX B. STANDARDS FOR THE REPORTING OF OBSERVATIONAL STUDIES IN EPIDEMIOLOGY

Table 1. **The STROBE Statement: a checklist of items that should be addressed in reports of observational studies**

Item	Item number	Recommendation
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any pre-specified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations and relevant dates, including periods of recruitment, exposure, follow-up and data collection
Participants	6	(a) *Cohort study* – Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study* – Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* – Give the eligibility criteria, and the sources and methods of selection of participants
		(b) *Cohort study* – For matched studies, give matching criteria and number of exposed and unexposed *Case-control study* – For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders and effect modifiers. Give diagnostic criteria, if applicable
Data sources/measurement	8[a]	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding
		(b) Describe any methods used to examine subgroups and interactions
		(c) Explain how missing data were addressed
		(d) *Cohort study* – If applicable, explain how loss to follow-up was addressed *Case-control study* – If applicable, explain how matching of cases and controls was addressed *Cross-sectional study* – If applicable, describe analytical methods taking account of sampling strategy
		(e) Describe any sensitivity analyses
Results		
Participants	13[a]	(a) Report the numbers of individuals at each stage of the study – e.g. numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up and analyzed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14[a]	(a) Give characteristics of study participants (e.g. demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate the number of participants with missing data for each variable of interest
		(c) *Cohort study* – Summarize follow-up time (e.g. average and total amount)
Outcome data	15[a]	*Cohort study* – Report numbers of outcome events or summary measures over time *Case-control study* – Report numbers in each exposure category, or summary measures of exposure *Cross-sectional study* – Report numbers of outcome events or summary measures

(Table 1, cont.)

Item	Item number	Recommendation
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g. 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(b) Report category boundaries when continuous variables were categorized
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done – e.g. analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarize key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalizability	21	Discuss the generalizability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

[a] Give such information separately for cases and controls in case-control studies, and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

APPENDIX C: REFERENCES INCLUDED IN ANALYSIS IN THE SYSTEMATIC REVIEW IN CHAPTER 5

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