

Prognosis for Danish patients with congenital heart defects

-Mortality, psychiatric morbidity, and educational achievement

PhD thesis

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Preface

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List of Abbreviations

CHD	Congenital heart defect
TOF	Tetralogy of Fallot
TGA	Transposition of great arteries
VSD	Ventricular septal defect
ASD	Atrial septal defect
PDA	Persistent arterial duct
PS	Pulmonary stenosis
AS	Aortic stenosis
CoA	Coarctation of aorta
RACHS-1	Risk Adjusted Classification for Congenital Heart Surgery
ICD	International Classification of Diseases
IPCCC	International Pediatric and Congenital Cardiac Code
CI	Confidence interval
HR	Hazard ratio
HKD	Hyperkinetic disorder
IQ	Intelligence quotient
ADHD	Attention deficit hyperactivity disorder
PDD-NOS	Pervasive developmental disorder not otherwise specified
DSM	Diagnostic and Statistical Manual of Mental Disorders
ISCED	International Standard Classification of Education

Introduction

Congenital heart defects

Congenital heart defects (CHDs) have been defined as gross structural abnormalities of the heart or intrathoracic great vessels that are actually or potentially of functional significance (1). Traditionally, CHDs have been categorized according to whether the defect may cause cyanosis. *Cyanotic* lesions cause the presence of desaturated blood in the systemic circulation due to right to left shunting and include tetralogy of Fallot (TOF), transposition of the great arteries (TGA), and Ebstein's anomaly. *Acyanotic* lesions include ventricular septal defect (VSD), atrial septal defect (ASD), patent arterial duct (PDA), pulmonary stenosis (PS), atrial stenosis (AS), and coarctation of the aorta (CoA) (2, 3).

CHD vary immensely in severity, natural history and management. Minor forms of CHD include mild PS, small ASD, and VSD, and they rarely require intervention. More severe CHDs with four heart chambers and 4 heart valves like CoA, severe AS, large VSD, TOF, and TGA require intervention to prevent heart failure, cyanosis, pulmonary hypertension or death. Highly complex CHD include atresia and hypoplasia of valve or chamber (4). Most CHDs are diagnosed in infancy (5), and cyanosis and cardiac failure are the principal signs. Later, in childhood or adolescence, CHD patients may present differently with e.g. a heart murmur, abnormal heart rate, absent pulses or hypertension.

Prevalence at birth and aetiology

Congenital heart defects comprise the most prevalent group of congenital anomalies. Most studies estimate the live birth prevalence of CHD to be around 6-10 per 1,000 (5-9). The discrepancy in the reported prevalence of CHD may reflect true geographical and or temporal differences in the prevalence, however it is more likely attributable to variations in recording and reporting practices. Thus, there are differences between the studies in e.g. case definition and inclusion/exclusion criteria, follow-up period and age at diagnosis (7). Hoffman et al reviewed 62 studies published after 1952 and found that prevalence estimates were highly dependent on the number of small VSDs included (5). Thus, there is no evidence of temporal variations in the prevalence of CHD. However, elective terminations of pregnancies due to severe CHD, diagnosed in prenatal investigations, happen with increasing frequency and may

eventually lower the prevalence at birth of severe CHD. Among all births with CHD in the Danish county of Odense, in the period 1980-2007, the proportion of terminated pregnancies for fetal cardiac anomalies after prenatal investigation was only 3% (10). But this proportion was probably larger in the most recent part of this period, which may have lead to a lower prevalence of severe CHD.

Despite continued research into the etiology of CHD, little is known about its origins. About 8-10% of the patients have a chromosomal abnormality, such as trisomy 21 or chromosome 22q11 deletion. Less than 5% are secondary to an established environmental risk factor, such as maternal rubella infection, alcoholism, anticonvulsants and/or maternal epileptic disease, thalidomide, or retinoids (11).

Treatment

Without treatment 1/3 of patients with CHD are estimated to die before the first year of life (12). However, diagnostic techniques and medical and surgical management of CHD continue to evolve and improve the survival of CHD patients. Two to three decades ago, cardiac catheterization was the cornerstone of CHD investigations. Today, cross sectional echocardiography and magnetic resonance imaging have reduced the need for diagnostic cardiac catheterization (13). The non-invasiveness of echocardiography and the portability of the equipment, enabling bedside investigation, have greatly improved the clinicians' ability to detect CHD at an early stage. Introduction of cardiopulmonary bypass in the 1950'ies facilitated surgery on the open heart. In the 1970'ies the discovery that prostaglandin analogues maintain ductal patency, enabled stabilization of children with ductus dependent arterial blood flow (14). Today, the range of conditions that may be amenable to catheter-based intervention continues to increase and include AS, PS, PDA, ASD, and VSD (15, 16). As catheter-based intervention causes less physical stress on the patient, the procedure has some obvious advantages over cardiac surgery. However, potential long term complications to the radiation exposure need to be further examined (17). Finally, the advances in cardiac surgical technique have made it possible to treat even complex CHDs such as hypoplastic left heart syndrome with low post operative mortality (18, 19).

Prognosis

Studies on outcome are required in order to understand, predict, and potentially change the prognosis of disease (20). They are relevant to clinical decision making and help clinicians provide relevant information to patients and their families. Also, health care policy makers base their decisions regarding the organization of health care on outcome studies (21, 22). Several factors may determine the clinical outcome of illness; the illness itself, diagnostic tests, potential treatments, clinical performance, and patient compliance (23). The most studied clinical outcome in the field of CHD has been post operative mortality. Due to advances in diagnostic tests, potential treatments, and clinical performance other measures of clinical outcome have also become relevant, as described in the following sections.

Classification/nomenclature

The great variation of CHD complexity and the wide range of therapeutic procedures in this field hampers meaningful and valid prediction of the prognosis of the individual patient, as well as comparison of outcomes of non-identical patient populations from different countries or centres (24, 25). Thus, scoring systems, such as the consensus-based Risk Adjusted Classification for Congenital Heart Surgery (RACHS-1) (26, 27) and also empirically-based methods (28), have been developed to try to categorize patients according to risk of in hospital mortality following congenital heart surgery. The ability of these systems to predict mortality is still limited and they do not encompass all surgical procedures for congenital heart surgery. No complexity stratification systems have been developed with regard to other outcomes than mortality. A high specificity of a classification system or nomenclature used to categorize the CHD or CHD-related procedures is essential to its ability to stratify on CHD complexity. Thus, even though the International Classification of Diseases (ICD) version 10 provides a more specific categorisation of CHD than the 8th version of this classification, there may still be great variation of defect severity within the available categories. Neither the 8th nor the 10th versions of the ICD provide sufficient specificity to allow complete stratification on CHD complexity. The International Pediatric and Congenital Cardiac Code (IPCCC) (29) is a much more detailed CHD classification that may help overcome some of the problems associated with complexity stratification. It has been proposed to incorporate the IPCCC in the 11th version of ICD.

Selection of patients

A large part of the literature on various aspects of the prognosis of CHD patients is based on studies of patients with specific, selected defects. An obvious strength of the studies on selected defects is the possibility to deal with defect specific issues in more detail. Results from studies on selected CHD types may also be more readily compared due to the lower risk of confounding that may be introduced when comparing populations with potentially different distributions of complexity of defects. However, substantial variation in defect and disease severity may be present, even among patients with the same type of CHD, depending on the classification system.

The selection of patients in studies on outcome may be due to processes under the control of the researcher such as restriction to specific CHD types. However, the selection of patients may also be influenced by factors beyond the control of the researcher. In studies carried out in health care systems without free access to care or in studies based on patient populations included at tertiary referral centres, the inclusion of patients may be affected by socioeconomic, geographic or cultural factors. Population-based studies (30), defined by inclusion of all patients in a geographical area, are less susceptible to this kind of selection. Overall estimates of prognosis based on unselected CHD populations including all patients and CHD types, irrespective of whether treatment has been carried out or not, are obviously less susceptible to the problems associated with patient selection. However, different populations may still have different registration practices in particular regarding mild defects such as small VSDs (5, 31), which may well influence the overall estimates of prognosis. Furthermore, overall estimates are often not as relevant to every day clinical practice and patient counselling as defect specific estimates. Due to the constant development of CHD management, results from outcome studies from different time periods can not readily be compared. This should also be considered before extrapolating the result of studies on long term prognosis to patients diagnosed today, as long term results are inherently based on patients diagnosed years ago (18).

Data sources

Different types of data have been used in the studies on CHD outcomes. These can be divided into primary or secondary data sources. Primary data are collected by the researcher for research purposes. This carries the advantage of data collection being under the control of the

researcher, who is able to decide which examinations to perform, what parameters to include, the level of detail etc. Collection of high quality data is often expensive and time consuming. Secondary data sources contain data gathered for other than research purposes, e.g. administrative data. The main advantage of using secondary data sources is that they already exist; the time spent on the study is therefore likely to be considerably less than the time spent on studies that use primary data collection. Furthermore, the costs of the project are reduced markedly. Other advantages include the size of the sample, its representativeness, and the reduced likelihood of bias due to, for example, non response and effect on the diagnostic process of attention caused by the research question. Thus, if the information on exposure is derived from a prospectively updated register, the outcome of the patients will have no influence on this exposure information.

The limitations of secondary data are related to the fact that their selection and quality, and the methods of their collection, are not under the control of the researcher (32). Thus, use of secondary data sources potentially implies that less detailed data are available (e.g., on potential confounders).

Study I – Mortality

Advances in treatment and diagnostics have resulted in an increase in the prevalence of adults with even complex CHD (33-35). This population is at risk of morbidity requiring medical follow up including arrhythmias (36, 37), hypertension, and reduced exercise capacity (38-42). This is also the case for patients with relatively mild defects who have not undergone interventions for their CHD (43). Studies on long-term mortality are important to add to our understanding of the extent and severity of these long term complications (44), and to provide information to the patients and their parents.

Existing literature

In the following, studies on the long-term mortality of patients with the most common isolated defects undergoing surgery or percutaneous catheter-based treatments are summarised. A review of the literature concerning unselected CHD populations will follow this summary.

ASD

Ross-Hesselink et al (45) found a 30-year survival of 99% following surgery for ASD in a study including all patients (n=135) who underwent surgical repair for secundum type ASD or sinus venosus type ASD at a tertiary referral centre (Thoraxcentre, Amsterdam) between 1968 and 1980 and who were <15 years of age at the time of the operation. Nieminen et al (46) found a 45-year survival of approximately 95% after the first operation. ASD patients are at increased risk of atrial fibrillation (47). However, it seems that the closure of the ASD before adulthood may reduce the incidence of postoperative atrial fibrillation (48).

VSD

The 30-year survival of patients with VSD operated before the age 15 years at the Thoraxcentre in Amsterdam (49) between 1968 and 1990 (n=176) was approximately 85%. In the study by Nieminen et al (46) the 45-year mortality was reported to be 80%.

PS

The surgical approach evolved from closed valvulotomy, first performed in 1948, to open valvulotomy using inflow occlusion and finally, open valvulotomy with the use of cardiopulmonary bypass. Late mortality is low: Survival after 25 years was 93% for 90 patients operated for pulmonary stenosis at the Thoraxcentre in Amsterdam between 1968 and 1980 (50). Re-intervention was reported to be necessary in up to half of the patients after 30 years of follow-up(50, 51). Clinically significant arrhythmias may occur especially in patients with severe pulmonary regurgitation.

TOF

The natural history was dramatically changed with the introduction of palliative procedures by Blalock and Taussig in 1945 and radical repair by Lillehei in 1954 and Kirklin in 1955. Since that time, operative mortality has decreased dramatically, and correction is now usually performed in infancy or early childhood (52). Fifty seven patients less than 24 months of age (median 8 months) underwent primary repair of tetralogy of Fallot between January 1972 and December 1977 at Children's Hospital, Boston, USA. Actuarial survival was 86% at 20 years (CI = 80%-92%) after initial repair (53). One hundred and eighty five patients underwent corrective repair of TOF with pulmonary stenosis at the Rigshospitalet, Copenhagen, Denmark between January 1960 and July 1977. Survival was approximately 85% at 30 years from successful repair, after exclusion of 60 patients who died in hospital (54). From December 1958 to May 1977, 739 patients with the diagnosis of TOF with pulmonary stenosis underwent complete surgical repair at the Clinic of Cardiac Surgery at the University of Munich. The 30-year from repair survival was approximately 60% (55). Nieminen et al (46) found a survival of approximately 55%, 45 years after the first operation. Over the long term pulmonary regurgitation may lead to progressive right-sided heart failure, reduced functional status, arrhythmias, and reoperations.

PDA

Samaneck et al (56) found a 15 year survival of 91% among 255 patients with PDA.

CoA

Nieminen et al (46) found a survival of patients with CoA of approximately 80 %, 45-years after the first operation. Two hundred and twenty nine patients were operated for CoA at Aarhus University Hospital, Denmark between 1965 and 1985. The survival in patients who were alive 30 days postoperatively was 95% 10 years after surgery, and 91%, 83%, and 69% after 20, 30, and 40 years, respectively (57). Long-term complications include recoarctation, systemic hypertension, cerebrovascular disease, and premature atherosclerosis.

TGA

Transposition of the great arteries was initially treated by palliative procedures, such as the surgical atrial septectomy in 1950 (58) and the balloon atrial septostomy in 1966 (59). By creating an atrial septal defect and allowing intra-atrial mixing of the pulmonary and the systemic circulations, these procedures were the first to permit survival of newborns with TGA and intact ventricular septum. Later atrial switch procedures with separation of the systemic and the pulmonary circulations were successfully established. The surgical technique, with the use of autologous tissue to create an intra-atrial baffle, was first described by Senning in 1958. In 1963, Mustard presented a similar approach using synthetic material. Until the mid 1980s, atrial switch procedures were the treatment of choice for TGA. Then this treatment was abandoned in favour of the arterial switch operation (60).

Three hundred and twenty nine patients underwent the Senning operation and 88 the Mustard operation at a single German centre between 1974 and 2001. The estimated survival at 25 years after the Senning operation was 91% and after the Mustard operation it was 76% (61). This difference in late survival between the two operative procedures is not confirmed in all investigations (62). Irrespective of the type of atrial baffle procedure, patients with previous VSD carry a higher risk of late death than patients with intact ventricular septum. In the Finnish study by Nieminen et al (46) the survival at 30 years of TGA patients was approximately 50%. Many of these patients were only palliated.

Studies including all CHD types

There are few population-based studies including all CHD types and also CHD patients who have not undergone, or did not survive to undergo, surgery or catheter-based intervention.

Boneva et al (63) and Pillutla et al (64) have examined time trends in the mortality associated with CHD in the United States using the nationwide Multiple Cause-of-Death Files, and made indirect estimates of survival based on the age at death. However, the estimates are potentially influenced by changes in the CHD prevalence at birth or changes in mortality rates due to other causes.

I searched the electronic Medline database (1966-2010) for relevant studies on long-term mortality of CHD patients using the following query:

("Heart Defects, Congenital/mortality"[Mesh] OR ("Heart Defects, Congenital"[Mesh] AND survival)) AND "population based"

I only included studies with more than 5 years of follow-up of patients with unselected defect types. One study was included after manual search of reference lists and one because it quoted one of the studies yielded by the search. This search strategy yielded the studies, listed in Table 1.

Samanek et al examined the mortality up to 15 years of age of CHD patients born from 1980 and 1990, also including those who did not undergo surgical treatment. All children in the study population were examined by a pediatrician at birth, at 14 days, and 6 weeks, and then four times in the first year of life, all children were next examined at age 5 years, and some of them at 7, 9, 11, 13, and 15 years of age. Patients diagnosed before the age of 15 years were included. All children suspected of having CHD were subjected to echocardiography and 28% of diagnosed VSDs closed spontaneously during the study period. Overall survival was 77% at 15 years of age (56).

Tennant et al (65) included patients diagnosed with CHD at ages up to 16 years who were born from 1985 to 2003 and report up to 20-year survival estimates with follow up from birth. Patients with extra cardiac defects or chromosomal anomalies were not categorized as having CHD. Overall survival was 90% at 20 years of age (65).

Nieminen et al (46) collected data on all individuals who underwent surgery for CHD between 1953 and 1989 in Finland. Data were obtained from surgical logs, diagnosis cards, and computer files of the hospitals. As these exposure data were prospectively registered before the outcome, this is a prospective study. Overall survival was 78%, 45 years

after the date of first surgery. Current patient status and dates of death and emigration were obtained from the Finnish Population Registry Center. The method of record linkage is not described in the study, however unique personal identification numbers are used in Finland (66).

Morris et al. also only included patients undergoing surgery and did not include patients with complex lesions undergoing palliative surgery. The study was restricted to eight CHD diagnostic subcategories and no overall survival estimates were reported (67). Patients were identified through a survey of medical records at all Oregon hospitals that performed cardiac or thoracic surgery, based on codes related to CHD in the ICD 9th revision. Relevant medical records were then reviewed and data abstracted by two research assistants, who had undergone relevant training.

I thus found few studies with long-term follow-up, including all CHD patients and not only patients undergoing surgical treatment. Differences in birth periods of the patients studied by Samanek et al (56) and Tennant et al (65) and different exclusion criteria hamper comparison of the mortality estimates of these two studies.

Limitations of the existing literature

The following limitations only concern the studies on unselected populations. Limitations of the studies include incomplete follow up (67;65) and lacking stratification on birth periods (56;65). Furthermore, the studies on surgical patients (46)(67) do not present estimates on the entire CHD population, including patients not undergoing heart surgery.

A study using Danish population-based registries would enable complete long-term follow-up of CHD patients for up to 30 years. It would be possible to assess mortality overall as well as in a subcohort of patients undergoing heart surgery or catheter based intervention, which would provide a more comprehensive picture of the mortality and changes thereof through the last three decades. It would also be possible to describe the CHD study population with regard to ECD or chromosomal anomalies. Furthermore, such a study would provide additional knowledge on the overall mortality of Danish CHD patients, as the last nationwide study on this was published in 1980 (6).

Table 1. Studies on long term mortality in unselected CHD populations, with more than 5 years of follow up.

Author, year, country	N/ Diagnoses	Age at diagnosis or surgery	Period of treatment or birth	End of follow up	Exclusion	Study design	Controls	Outcome measure	Results
Samanek, 1999, Czech Republic	5030 / All	Diagnosed before 15 years of age	1980-1990	1995	None excluded	Time measured from birth.	None	Survival based on the Kaplan Meier estimator.	Overall survival was 77%, at 15 years of age.
Tennant, 2010, UK	4299 / All	Diagnosis before 16 years of age	1985-2003	2008	Individuals with extra cardiac defects	Time measured from birth	General population	Survival based on the Kaplan Meier estimator.	Overall survival was 90% at 20 years of age.
Nieminen, 2001, Finland	6461 / All undergoing surgical treatment	Surgery before 15 years of age	1953-1989	1998	None excluded	Time measured from the date of the first operation.	Age and sex matched general population.	Survival based on the Kaplan Meier estimator.	Overall survival was 78 %, 45 years after the date of first surgery.
Morris, 1991, USA	2701 / ASD, VSD, CoA, TOF, TGA, PDA, AS, or PS undergoing surgery	Surgery before 18 years of age	1958-1989	1989	Patients with complex lesions undergoing palliative surgery.	Time measured from the date of the first operation.	Age and sex matched general population.	Survival based on the Kaplan Meier estimator.	Overall survival ranged from 76% to 96% dependent on defect type, 25 years after the date of first surgery.

Congenital heart defects and the brain

Before proceeding to the background of the studies on psychiatric morbidity and educational attainment the following section gives a short introduction to why CHD may involve the brain.

The mechanisms behind potential brain injury in CHD patients are multifactorial and involve patient-related, intraoperative, and postoperative factors. Neurologic dysfunction may occur because of chromosomal abnormalities, associated dysgenesis of the brain, or acquired hypoxic-ischemic brain injury e.g. due to ongoing hemodynamic instability (68). The CHD may have impact upon fetal cerebrovascular blood flow distribution and this may have implications for later development of neurological sequelae (69, 70). Infants with complex CHD have brains that are smaller and structurally less mature than expected (71), and the MRI findings are similar to those from premature newborns (72). Intraoperative factors include hypoxic-ischemic reperfusion injury that may result from inadequate cerebral perfusion and metabolism, temperature alterations, and cardiogenic emboli (73). After surgery, complications such as cardiac arrest, infection, and poor cerebral perfusion can pose a risk for additional brain injury (74, 75).

The overall pattern of the symptoms of the neurological dysfunction described in the CHD population consists of mild cognitive impairment, speech and language difficulties, impaired motor skills, and attention deficit/hyperactivity disorder (76). Most studies have reported that while cognitive abilities ('Intelligence Quotient' (IQ)) of these children are generally within the normal range (in the absence of an associated brain abnormality or syndrome) group mean values are significantly less than expected (77). Parental education, IQ, and socioeconomic status are strongly associated with a child's IQ.

Study II – Psychiatric morbidity

The cognitive impairment, speech and language difficulties, and impaired motor skills observed in the CHD population are all consistent with neurodevelopmental disorders that are defined by limitations in core functional domains (e.g., motor, communication, social, academic) resulting from aberrant development of the nervous system. These deficits cross multiple disciplinary boundaries. Thus, a child displaying one or some of these deficits may be referred to e.g. a psychiatrist, a neurologist, or a paediatrician, and the clinical work up and subsequent treatment is likely to differ accordingly (78).

Attention deficit hyperactivity disorder (ADHD) observed in the CHD population is also often categorized as a neurodevelopmental disorder (79), although some authors have recently proposed a different categorisation (80). ADHD affects 8-12% of children worldwide, and results in inattention, impulsivity, and hyperactivity (81). There is some controversy about how to diagnose ADHD as seen in the differences between US diagnostic criteria for the disorder, as defined by the Diagnostic and Statistical Manual of the American Psychiatric Association (4th edition; DSM-IV), and the European diagnostic criteria for hyperkinetic disorder (HKD), as defined by the ICD-10. Both classifications include children displaying developmentally inappropriate levels of inattention, hyperactivity, and impulsivity that begin in childhood and cause impairment to school performance, intellectual functioning, social skills, driving, and occupational functioning. But the HKD criteria are more restrictive than the DSM-IV diagnosis of ADHD because they need a greater degree of symptom expression. Thus, ADHD is more prevalent than HKD (82).

Other neurodevelopmental psychiatric disorders have also been suspected of being associated with CHD, including autism (83) which is a pervasive developmental disorder, characterised by impairment in adaptive behaviour, aberrant regulation of emotion, neurological problems such as sensory/motor symptoms, epilepsy, and cognitive dysfunction. The DSM-IV and ICD-10 include autistic disorder, Asperger's syndrome, pervasive developmental disorder not otherwise specified (PDD-NOS), Rett's syndrome, and childhood disintegrative disorder as pervasive developmental disorders. The prevalence of autism spectrum disorders is approximately 60 per 10,000 children, although reported estimates vary (84).

Schizophrenia has also been associated with CHD, though not through actual observations of patients with this psychotic disorder, but through studies of genetic

syndromes implying increased risk of both CHD and schizophrenia (85). The 22q11.2 deletion syndrome, also known as velocardiofacial syndrome or DiGeorge syndrome, is the most common microdeletion genetic disorder known in human beings, occurring in at least 1:5,000 live births. It is caused by a microdeletion in the long arm of chromosome 22 and is associated with congenital malformations and cognitive deficits. One-third of all individuals with 22q11.2 deletion syndrome develop schizophrenia-like psychotic disorders (86). Psychosis is not exclusive to schizophrenia and occurs in various diagnostic categories of psychotic disorder. Symptoms of psychotic disorders can be clustered into five main categories; (i) psychosis (encompassing delusions and hallucinations - also called the positive-symptom dimension); (ii) alterations in drive and volition (lack of motivation, reduction in spontaneous speech, and social withdrawal - the negative-symptom dimension), (iii) alterations in neurocognition (difficulties in memory, attention, and executive functioning - the cognitive-symptom dimension), and (iv and v) affective dysregulation giving rise to depressive and manic (bipolar) symptoms (87).

Factors associated with mental disorders include demographic characteristics (social class, ethnicity, gender and age), predisposing factors (familial and genetic background, pregnancy and birth complications), and precipitating factors (stressful life events) (88-91).

Assessing psychopathology

The brain obviously plays a central role in the aetiology and development of psychopathology. However, due to e.g. the difficulty of characterizing the circuitry and mechanisms that underlie higher brain function, the precise neural abnormalities that underlie the different mental disorders have not yet been identified (92). The lack of biological markers for the majority of psychiatric disorders means that psychiatric diagnoses are derived through a phenomenological approach; psychiatric diagnoses are mostly made on the basis of symptoms - patients' reports of their subjective experiences - and not signs, like fever in general medicine. Moreover, there are no pathognomonic symptoms or signs (93). There are mainly two types of tests or instruments used to systematically assess psychiatric disorders; scales and schedules (88).

The scale consists of a series of questions that can be aggregated to provide an overall score. Norms have been made available, so that the scores of any individual person can be compared to population standards by age and gender. The parent-reported Child Behavior Checklist (CBCL) and parallel versions for child, youth, and teacher report are among the most commonly used scales assessing child and adolescent psychopathology. This instrument incorporates a series of questions covering a wide range of problematic behaviours. Authors often provide cut-offs for classifying a person's score as borderline or in the pathological range.

According to the schedule, based on a categorical approach, mental disorders are discrete clinical disorders that are qualitatively different from the healthy state. The Diagnostic Manual of Mental Disorders (DSM) (94) and the ICD (95) are the two diagnostic systems that list the currently recognized mental disorders and the criteria for diagnosing them (88). The Structured Clinical Interview for DSM-IV (SCID) is an example of such a schedule (88).

Assessment of psychopathology in the CHD population have both been based on patients self-report and reports from parents or teachers, so called proxy report (96). It has been noted that defensive reporting is common for the parents, and that this may lead to an incomplete picture of the behavioral symptoms of the child with CHD, potentially underestimating the extent of behavioural problems (83). However, other studies indicate, that the children with CHD report less behavioural problems than their parents (97).

While the existing studies in the CHD population are based on primary data collected for study purposes, another method relies on quantification of the study population's use of mental health care services such as psychiatric hospitalization or outpatient visits at speciality clinics. Examples include a study on the occurrence of psychiatric hospitalization among survivors of childhood cancer (98), and in a cohort of polio patients (99). This method assesses the proportion of patients whose symptoms are of such severity that the threshold of referral to mental health care has been reached. It thus relies on clinically significant mental disorders, and the diagnostic categorisation made by clinicians for clinical purposes. Various scales and schedules are implemented in the clinical diagnostic process (100)

While the reliance on clinically based diagnoses will ensure that most of the disorders included in the study are clinically significant, which is a strength of the method, herein lies also one of its limitations. Thus, the true prevalence of psychiatric disorders in a

population will be underestimated as only an incomplete proportion of those with mental health problems comes to the attention of mental health services (101). Furthermore, these studies may be affected by a referral bias as those already in contact with the health care system may be more likely to be referred to psychiatric departments.

Congenital heart defects and psychiatric disorders

Several studies have indicated increased occurrence of psychiatric morbidity among adult survivors of congenital heart defects (85, 102). In the following review of the existing literature I will focus on studies including more than one type of CHD. I used the following query to search the electronic Medline database (1966-2010) for relevant studies on psychiatric hospitalization among CHD patients;

("psychiatric hospitalization" OR "psychiatric outpatient" OR "psychiatric outcome" OR "psychiatric outcomes") AND ("Heart Defects, Congenital"[Mesh] OR "congenital heart") which yielded no results. I then searched for studies with other outcome measures of psychopathology using the following search query;

("Mental Disorders"[Mesh] OR "Psychiatry"[Mesh]) AND ("Heart Defects, Congenital"[Mesh] OR "congenital heart") AND (prognosis OR prognostic OR outcome OR "long term" OR "short term").

Some of the studies were found by manual search in reference lists. I only considered studies that compared the CHD patients with a control group or normative data. Reviews were not included.

The included studies were published from 1998 to 2009 and were conducted in either USA, Canada, or Europe. The studies have generally focused on patients undergoing surgery. Apart from one cross-sectional study (103) all the studies are follow-up studies, and the age at follow-up ranges from 1 to 32 years. Some of the studies included all types of CHD (83, 104), some included patients with a few specific CHD types (97, 105) or excluded patients with hypoplastic left heart syndrome because of an elevated risk of disability associated with this disorder (106). All studies excluded patients with congenital syndromes and some of them also excluded patients born preterm (107) or with low birth weight (104). The studies were based on a range of assessment instruments that are also used in studies on the general prevalence of psychopathology such as the Child Behaviour Checklist used to

asses emotional and behavioural problems, the Griffiths developmental scales used to assess motor function, and Wechsler Preschool and Preliminary Scale of Intelligence used to assess intelligence quotient (108, 109). This is an example of the overlap between the specialities of neurology or paediatrics, which have produced most of these studies, and psychiatry. One study used a schedule, the Structured Clinical Interview for DSM-IV (SCID) (103).

Various aspects of neurodevelopmental disorders have been examined and the findings indicate worse scores for emotional and behavioural problems (97, 105, 107), attention problems (83, 110) as well as neuromotor deficits (106, 111) compared with normative data or healthy controls. Studies examining the intelligence quotient of CHD patients found mean IQ scores in the low average range (90-94).

Van der Rijken et al found that open-heart surgery performed at school age, using full-flow cardiopulmonary bypass at moderate hypothermia did not negatively affect the children's neurocognitive functioning (112). In a later study van Rijken found that school age children with CHD awaiting their first cardiac surgery showed more neurocognitive problems compared with healthy controls, in terms of attention, motor planning and visual memory (113). Gaynor et al also found an increased occurrence of attention problems among patients with CHD compared with normative data. This study reports an increased occurrence of attention deficit hyperactivity disorder among CHD patients and also reports an increased occurrence of pervasive developmental problems suggesting possible increased occurrence of autism spectrum disorders (83). Two studies found that CHD patients do not have more behavioural problems than controls judged from self reports (97, 114). In one of these studies the parents reported increased behavioural problems in their children with CHD (97).

Limitations of existing literature

Limitations of the existing literature include small sample sizes and inclusion of patients from tertiary referral centers as well as lacking control of factors associated with neurodevelopmental disorders, such as socioeconomic factors or parental psychiatric morbidity, in the comparisons with reference populations. The psychiatric sequelae of CHD may not become apparent until adult age, but few studies have follow-up beyond preschool or school age.

The prospectively collected data of the The Danish Psychiatric Central Registry would allow me to address some of the limitations of the existing studies by providing long term follow-up of a large sample of CHD patients in a population-based study. Furthermore, I would be able to control for parental psychiatric disorders and socioeconomic factors when comparing with a healthy control cohort. Much of the literature neurodevelopmental outcomes focus on CHD patients who have undergone surgery, even though it is commonly accepted that other factors than those related to treatment may be involved in the development of impairment (115). It would be possible to extend the current knowledge by examining the risk of psychiatric disorders among CHD patients who do not undergo surgery.

Table 2 Studies on psychiatric morbidity.

Author, year, country	N	Diagnoses/age*	Study design	Exclusion	Controls	Outcome measure	Results **
Van der Rijken R, 2010, Netherlands(113)	45	Various defect types, with a wide range of complexity / 11	Follow-up	Physical and mental comorbidities, serious family problems (severe parental illness).	41 healthy controls	Neurocognitive assessment battery	+neurocognitive impairment before surgery.
Gaynor JW, 2009, USA(83)	380	HPLS, TOF, VSD, TGA, misc. / 4-5	Follow-up	Multiple congenital anomalies, genetic or phenotypic syndrome.	Normative data	CBCL, WPPSI,PLS-4, NEPSY, ADHDRating scale, PKBS	+Pervasive developmental problems +Attention problems
Kovacs, 2009, Canada, USA (103)	280	Various defect types, with a wide range of complexity / 32	Cross sectional	-	Published data on general US population	SCID	+Mood disorders
Frederiksen 2009, Norway(114)	488	Various defect types, with a wide range of complexity / 11-16	Follow up	Serious mental disorders	Published data on healthy children	CBCL, Youth Self Report	-Behavioural problems
Van der Rijken R, 2008, Netherlands (112)	43	Various defect types, with a wide range of complexity / 6-16	Follow-up	Physical and mental comorbidities, serious family problems (severe parental illness).	Same patients after surgery.	Neurocognitive assessment battery	=neurocognitive function =Behavioural problems =Emotional problems Before and one year after surgery at school age.
Majnemer A, 2008, Canada (107)	94	TGA, TOF, VSD, UVH, DORV/ 5	Follow-up	HLHS, preterm, perinatal asphyxia, brain malformation, chromosomal anomalies	Normative data	CBCL, WPPSI, PPVT, VABS, WeeFIM	+ Low intelligence + Behavioural problems +Attention problems + Functional limitations
Spijkerboer, 2008, Netherlands (97)	125	ASD, VSD, PS, TGA / 7-17	Follow-up	Syndromes of mental retardation	Normative data	CBCL, Youth Self Report	Parent report: +emotional problems +behavioural problems Self report: =behavioural
Hövels-Gürich HH, 2007, Germany (105)	40	TOF, VSD / 7.4	Follow-up	-	Normative data	CBCL (German version)	+ Behavioural problems
Miatton (104) M, 2007, Belgium	43	"spectrum of CHD" / 8.6	Follow up	Birth weight <2000g, non cardiac malformations or genetic abnormalities	43 healthy controls	WISC, NEPSY	+Mild motor deficits +Language problems +Low intelligence

Continued....

Hövels-Gürich HH, 2007, Germany (110)	40	TOF, VSD / 7.4	Follow-up	-	20 healthy controls	ANT, CBCL	+Attention dysfunction
Majnemer, 2006, Canada(106)	94	TGA, TOF, VSD, UVH, DORV / 5	Follow-up	Chromosomal anomalies, perinatal asphyxia, HLHS	Normative data	PDMS	+Delayed neuromotor development
Van rijen, 2005, Netherlands (116)	251	ASD, VSD, TOF, TGA, PS / 20-32	Follow-up	Mentally handicapped	1441 population controls	Young Adult Self Report, Young Adult Behaviour Checklist	+Emotional and behavioural problems.
Dittrich H, 2003, Germany (117)	90	TGA, CoA, ASD, VSD, TOF, misc. / 1	Follow-up	Perinatal factors, brain malformation, Downs, DiGeorge	20 healthy controls (some with mild ASD or VSD)	Griffiths	+ Neurodevelopmental delay
Limperopulos, 2002,Canada (118)	98	Cyanotic and acyanotic / 1.6	Follow-up	HLHS, brain malformations, genetic syndromes	Normative data	Griffiths developmental scales, PDMS	+Neurologic, motor , and developmental deficits
Wray,1999,UK (119)	25	Cyanotic and acyanotic / 1.5	Follow-up	Mental handicap	Normative data / 15 healthy controls	Griffiths developmental scales, semistructured interview (behaviour).	+Developmental and cognitive deficits
Utens, 1998, Netherlands (120)	166	ASD, VSD, TOF, TGA, PS/21.7	Follow-up	Downs syndrome	Normative data	Young Adult Self Report, Groninger Intelligence test	+Problem behaviour

ASD: Atrial Septal defect. **ADHD:** Attention Deficit Hyperactivity Disorder. **ANT:** Attention Network Test. **CBCL:** Child Behaviour Checklist. **CoA:** Coarctatio of the aorta. **DORV:** Double outlet right ventricle. **HLHS:** Hypoplastic Left Heart Syndrome. **NEPSY:** Neuropsychological Assessment. **PDMS:** Peabody Developmental Motor Scale. **PKBS:** Preschool and Kinder garden Behaviour Scale. **PLS-4:** Preschool Language Scale. **PPVT:** Peabody Picture Vocabulary Test. **PS:** Pulmonary Stenosis. **SCID:** Structured Clinical Interview for DSM-IV Axis 1 Disorder. **TGA:** Transposition of the great arteries. **TOF:** Tetralogy of Fallot. **UVH:** Univentricular heart. **VABS:** Vineland Adaptive Behaviour Scale. **VSD:** Ventricular Septal Defect. **WeeFIM:** Functional Independence Measure for Children. **WISC:** Wechsler Intelligence Scale for Children-3rd edition, Dutch version. **WPPSI:** Wechsler Preschool and Primary Scale of Intelligence.

*Mean age or age range in years . **+ indicates worse scores among CHD patients compared with normative data or controls, = indicates normal range, - indicates lower scores.

Study III – Educational achievement

Neurocognitive deficits may remain unrecognized until school age when increasing demands may reveal former unrecognized subtle deficits. Specific neurocognitive disabilities potentially affecting educational attainment include language problems and motor skills. Around 30% to 60% of classroom activities involve fine motor skills, including handwriting (106). Thus, educational attainment may be a more sensitive measure of neurocognitive deficits than preschool tests (115). This measure may also provide additional information on the actual impact of these deficits on daily living in terms of functional limitations (121). However, several factors may affect an individual's educational achievement apart from neurocognitive abilities including motivation, socioeconomic factors, encouragement etc. Therefore, educational achievement reflects several aspects of life.

Several studies have reported on school performance, learning disabilities, grade retention and need of remedial services of CHD patients. Mitchell et al, in an American study, found that school performance of approximately 300 patients who had undergone the Fontan procedure was average or above average for most patients, as assessed by their parents. The study did not include a control group (122). Shillingford et al (123) found that 18% of a group of 109 patients having undergone surgery for complex CHD had repeated a grade, according to their parents. Only half of these patients received no school support, and 15% had been placed into a full time special education. In a group of patients with total anomalous pulmonary venous connection (n=45), 27% were in special education classes or had repeated grades, 69% attended regular education with average or above average performance, based on parent report (124).

Existing literature

I wanted to examine the impact of CHD on educational achievements, specifically on the educational levels completed, and on the time used to complete educations. I used the following query to search the electronic Medline database (1966-2010) for relevant studies on educational attainment among CHD patients;

"Heart Defects, Congenital"[Mesh] AND ("Educational Status"[Mesh] OR "educational attainment" OR "educational level" OR "academic status" OR "academic attainment" OR "academic level"). This search strategy yielded 58 studies. Five of these included patients

with a broad range of CHD types and comparison with population based controls or data on the general population (Table 3).

The studies that only included surgically treated patients display conflicting results. Nieminen et al (125) and Ternestedt et al (126) found that the educational level of CHD patients is comparable to or higher than expected in the general population in Finland and Sweden. Van Rijen et al found that the highest educational level completed by CHD patients in the Netherlands was more often a lower level compared with the reference group (47 vs. 39%, $p<0.01$) (127). Two studies that also included patients who did not undergo surgery found decreased educational attainments of CHD patients (128, 129).

Table 3 Studies on educational achievement of CHD patients, with special focus attainment of educational levels.

Author, year, country	N	Diagnoses/age*/ Surgery	Study design	Exclusion	Controls	Outcome measure	Results
Nieminen, 2003, Finland (125)	2896	Various defect types, with a wide range of complexity/31.7/yes	Follow up	No exclusion	Data on the genral population from Statistics Finland	Compulsory, vocational (vocational school or high school), and university degree.	The educational profile of patients is comparable to the expected in the general population.
Van Rijen, 2003, Netherlands(1 27)	362	ASD, VSD, TOF, TGA, PS/20-39/yes	Follow up	Mentally handicapped	Normative data from the Netherlands Central Bureau of Statistics	Lower, average, higher educational attainment.	Highest educational level completed was more often a lower level compared with the reference group (47 vs. 39%, $p<0.01$)
Ternstedt, 2001, Sweden(126)	32	TOF, ASD/34-44/yes	Follow up	No exclusion	Published data on average educational level in Sweden	Compulsory school, Upper secondary school, university degree.	Average educational level higher than average level in Sweden.
Kokkonen, 1992, Finland (128)	71	Various defect types, with a wide range of complexity/22.1/yes and no	Follow up	Mental retardation	211 population controls	Elementary school, High school, Vocational education, University	3 % studied at university level compared with 17 % of controls.
Nuutinen, 1989, Finland (129)	50	Various defect types, with a wide range of complexity/14/yes and no	Follow up	Downs syndrome	Remainder of birth cohort	School class level at age 14.	7.1% attended a class lower than their age would have required compared with 3.8% of controls. 4% not attending school. 0.5% in comparison cohort.

Limitations of existing literature

Nieminen et al (125) based their study on self report data from mailed questionnaires with a response rate of 76% percent. Thus, the study was susceptible to selection bias if those who did respond were better educated than non-responders. Interpretation of the studies on educational achievement is further hampered by small sample sizes, follow-up ending after basic schooling, and failure to control for socioeconomic factors related to educational attainment.

A population-based study with complete long-term follow-up regarding attainment of educational levels would add to the current knowledge regarding the functional abilities of CHD patients, beyond school age. This would be possible to conduct using socioeconomic registries from Statistics Denmark.

Hypotheses and aims

The overall aim of the following thesis was to examine the long-term prognosis of Danish patients with congenital heart defects. The specific hypotheses and aims were addressed in three studies:

Study 1:

Hypothesis: congenital heart defect patients have higher long-term mortality than the background population, and their long term survival has improved during the last 30 years.

Aim: to examine the long term mortality of congenital heart defect patients compared with a population based comparison cohort.

Study 2:

Hypothesis: the risk of psychiatric disorders is increased for congenital heart defect patients.

Aim: to examine the risk of psychiatric in- or outpatient admissions among patients with congenital heart defects compared with a population based comparison cohort.

Study 3:

Hypothesis: the ability of CHD patients to obtain an education may be reduced in the long term.

Aim: to examine the educational achievements of congenital heart defect patients compared with a population based comparison cohort.

Subjects and methods

Data sources

The Danish Civil Registration System

The Danish Civil Registration System has kept electronic records on gender, date of birth, change of address, date of emigration, and changes in vital status since 1968. The records carry a unique 10-digit civil registration number, assigned to every Danish citizen and used in all Danish registries, enabling unambiguous linkage among them (130, 131).

The National Patient Registry

This registry, established in 1977, holds data on all hospitalizations from all Danish non-psychiatric hospitals, including dates of admission and discharge, procedure(s) performed, and up to 20 discharge diagnoses assigned by the treating physician and coded according to the ICD 8th revision (ICD-8) until the end of 1993, and 10th revision (ICD-10) thereafter. Visits to emergency departments and outpatient clinics have also been recorded since 1995 (132).

The Integrated Database for Labour Market Research (IDA)

The IDA database was established in 1980 and is administered by Statistics Denmark. It consists of more than 250 variables characterizing the educational level of the Danish population and the population's attachment to the labour market. All Danish citizens are characterized by data on their education, family and household, employment, and income. The data are supplied by tax authorities, educational institutions, and employment services. The IDA database is updated annually (133).

The Danish Psychiatric Central Registry

This nationwide registry contains computerized data on all admissions to psychiatric hospitals or psychiatric wards in general hospitals. Since January 1, 1995 information on all outpatient contacts has been included in addition to inpatient data. The main variables are; civil registration number, admission and discharge dates, and all discharge diagnoses (ICD-8 until the end of 1993, and ICD-10 thereafter). The registry covers both adult and pediatric contacts (134).

Danish Medical Birth Registry

Since 1973, the Danish medical Birth Registry has kept records of all births in Denmark, including home births. Data in the registry were obtained from birth notifications filled in by midwives, and since 1995 data has been transferred electronically from The National Patient Registry. The variables include the civil registration number for mother and child (for live-born children), date and place of birth, birth weight, gestational age, and whether a congenital abnormality was present at time of birth (there are no data on specific type of abnormality) (135).

Variable definitions

Congenital heart defect

The ICD-8 codes used to identify CHD patients in The National Patient Registry were 746-747 (except for 746.7 and 747.5-747.9, which were not specific to CHD) and ICD-10 codes Q20-Q26 (except for Q26.5-Q26.6 which were not specific to CHD).

Diagnoses of patent ductus arteriosus were only considered for infants with gestational age ≥ 37 weeks (136). To increase validity I did not include patients who were only seen at outpatient clinics or patients with only hospital admissions in which CHD was coded as a secondary diagnosis. However, should such a patient at any time during follow-up receive an inpatient, primary CHD diagnosis he or she would be included.

I assigned each patient one CHD diagnostic code, i.e. the first primary discharge diagnosis of CHD. I subsequently grouped ICD-10 diagnostic codes according to the corresponding ICD-8 diagnostic codes, to uniformly categorize the study cohort during the study period (Table 4).

Table 4. Diagnostic categories with corresponding ICD-8 and ICD-10 codes

Diagnostic category		ICD-8 codes	ICD-10 codes
Common arterial trunk		7460	Q200
Transposition of great vessels		7461	Q203, Q205
Tetralogy of Fallot		7462	Q213
Ventricular septal defect		7463	Q210
Atrial septal defect		7464	Q211
Atrioventricular septal defect		7465, 74641	Q212, Q218B
Anomalies of heart valve		7466	Q220-Q229, Q230-Q239
Other	Other specified anomalies of heart	7468	Q201, Q202, Q204, Q206, Q208, Q209, Q214, Q218, Q219, Q240-Q248
	Unspecified anomalies of heart	7469	Q249
Patent ductus arteriosus		7470	Q250
Coarctation of aorta		7471	Q251
Other anomalies of great arteries	Other anomalies of aorta	7472	Q252-Q254
	Stenosis or atresia of pulmonary artery	7473	Q255-Q256
			Q257-Q259
Malformations of great veins		7474	Q260-Q264, Q268-Q269

Outcomes

Mortality

The date of death was obtained in the Civil Registration System.

Educational achievement

Using the Integrated Database for Labour Market Research I generated variables indicating the year of completion of the following educational levels (with the corresponding International Standard Classification of Education [ISCED] level (137); basic schooling (9 or 10 years of compulsory education) (ISCED level 2); youth education (ISCED level 3), including upper secondary school and vocational education (the latter leading to jobs such as skilled craftsman or assistant nurse); higher education, designated as short-cycle (ISCED level 4), leading to jobs such as programmer or laboratory technician, medium-cycle (ISCED level 5), leading to jobs such as primary school teacher or nurse, and long-cycle (ISCED level 5), leading to jobs such as attorney or physician.

Psychiatric morbidity

I generated an indicator of the date of first hospital admissions for psychiatric care or attendance at outpatient psychiatric clinics of the study subjects using the Danish Psychiatric Central Registry. Outcomes included any psychiatric diagnosis (F.00-F.99) and specific psychiatric disorders of special interest in the CHD population: psychotic disorders (F.20-F.29) (86), pervasive developmental disorders (F.84) (83), specific developmental disorders of speech, motor function and learning (F.80-F.83) (111), ADHD (F.90) (83), and mental retardation of any degree (F.70-F.79).

Covariates

Extra-cardiac defects, chromosomal abnormalities

I used the following codes to identify diagnoses of extra-cardiac defects (ECD) and chromosomal abnormalities in the National Patient Registry: ICD-8: 310.40-310.41, 310.5, 311.40-311.41, 311.5, 312.40-312.41, 312.5, 313.40-313.41, 313.5, 314.40-314.41, 314.5, 315.40-315.41, 315.5, 740.99-759.99 and ICD-10: DQ00.0-DQ99.9. According to a guideline from the European Surveillance of Congenital Anomalies (Eurocat), I disregarded isolated minor defects such as subluxation or unstable hip, cryptorchidism torticollis, or protuberant ears (138).

Preterm birth

I obtained data on gestational age from the National Medical Birth Registry and defined preterm birth as gestational age < 37 weeks.

Surgery or catheter-based intervention

I identified procedure codes of cardiac intervention in the National Patient Registry. Several procedure codes covered both heart surgery and catheter-based therapeutic interventions. It was therefore not possible to readily distinguish between surgery and catheter-based interventions (139).

Study design

Study populations

The studies of the thesis are all cohort studies. All studies were conducted within the entire Danish population (approximately 5.3 million) and were based on population-based Danish medical and administrative registries. The Danish National Health Service provides tax-supported health care for all inhabitants, guaranteeing free access to general practitioners and hospitals (140).

The following patients were included:

- Study I:
 - CHD patients born from January 1, 1977 to January 1, 2006 who were diagnosed with CHD before the age of one year.
- Study II,
 - Patients diagnosed at any age who were born between January 1, 1977 and January 1, 2002 and were alive on January 1, 1995 or later. I excluded those who had a psychiatric diagnosis before study entry. This was to avoid prevalent cases at start of follow up.
- Study III
 - CHD patients born from January 1, 1977 to January 1, 1991 who were diagnosed at any age before and alive at the age of 13 years.

I used the Civil Registration System to identify comparison cohorts. In the mortality study (Study I) I identified all Danes without a primary discharge diagnosis of CHD, born from January 1, 1977 to January 1, 2006 as a comparison cohort. In the study on psychiatric morbidity (Study II) and the education study (Study III) I identified a population based sample of 10 persons per patient matched on gender and year of birth. In study II I excluded patients and their controls diagnosed with any psychiatric disorder before the beginning of the study period on January 1, 1995 from the analysis. I did this

to avoid prevalent cases of psychiatric disease, as they would make it difficult to distinguish between an effect on prognosis or risk of psychiatric disorders.

Follow-up

In the mortality study (Study I), patients were followed from birth until death, emigration or January 1, 2007, whichever came first. In the analyses regarding patients undergoing surgery or catheter-based intervention, follow-up started at discharge after the first therapeutic procedure.

In the study on psychiatric morbidity (Study II), follow-up started on January 1, 1995 or on time of CHD diagnosis, if CHD was diagnosed after January 1, 1995. Persons were followed until first psychiatric diagnosis or until death, emigration or the end of the study period, whichever came first. Follow-up started at discharge after the first procedure in the analysis regarding patients undergoing surgery or catheter-based intervention. Each CHD patient's control persons, matched on gender and year of birth, were followed with delayed entry at the same date as the CHD patient.

In the education study (Study III), person-years at risk were calculated based on a prespecified age preceding the earliest age at which each educational level could be completed. Persons were followed until the level of education under investigation was attained or until death, emigration or the end of the study period, whichever came first.

Confounding

In the mortality study (Study I), I compared the mortality of patients born in different birth periods across a time span during which development of diagnostic abilities had most likely lead to an increased detection of mild CHDs. I therefore considered the proportion of mild CHDs as a potential confounder.

In the study on psychiatric disorders (Study II), I considered parental psychiatric morbidity as a potential confounder (88). Parental psychiatric morbidity was defined by presence of any psychiatric diagnosis before the birth date of the CHD patient or control individual. I restricted this indicator to diagnoses occurring before the birth of a child with CHD because having a critically ill child is likely to increase

parental risk of psychiatric morbidity. I also regarded socioeconomic background to be a potential confounder, and identified parental educational level (basic, youth, or higher education) using the Integrated Database for Labour Market Research.

In the study on educational attainment (Study III), I considered parental education (basic, youth, or higher), parental income (low, medium, high, very high), number of siblings, “broken family” (that is having lived with a single parent at any time before age 15 years) as potential confounders as these factors were previously found to be associated with educational attainment (141).

In Study II and III, I repeated analyses after restriction to a subcohort of CHD patients and controls without ECD or chromosomal anomalies. I did this in an attempt to examine the effect of CHD independent of ECD and preterm birth. However, preterm birth could be considered to be an intermediate step in the causal pathway from CHD to psychiatric morbidity or educational attainment. Adjusting for an intermediate step in the analysis may conceal the effect of the exposure, CHD. Therefore, I chose to present result both before and after restriction to the subcohort without ECD and born at term.

In all three studies age and gender were also considered as potential confounders.

Statistical analysis

I chose to use survival analysis in Study II and III because I was looking at long-term outcomes and thus differences in follow-up time between CHD patients and controls due to e.g. emigration or death were likely. Survival analysis based on person time at risk is able to handle this, as opposed to analysis based on proportions of person in each cohort experiencing an event. By using survival analysis I also took full advantage of the longitudinal nature of the available data as differences in time-to-event, between CHD patients and comparison cohort, were reflected in the relative risk estimates. This is of obvious relevance in Study I, where the timing of the outcome event, death, is the key issue and not just whether death occurred or not (we probably all die some day). But it would also be of great importance if educational attainment is delayed due to e.g. grade retention, or if psychiatric disorders develop at an earlier age, among CHD patients than in the comparison cohort.

Cox proportional hazards regression is a time-to-event analysis that enables estimation of the hazard ratio (HR), while adjusting for potential confounders. I interpreted the HR as an estimate of the relative risk. The assumption of proportional hazards, implying that the HR is constant during follow-up, was graphically verified. In the education study (Study III), we used discrete time Cox regression because the outcome was recorded at the same time for all subjects at the end of the year and we used calendar time as the underlying time axis.

In studies of outcomes occurring after several years, censoring due to emigration is expected and outcomes may also be subject to competing risks, that is, competing events which prevent the outcome of interest from happening. This may lead to overestimation of the cumulative incidence if this is based on the Kaplan Meier estimate.

In Study I, all cause mortality was the outcome. In study II, the cumulative incidence of psychiatric admissions was estimated in a population with high mortality and was therefore subject to competing risks. I therefore computed the cumulative incidence of psychiatric admissions at 15 years of age assuming death to be a competing risk (142).

Analyses were performed using the Stata[®] 10.1 package (StataCorp LP, Texas, US) (Study I and II) and SAS[®] software (version 9.2; Institute Inc., NC, USA) (Study III).

Results

Study I – Mortality

We identified 6646 CHD patients, 1559 (23%) had VSD and 5-7% had TGA, TOF, ASD, AVSD, CoA, or PDA, respectively. Overall, approximately one out of five had ECDs or chromosomal anomalies and 11% were born preterm.

Proportion undergoing invasive treatment

Fifty two percent of the CHD patients received invasive treatment (surgery and/or catheter-based procedure) and as expected the proportion of treated patients was closely associated with the type of CHD. The highest treatment rates were found in patients diagnosed with TOF, CoA, AVSD, and TGA. The proportion of patients undergoing treatment in infancy increased during the study period; approximately 20% of the patients from the period 1977-1986 received invasive treatment in infancy compared with 60% of the patients from the most recent period (1997-2005).

Mortality

In this cohort of patients diagnosed with CHD before the age of 1 year, one-fifth died within the first year of life. Mortality remained high throughout the follow-up period; an additional 5% died before reaching the age of 10 years and further 3% died between 10 and 25 years of age. In the comparison cohort (the remaining Danish population) only 0.6% died as infants and an additional 0.7% had died by the age of 25 years. Mortality varied by type of CHD, and presence of ECD or chromosomal abnormalities (Table 5).

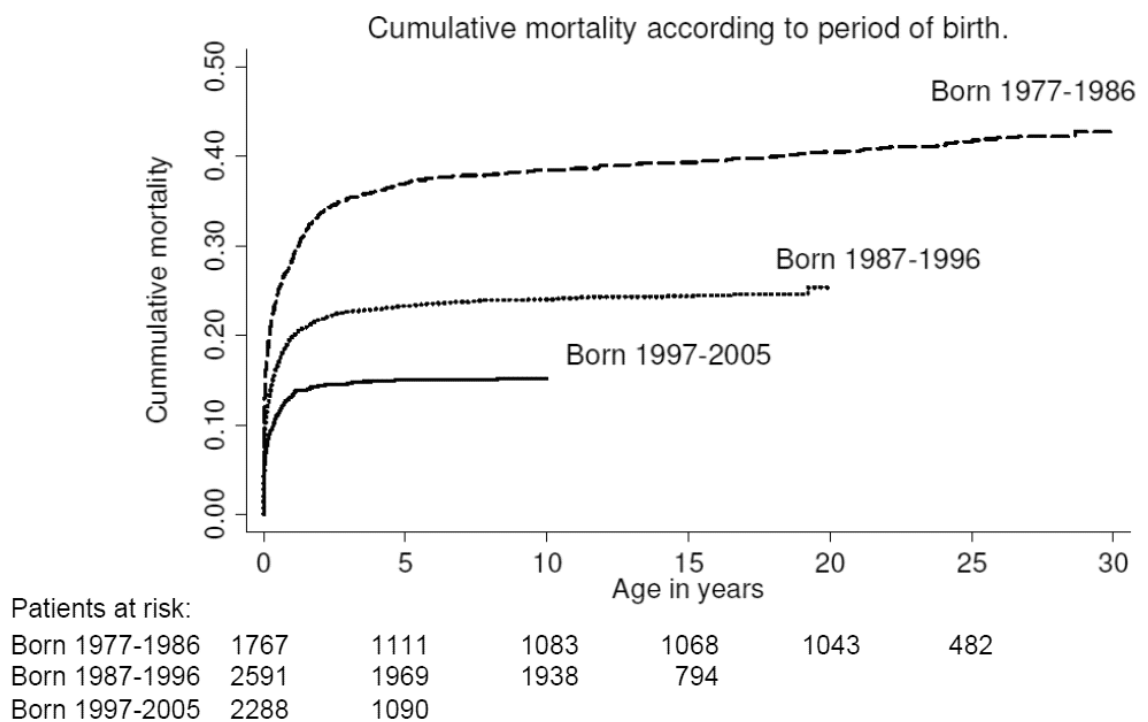
Table 5. Cumulative mortality proportion at 1, 10, and 25 years of age based on the Kaplan Meier estimator. The mortality proportions at one year of age are presented both for the entire study population (born 1977-2005) and for patients born during 1997-2005 (*italic type*).

	CMP ₁ (95% CI)	CMP ₁₀ (95% CI)	CMP ₂₅ (95% CI)
Danish population	0.6% (0.6-0.6)	0.8% (0.7-0.8)	1.3% (1.3-1.3)
All CHD	20% (19-21) <i>13% (12-15)</i>	25% (24-26)	28% (27-30)
Diagnostic category			
Common arterial trunk	55% (45-66) <i>27% (14-46)</i>	55% (45-66)	55% (45-66)
Transposition of great arteries*	26% (22-30) <i>19% (14-25)</i>	38% (33-42)	50% (41-59)
Tetralogy of Fallot	17% (13-21) <i>9% (6-15)</i>	30% (26-35)	33% (26-42)
Ventricular septal defect	6% (5-7) <i>3% (2-5)</i>	10% (8.3-11)	11% (9.0-13)
Atrial septal defect	7% (4.7-10) <i>4% (2-8)</i>	9% (6.4-12)	16% (8.8-28)
Atrioventricular septal defect	25% (21-30) <i>21% (16-29)</i>	35% (30-41)	41% (35-49)
Anomalies of heart valve	34% (30-38) <i>32% (27-38)</i>	38% (34-42)	60% (31-89)
Other anomalies of heart	27% (26-29) <i>24% (16-35)</i>	32% (30-34)	35% (33-37)
Patent ductus arteriosus	6% (4-10) <i>2% (1-7)</i>	10% (6.8-14)	10% (6.8-14)
Coarctation of aorta	16% (13-21) <i>4% (2-9)</i>	18% (15-23)	27% (18-39)
Other anomalies of great arteries	32% (25-39) <i>17% (14-22)</i>	37% (30-44)	37% (30-44)
Malformations of great veins	36% (23-53) <i>26% (13-47)</i>	36% (23-53)	-
Extra-cardiac defect or chromosomal anomalies**			
No	20% (18-21) <i>13% (11-14)</i>	24% (23-25)	27% (26-28)
Yes	21% (19-24) <i>16% (13-19)</i>	31% (28-34)	36% (32-41)

Among the patients born in the early period (1977-1986) who underwent a cardiac therapeutic intervention during this period 30% (95% CI: 27-34) died within one year after the first intervention. In comparison, only 12% (95% CI: 10-14) died within one year after the first intervention in the late period (1997-2005). The decrease in postoperative mortality was reflected in a drop in the mortality of the overall cohort;

thus, during the study period the overall cumulative mortality at the age of one year dropped from 28% (95% CI: 26-31) in the early period to 13% (95% CI: 12-15) in the most recent period (Figure 1).

Figure 1. Cumulative mortality of congenital heart defect patients diagnosed before one year of age, according to period of birth.



Study II – Psychiatric morbidity

The overall cumulative incidence of psychiatric admission or outpatient clinic visit of CHD patients at age 15 years was 5.85% (95% CI: 5.15-6.61). The overall HR for psychiatric admission or outpatient clinic visit among CHD patients compared with the control cohort was 1.60 (95% CI: 1.44-1.77) and the risk of admissions for both psychotic disorders, developmental disorders, ADHD, and mental retardation of any degree was also increased among CHD patient (Table 6).

The risk of psychiatric disorders was increased for CHD patients compared with the control cohort in the younger age group (0-14 years) independent of the need for surgery or catheter-based intervention (Table 7). Patients who did not undergo surgery or catheter-based intervention were at increased risk in the older age group as well, compared with the control cohort [adjusted HR: 1.34 (95% CI: (1.08-1.66)]. Both male and female CHD patients under age 15 were at increased risk of psychiatric disorders [adjusted male HR: 1.76 (95% CI: 1.48-2.09), adjusted female HR: 2.49 (95% CI: 2.00-3.11)]. Male CHD patients aged 15-30 years were also at increased risk of psychiatric disorders [adjusted HR: 1.57 (95% CI: 1.22-2.01)]. In contrast, we did not observe an elevated risk of psychiatric disorders in female patients aged 15-30 years, compared with the control cohort [adjusted HR: 1.04 (95% CI: 0.84-1.30)]. When patients and controls with ECD or syndromes, and those born preterm, were excluded from the analysis, the estimates were not substantially changed, although some reduction of risk was seen in the younger age group below 15 years (Table 7).

Table 6. Cumulative incidence and hazard ratios of psychiatric in- or outpatient admission for specific psychiatric disorders among congenital heart defect patients compared with the population control cohort. Data are presented for all study subjects and for a subgroup of patients and control cohort members born at term without extracardiac defects.

	Hazard ratio (95% confidence interval)*		15-year cumulative incidence, % (95% confidence interval)
	All	No extra-cardiac defect [†] and born at term	All
Any psychiatric disorder	1.60(1.44-1.77)	1.41(1.24-1.60)	5.85(5.15-6.61)
Psychotic disorders (e.g. schizophrenia)	1.44(0.99-2.11)	1.57(1.04-2.37)	0.09(0.03-0.24)
Pervasive developmental disorders (e.g. autism spectrum disorders)	2.01(1.49-2.72)	1.66(1.13-2.45)	0.96(0.71-1.29)
Specific developmental disorders (speech, motor, and learning disorders)	1.47(0.93-2.33)	1.17(0.65-2.11)	0.47(0.30-0.72)
Attention deficit hyperactivity disorder	1.80(1.31-2.48)	1.64(1.11-2.42)	0.91(0.67-1.22)
Mental retardation (mild to severe)	6.18(4.54-8.40)	4.25(2.78-6.50)	1.17(0.89-1.53)

*Adjusted for: paternal psychiatric disorder, maternal psychiatric disorder, paternal educational level, and maternal educational level. [†]Including syndromes and chromosomal anomalies.

Table 7. Hazard ratios of psychiatric in- or outpatient admission among congenital heart defect patients compared with the population control cohort by age, gender, and surgery or catheter-based intervention. Data are presented for all study subjects and for a subgroup of patients and control cohort members born at term without extra-cardiac defects.

	Hazard ratio by age group in years (95% confidence interval)*			
	All		No extra-cardiac defect [†] and born at term	
	<15 years	15-30 years	<15 years	15-30 years
All	1.99(1.73-2.27)	1.22(1.04-1.44)	1.61(1.35-1.91)	1.21(1.00-1.46)
Gender				
Male	1.76(1.48-2.03)	1.57(1.22-2.01)	1.47(1.19-1.83)	1.54(1.15-2.06)
Female	2.49(2.00-3.10)	1.04(0.84-1.30)	1.89(1.42-2.51)	1.06(0.83-1.35)
Surgery or catheter- based intervention				
Yes	2.22(1.86-2.65)	1.15(0.90-1.48)	1.64(1.29-2.08)	1.05(0.78-1.41)
No	1.72(1.41-2.10)	1.34(1.08-1.66)	1.55(1.22-1.98)	1.41(1.11-1.78)

*Adjusted for: paternal psychiatric disorder, maternal psychiatric disorder, paternal educational level, maternal educational level. †Including syndromes and chromosomal anomalies.

Study III – Educational achievement

Of the CHD patients born between 1977 and 1991, 2,986 were alive at the age of 13 years. The proportion of patients born with ECD or chromosomal abnormalities (19%) or born preterm (8%) was higher in the CHD cohort than in the comparison cohort (4% and 4%, respectively).

The proportion of all CHD patients who completed basic schooling (85.0%) was lower than the corresponding proportion in the comparison cohort (87.5%) (adjusted HR: 0.79 (95% CI: 0.75-0.82)). Also in the subcohort, after excluding persons born with ECD or chromosomal abnormalities or born preterm, the probability of attaining basic school education among CHD patients was lower than that for the comparison cohort [adjusted HR: 0.87 (95% CI: 0.83-0.92)]. We repeated this analysis after grouping some of the patients as severe CHDs (including common arterial trunk, transposition of great vessels, tetralogy of Fallot, atrioventricular septal defect, anomalies of heart valve, other malformations of great arteries, and malformations of great veins) and as moderate severity CHDs (ventricular septal defect, atrial septal defect, patent ductus arteriosus, and coarctation of aorta). CHD patients in both subgroups had a lower probability of attaining basic schooling than controls and the estimates did not differ according to severity (severe CHDs: adjusted HR: 0.87 (95% CI: 0.76-1.00), moderate severity CHDs: HR: 0.92 (95% CI: 0.85-1.00)).

Among patients who completed a basic schooling, the proportion then completing a youth education was lower among CHD patients (57.8%) than in the comparison cohort (67.4%) [adjusted HR: 0.76 (95% CI: 0.72-0.81)]. The lower probability of attaining a youth education held in the subcohort analysis, due to differences in attainment of upper secondary school education [adjusted HR: 0.80 (95% CI: 0.73-0.86)] but not vocational education [adjusted HR: 1.03 (95% CI: 0.87-1.25)]. Among patients completing youth education, the probability of then attaining a higher education was lower overall than that for the comparison cohort [adjusted HR: 0.92 (95% CI: 0.79-1.07)]. However, the probability of completing a short-cycle higher education was not reduced in the patient cohort compared with controls [adjusted HR: 1.08 (95% CI: 0.79-1.48)] (Table 8)

Table 8. Educational attainment of all CHD patients and the subcohort excluding patients born preterm or with ECD.

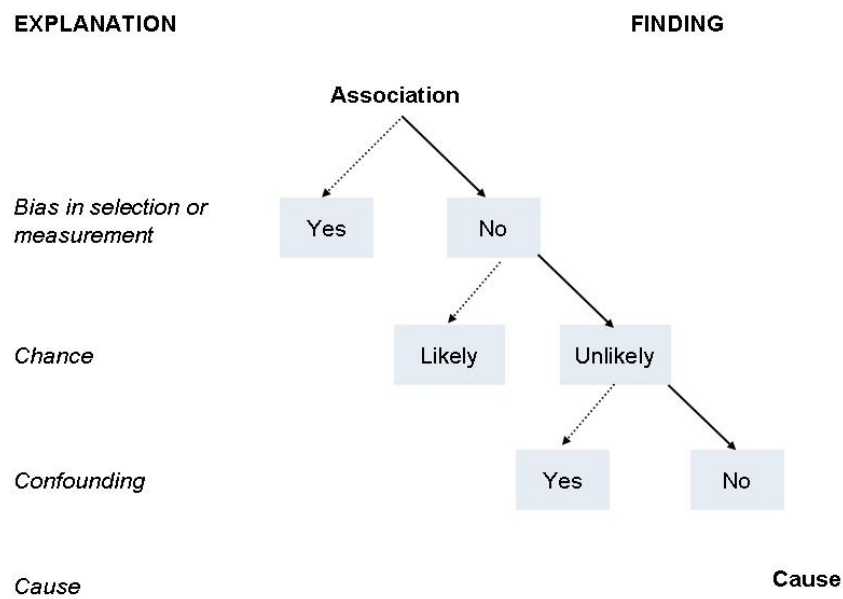
Educational level		All patients				After exclusion of individuals born preterm or with ECD or chromosomal anomalies			
		Number at risk (n)*	Proportion who completed education (%)	Median age at completion (Years)	Hazard ratio, adjusted (95% CI) [§]	Number at risk (n)*	Proportion who completed education (%)	Median age at completion (Years)	Hazard ratio, adjusted (95% CI) [§]
Basic school (Born before 1991) [†]	Comparison cohort	29,246	87.5	16.5	1	26,904	87.6	16.5	1
	CHD patients	2,986	85.0	16.6	0.79(0.75-0.82)	2,260	86.6	16.6	0.87(0.83-0.92)
Youth education (Born before 1987) [†]									
<i>Overall</i>	Comparison cohort	20,531	67.4	20.4	1	18,923	68.0	20.4	1
	CHD patients	2,072	57.8	20.6	0.76(0.72-0.81)	1,617	62.3	20.6	0.83(0.78-0.89)
<i>Upper sec.</i>	Comparison cohort	20,531	48.1	20.1	1	18,923	48.7	20.1	1
	CHD patients	2,072	38.8	20.3	0.74(0.69-0.80)	1,617	41.8	20.2	0.80(0.73-0.86)
<i>Vocational</i>	Comparison cohort	20,531	24.7	22.1	1	18,923	24.8	22.1	1
	CHD patients	2,072	24.1	22.2	0.94(0.79-1.12)	1,617	26.6	22.3	1.03(0.87-1.25)
Higher education (Born before 1982) [†]									
<i>Overall</i>	Comparison cohort	8,554	31.1	25.3	1	7,982	31.3	25.3	1
	CHD patients	770	26.9	25.1	0.88(0.76-1.01)	657	28.3	25.1	0.92(0.79-1.07)
<i>Short-cycle</i>	Comparison cohort	8,554	6.46	24.5	1	7,982	6.5	24.5	1
	CHD patients	770	6.10	23.8	0.98(0.72-1.32)	657	6.7	23.8	1.08(0.79-1.48)
<i>Medium-cycle</i>	Comparison cohort	8,554	11.2	25.8	1	7,982	11.2	25.8	1
	CHD patients	770	8.8	25.8	0.82(0.64-1.05)	657	9.3	25.8	0.82(0.64-1.05)
<i>Lon- cycle</i>	Comparison cohort	8,554	14.1	25.1	1	7,982	14.3	25.1	1
	CHD patients	770	12.3	24.9	0.89(0.72-1.11)	657	12.8	25.1	0.91(0.73-1.14)

*Conditional on being alive at age 13. Results are also conditional on completion of basic school before youth education and completion of youth education before higher education. † Restrictions based on birth year were made to enable attainment of educational level within the study period. § Adjusted for current age, sex, parental income, number of siblings, having a single parent, and parents' highest educational level. CI: Confidence interval. ECD: Extra-cardiac defect.

Methodological considerations

When interpreting the results of the thesis it is necessary to consider whether they reflect artifacts arising from bias or random variation, and not causal mechanisms (Figure 2).

Figure 2. Possible explanations of an observed association (20).



Selection bias

Selection bias is present when the association between exposure and outcome differs between subjects actually eligible for analysis and those theoretically eligible (143). It may occur both when identifying the patients to be included in the studies and during the follow-up period. I used population-based registries with data collected independently of my study hypotheses. To increase the validity of the exposure I only included CHD patients if the CHD was a primary diagnosis and not an additional diagnosis. This may have introduced selection bias, if patients with an additional discharge diagnosis of CHD differed from patients included in the study with regard to mortality, education, and psychiatric morbidity. Thus preterm infants who die shortly after birth will receive a primary discharge diagnosis stating the main cause of death, which may very well be prematurity/immaturity or respiratory collapse and not the CHD that such an infant may have. In Study I, this may have lead us to underestimate the

mortality of CHD patients. The restriction to patients with a primary discharge diagnosis of the condition in question is widely applied in research based on administrative data (144).

Lack of information on individuals who died with undiagnosed CHD would also cause selection bias if these individuals differed from those with diagnosed CHD with regard to the probability of experiencing the outcomes.

Losses to follow-up may introduce selection bias if the association between exposure and outcome differs between those lost to follow up and those remaining in the study. With the virtually complete follow-up provided by the Civil Registration System, the Integrated Database for Labour Market Research, and the Danish Psychiatric Central Registry regarding all three outcomes of death, educational attainment, and psychiatric admissions or outpatient contacts selection bias due to loss to follow-up is not expected to affect our result (131).

Information bias

Information bias is a consequence of measurement error or misclassification. Much of the data used in the studies of this thesis are collected for administrative purposes and not for research. While these secondary data sources provide great potential for research at a relatively low cost (32), the effect of misclassification on our findings needs to be considered. Misclassification can either be non-differential with the measurement error evenly distributed between comparison groups, or differential with an uneven distribution of the error among the comparison groups. Non-differential misclassification of a dichotomous exposure and/or outcome will most likely bias the association toward the null, if the classification errors of exposure and outcome are independent (145). Differential misclassifications lead to systematic error resulting in an over- or underestimation of the true association. In the studies of this thesis any misclassification of exposure (CHD) and outcome (death, specific educational level, or psychiatric diagnosis) is assumed to be independent.

Misclassification of the CHD diagnosis

The positive predictive value of a CHD diagnosis in The National Patient Registry is reported to be approximately 90% (146), and any misclassification is assumed to be non-differential. Thus, in the mortality study (Study I) the degree of misclassification of

the exposure status, CHD or not, is assumed to have been the same whether patients later died or not. Therefore, misclassification cannot explain the increased mortality of CHD patients compared with the general population. However, defect specific estimates of cumulative mortality may be biased due to misclassification of the defect type. Thus, mortality estimates specific to mild defect categories such as ASD, may be biased in an upward direction because some of the patients may have had multiple defects, but I categorized patients according to their first primary discharge diagnosis. On the other hand, some of the patients in the ASD category may have had very mild defects, of no hemodynamic significance, which would bias the mortality estimates downward.

In the education study (Study II) and the study on psychiatric morbidity (Study III), misclassification of CHD status was most likely the same whether patients later attained specific educational levels or experienced psychiatric admissions, or not. The associations found in these studies are therefore not a result of misclassification of CHD status.

Misclassification of the outcomes

The registration of dates of death in the Civil Registration System is considered to be virtually without error (130). The validity of the Danish Psychiatric Central Registry is considered to be high, reflected in validation studies regarding diagnoses such as schizophrenia, affective psychoses, and childhood autism (147, 148). If CHD patients were more likely to be referred to psychiatric treatment because they were already in contact with the health care system, I would overestimate their relative risk of psychiatric disorders compared with controls. However, given previous research showing an increased risk of neurodevelopmental disorders (83, 107, 111) and psychological maladjustment (149, 150), as well as the strength of the associations in our study, I do not believe that this potential weakness can explain the increased occurrence of psychiatric admissions that I found among CHD patients compared with the comparison cohort. On the other hand, psychiatric admission is only a proxy measure for actual psychiatric disorder, and it is likely to underestimate the true occurrence of psychiatric disorders. The validity of the Integrated Database for Labour Market Research is considered to be high, and any misclassification would have been non-differential according to CHD status. Misclassification of attainment of specific educational levels or not is therefore not likely to explain the associations found in our education study (study III).

Confounding

Confounding means mixing of effects and implies that the effect of the study exposure is mixed with - or masked by - the effect of an extraneous variable, leading to bias (143).

In the mortality study (Study I), I compared mortality in the early and late birth period. I adjusted for gender in the regression analysis and controlled for age by making it the underlying time scale. Furthermore, I stratified the analysis according to defect type. However, residual confounding is likely in this analysis due to the rather crude categorization of CHD types. Thus, mortality rate ratios in the strata of relatively mild defects such as ventricular septal defects and atrial septal defects are probably still confounded, and thereby overestimate the decrease in mortality. This is due to the higher proportion of mild defects being diagnosed in the late birth period compared with in the early birth period. In the strata of relatively severe defects, such as TOF and transposition of the great arteries, the confounding due to improved diagnostics is probably less pronounced. The severity of these defects would have led to a high detection rate, also in the early birth period. I do not expect that abortions due to prenatal investigations have led to a substantial decrease in the prevalence of severe CHD during the study period (10), and this would to some extent have been controlled for in the type specific analysis.

When studying the risk of psychiatric disorders among CHD patients compared with population controls I adjusted for parents' educational level and parental psychiatric morbidity. The aetiology of psychiatric disorders is poorly understood, and thus, unknown risk factors are potentially associated with CHD.

In our education study (study III), I adjusted for parental education (basic, youth or higher), parental income (low, medium, high, very high), number of siblings, "broken family" (that is having lived with a single parent at some time before age 15 years) as these factors were previously found to be associated with educational attainment (141). I had no information on personal motivation or other personal characteristics that may affect educational attainment.

Although prematurity may be viewed as an intermediate steps in the causal pathway from CHD to psychiatric disorders or educational attainment, I chose to repeat analyses after restriction to a subcohort without ECD and born at term. However, in this analysis residual confounding from prematurity may still occur, as prematurity was categorized as a dichotomous variable.

Discussion

In this thesis I used population-based administrative registries to investigate the prognosis of CHD patients. I was limited by the rather crude categorization of CHD types provided by the ICD, which among other factors hampered the presentation of data in a way that would readily enable patient counselling regarding CHD type specific prognosis. However, the registries enabled very long and complete follow-up of unselected populations.

Study I – Mortality

Multiple studies have examined the long-term mortality of CHD patients undergoing surgery for selected defects, at single centers. Our study provide population-based long-term mortality estimates for Danish CHD patients, including those not undergoing surgery and those with ECD or chromosomal anomalies.

In a population-based Czech study that, equivalent to our study, included all CHD patients both with and without surgery or catheter-based intervention, Samanek et al. classified complex CHDs according to the malformation that dominated in the pathological hemodynamics (56). The overall one- and ten-year mortality of CHD patients in this study population that was born from 1980 to 1990 (20% and 23%) was comparable to our findings. However, one year mortality rates for specific defects such as TGA (38.4%), AVSD (37.8%), and CoA (32.0%) were higher than our estimates. Despite the similarities, the Czech study is not directly comparable to ours due to differences in study period and age at diagnosis of CHD. Thus, Samanek et al included all patients diagnosed at any age up to 15 years which may explain that the proportion of patients with VSD and ASD was higher (41.6% and 8.7 % respectively) compared with our study.

Nieminen et al found that the overall late survival of CHD patients, who had undergone surgery, decreased from the 1950s to the 1980s because more children with complicated CHDs underwent surgery in the last decades, and were operated at a younger age (151). In contrast to this, I saw an increase in survival among patients undergoing therapeutic interventions during the years from 1977 to 2007, including survival specific to patients with TGA, TOF, and AVSD (data not shown). This difference may reflect that I covered a later calendar period in our study, and thus, more experience regarding surgery for complex CHD had been gained.

Study II – Psychiatric morbidity

To our knowledge, this is the first study to examine clinically verified psychiatric disorders among CHD patients. It extends the findings of former studies that reported an increased risk of neurodevelopmental impairment and behavioural problems among patients with CHD, by providing population-based estimates of the long-term cumulative incidence of admissions due to psychiatric disorders in the CHD population, including estimates specific to pervasive and specific developmental disorders and ADHD that have all been associated with CHD in single center studies.

Possible mechanisms underlying risk of psychopathology among CHD patients include patient-related factors such as genetic syndromes (85) and preterm birth (90). However, I also identified an association between CHD and psychiatric disorders after excluding patients with these characteristics. Abnormal intrauterine blood flow among patients with complex CHD (69), as well as white matter lesions (72) or cerebral hypoxia, may also impair neurological development and increase the risk of psychiatric disorders (91, 152). Treatment-related factors that may cause neurological damage include cerebral embolization (153) or reduced cerebral blood flow due to inadequate cardiopulmonary bypass technique (74). These factors do not, however, explain the increased risk of psychiatric disorders found among CHD patients who did not undergo surgical treatment. As need for surgery is related to CHD severity, this finding also indicates that severity of CHD is not strongly related to the risk of psychiatric disorders. Accordingly, Hövels-Gürich et al (105) noted that children with TOF are not at increased risk of behavioral problems compared with children with ventricular septal defects, in a study of children undergoing cardiac surgery. The results from a study of children with a range of cyanotic and acyanotic defects, who underwent either corrective or palliative surgery, highlight the sometimes larger relevance of family processes (e.g. parenting style, maternal mental health and worry), rather than disease or surgical factors, in predicting behavioral outcomes in particular in this context (154). Thus, interactions among several biological and psychological risk factors are likely.

Study III – Educational achievement

I found a lower probability of completing basic and upper secondary school among CHD patients compared with a population-based control cohort. For all CHD patients who had completed youth education, the likelihood of completing a medium or long cycle higher education was also lower than that for population controls.

Our study findings extend previous research on this topic (125-127, 129, 155, 156). Thus, it is well known that CHD is associated with neurodevelopmental impairment that may affect educational abilities (76, 157). However, knowledge on the long-term educational attainment of CHD patients beyond basic school is limited. According to our data, even patients who have obtained a youth education may have a lower probability of educational attainment than controls.

In line with our results, van Rijen et al found lower than expected educational achievement in a study among adult Dutch patients with a wide range of CHD diagnostic categories, after exclusion of mentally retarded patients (127). In contrast to our findings, Nieminen et al found that the educational level among CHD patients was comparable to that of the general population in a Finnish nation-wide study encompassing all CHD diagnostic categories (125). However, this study was based on self-reports from CHD patients, with a response rate of 76%, using data from Statistics Finland on the educational level of the general population as a comparison. It was thus susceptible to both information and selection biases and did not control for socioeconomic variables.

In this study I focused on attainment of different educational levels, but other relevant outcomes could have been considered as measures of educational difficulties in the CHD population such as performance on standardized tests, grade retention, and need for remedial or special services (123)(124). We did not have access to data on standardized test, or special education services. With regard to grade retention, this would be reflected by the relative probability estimates of our present study owing to the time-to-event analysis performed.

Main conclusions

Study I – Mortality

Mortality among Danish congenital heart defect patients decreased during recent decades, but it was high compared with the general population. This was also true for patients more than ten years of age, emphasizing the need for long-term medical follow-up of this growing patient population.

Study II – Psychiatric morbidity

I identified increased risks of psychiatric disorders among male and female CHD patients below 15 years of age, and among male patients aged over 15 years, compared with a population control cohort. Patients who did not undergo surgery or catheter-based interventions were also at increased risk. When patients and controls with ECD or chromosomal abnormalities and those born preterm were excluded, the risk was still elevated. Nonetheless, the majority of CHD patients appear to have a favorable mental health prognosis.

Study III – Educational achievement

I found an association between CHD and a reduced probability of completing basic and upper secondary school as well as medium- and long-cycle higher education. Attainment of vocational and short-cycle higher education did not differ among CHD patients and their controls.

Perspectives

The mortality among patients with CHD diagnosed before one year of age was elevated compared with the general population among patients above 10 years of age. This emphasizes the need for long-term medical follow-up of this patient population. Surgical procedures for non-cardiac diseases, pregnancy and child birth are important physical challenges that this cohort of patients face in their future life and little is known about the impact on mortality and morbidity. Future studies might examine the incidence of non-cardiac morbidity in CHD patients and its potential impact on late mortality.

Our finding of an association between CHD and clinically-verified psychiatric disease may have clinical implications. Our data may reflect a lower threshold for referring this patient group to mental health care services. More likely, patients may benefit from increased attention to this matter. The fact that there was no difference between surgically treated patients and the remaining patients may suggest that the pathogenesis could be found in underlying genetic defects or in the psychological setting of having a potentially life-threatening disease (154).

The reduced probability of educational attainment found among CHD patients in our study population underlines that these patients experience limitations. I did not examine the extent to which special educational services were already offered to CHD patients. This issue may be a subject for further research.

I found that the Danish population-based registries are valuable data sources for studies on long-term prognosis in particular. The unique potential for long-term follow-up and data linkage enables research regarding multiple aspects of the prognosis of this growing patient population. Further development of the CHD classification in this registry, based on e.g. medical record review or application of procedures codes, would improve the applicability of the data.

Summary

Congenital heart defects (CHD) occur in around 6-10 per 1,000 live births and are among the most frequent congenital anomalies. During recent decades there have been major improvements in the diagnostic possibilities and in the medical and surgical treatment of CHD patients, and the population of adults living with CHD is increasing. More knowledge on the long-term mortality of CHD patients is important to evaluate treatment results beyond in-hospital mortality, to evaluate the need for additional long-term medical follow-up, and to provide information to the patients and their parents.

Along with the improved treatment results there has been a gradual shift in focus from the heart to the brain. The mechanisms behind potential neurologic dysfunction in CHD patients are multi-factorial and include chromosomal abnormalities, associated dysgenesis of the brain, or acquired hypoxic-ischemic brain injury. Studies including a wide range of CHD types have reported an association between CHD and neurodevelopmental impairment as well as behavioural and emotional problems. No studies have examined the occurrence of clinically verified psychiatric disorders. Knowledge on this would increase our understanding of the clinical course of CHD and facilitate the prevention or treatment of potential mental health problems.

The potential neurologic dysfunction might affect the educational attainment of CHD patients. The findings of existing studies are conflicting. More knowledge on the long-term educational outcome is needed to provide appropriate care and follow-up, and to better understand the effect of CHDs on the brain as well as the extend of potential functional limitations.

The aims of this thesis were to examine the long-term prognosis of CHD patients compared with a population-based control cohort with regard to long-term mortality (Study I), psychiatric morbidity (Study II), and educational attainments from basic schooling to higher education (Study III).

The studies are cohort studies based on data from Danish nation-wide administrative registries. In Study I, I found that mortality among Danish CHD patients decreased during recent decades. Yet, mortality was high compared with the general population, also among patients more than ten years of age. This emphasizes the need for long-term medical follow-up of this growing patient population. In Study II, I found an

increased risk of psychiatric disorders among CHD patients compared with a population control cohort. Patients who did not undergo surgery or catheter-based interventions were also at increased risk. Also, when patients and controls with extra-cardiac defects or chromosomal abnormalities and those born preterm were excluded, the risk was still elevated. Nonetheless, the majority of CHD patients appear to have a favorable mental health prognosis. In Study III, I found an association between CHD and a reduced probability of completing basic and upper secondary school as well as medium- and long-cycle higher education. Attainment of vocational and short-cycle higher education did not differ among CHD patients and their controls.

In summary, I found that the survival of CHD patients has markedly improved. I also found that CHD patients have an increased risk of psychiatric morbidity and a reduced probability of educational attainment.

Danish summary

Medfødte hjertefejl (MH) findes hos cirka 6-10 per 1.000 levende fødte børn og udgør den hyppigste gruppe af medfødte misdannelser. I løbet af de seneste årtier er der sket store fremskridt inden for diagnostik samt medicinsk og kirurgisk behandling af patienter med MH, og populationen af voksne, der lever med MH, er stigende. Mere viden om MH patienters mortalitet på lang sigt er vigtig for at kunne vurdere kvaliteten af behandlingen og eventuelle behov for yderligere lægelig opfølgning og for at kunne informere patienter og pårørende.

Samtidig med de forbedrede behandlingsresultater er fokus gradvist flyttet fra MH patienternes hjerte til hjernen. Adskillige faktorer kan potentielt føre til påvirkning af funktionen af hjernen hos patienter med MH og de omfatter kromosomfejl, samtidige medfødte misdannelser af hjernen og erhvervet hjerneskade grundet iltmangel. Studier vedrørende patienter med en bred vifte af forskellige typer MH har rapporteret en association mellem MH og hæmmet neurologisk udvikling samt adfærdsmæssige og følelsesmæssige problemer. Ingen studier har undersøgt forekomsten af klinisk diagnosticeret psykiatrisk sygdom. Viden herom vil øge vor forståelse af sygdommen MH og forbedre mulighederne for forebyggelse og behandling af potentiel psykisk sygdom.

Den potentielt påvirkede funktion af hjernen hos MH patienter fører muligvis til nedsat uddannelsesmæssig formåen. De eksisterende studier på området er modstridende. Mere viden om langtidsprognosen vedrørende uddannelse er nødvendig for at sikre optimal varetagelse af patienternes behov og for bedre at forstå MHs potentielle påvirkning af hjernen.

Formålet med denne afhandling var at undersøge langtidsprognosen for patienter med MH sammenlignet med en populationsbaseret kontrol kohorte med hensyn til henholdsvis mortalitet (Studie I), psykisk sygdom (Studie II) og uddannelsesniveau (Studie III).

Studierne er kohortestudier baseret på data fra danske landsdækkende administrative registre. I Studie I fandt vi, at mortaliteten blandt danske patienter med MH faldt over de seneste 30 år. Men sammenlignet med baggrundsbefolkningen var mortaliteten høj, også blandt mere end 10 år gamle patienter. Dette understreger behovet for langsigtet medicinsk opfølgning af denne voksende patient population. I Studie II fandt vi en forhøjet risiko for psykiatrisk sygdom blandt patienter med MH. Patienter, der ikke havde fået foretaget kirurgi eller kateterbaseret behandling af deres hjertefejl, havde også en forhøjet

risiko. Det samme gjorde sig gældende, når patienter og personer i kontrol kohorten, der var født for tidligt eller med andre medfødte misdannelser end hjertefejlen eller med kromosomfejl, blev ekskluderet fra analysen. Størstedelen af patienter med MH lever dog tilsyneladende uden psykiatrisk sygdom. I Studie III fandt vi en nedsat sandsynlighed for at gennemføre folkeskole, gymnasiale uddannelser samt mellem- og længerevarende højere uddannelser blandt patienter med MH. Sandsynligheden for opnåelse af erhvervsfaglige uddannelser samt korterevarende højere uddannelser var ikke nedsat.

Sammenfattende fandt vi at overlevelsen for patienter med MH er forbedret betydeligt. Vi fandt også at denne patientgruppe har en øget risiko for psykiatrisk sygdom og en nedsat sandsynlighed for at opnå en uddannelse.

References

1. Mitchell SC, Korones SB, Berendes HW. Congenital Heart Disease in 56,109 Births Incidence and Natural History. *Circulation* 1971;43:323-32.
2. Brickner ME, Hillis LD, Lange RA. Congenital heart disease in adults. First of two parts. *N Engl J Med* 2000;342:256-63.
3. Brickner ME, Hillis LD, Lange RA. Congenital heart disease in adults. Second of two parts. *N Engl J Med* 2000;342:334-42.
4. Camm AJ, Lscher TF, Serruys PW, European Society of Cardiology. The ESC textbook of cardiovascular medicine. /20;2nd ed.
5. Hoffman JIE, Kaplan S. The incidence of congenital heart disease. *Journal of the American College of Cardiology* 2002;39:1890-900.
6. Laursen HB. Some epidemiological aspects of congenital heart disease in Denmark. *Acta Paediatr Scand* 1980;69:619-24.
7. Dadvand P, Rankin J, Shirley MD, Rushton S, Pless-Mulloli T. Descriptive epidemiology of congenital heart disease in Northern England. *Paediatr Perinat Epidemiol* 2009;23:58-65.
8. Øyen N, Poulsen G, Boyd HA, Wohlfahrt J, Jensen PKA, Melbye M. National time trends in congenital heart defects, Denmark, 1977-2005. *American Heart Journal* 2009;157:467-73.
9. Garne E. Congenital heart defects -- occurrence, surgery and prognosis in a Danish County. *Scand Cardiovasc J* 2004;38:357-62.
10. UK EUROCAT Central registry. Prevalence data tables 1980-2007. Available at: <http://www.eurocat-network.eu/>. 2010.
11. Werler M. Additional insights into the etiology of cardiac anomalies. *Epidemiology* 2001;12:482-4.

12. Samanek M. Children with congenital heart disease: probability of natural survival. *Pediatr Cardiol* 1992;13:152-8.
13. Wood JC. Anatomical assessment of congenital heart disease. *J Cardiovasc Magn Reson* 2006;8:595-606.
14. Olley PM, Coceani F, Bodach E. E-type prostaglandins: a new emergency therapy for certain cyanotic congenital heart malformations. *Circulation* 1976;53:728-31.
15. Andrews RE, Tulloh RMR. Interventional cardiac catheterisation in congenital heart disease. *Archives of Disease in Childhood* 2004;89:1168-73.
16. Sideris EB, Macuil B, Justiniano S, Rao PS. Total percutaneous correction of a tetralogy of Fallot variant with dominant pulmonary valve stenosis. *Heart* 2005;91:345-7.
17. Beels L, Bacher K, De Wolf D, Werbrouck J, Thierens H. {gamma}-H2AX Foci as a Biomarker for Patient X-Ray Exposure in Pediatric Cardiac Catheterization: Are We Underestimating Radiation Risks? *Circulation* 2009;120:1903-9.
18. Schultz AH, Wernovsky G. Late outcomes in patients with surgically treated congenital heart disease. *Pediatric Cardiac Surgery Annual* 2005;8:145-56.
19. Mahle WT, Spray TL, Wernovsky G, Gaynor JW, Clark III BJ. Survival after reconstructive surgery for hypoplastic left heart syndrome: A 15-year experience from a single institution. *Circulation* 2000;102.
20. Fletcher RH, Wagner EH, Fletcher SW. *Clinical epidemiology the essentials*. 3rd ed ed. Baltimore: Williams & Wilkins, 1996.
21. Altman DG. Systematic reviews in health care: Systematic reviews of evaluations of prognostic variables. *BMJ* 2001;323:224-8.
22. Hemingway H. Prognosis research: Why is Dr. Lydgate still waiting? *Journal of Clinical Epidemiology* 2006;59:1229-38.
23. Sackett DL, Haynes RB, Tugwell P. *Clinical epidemiology a basic science for clinical medicine*. 1st ed ed. Boston: Little, Brown, 1985.

24. Jacobs J, Jacobs M, Lacour-Gayet F, et al. Stratification of Complexity Improves the Utility and Accuracy of Outcomes Analysis in a Multi-Institutional Congenital Heart Surgery Database: Application of the Risk Adjustment in Congenital Heart Surgery (RACHS-1) and Aristotle Systems in the Society of Thoracic Surgeons (STS) Congenital Heart Surgery Database. *Pediatric Cardiology* 2009;30:1117-30.
25. Lacour-Gayet F, Jacobs JP, Clarke DR, et al. Performance of surgery for congenital heart disease: Shall we wait a generation or look for different statistics? *Journal of Thoracic and Cardiovascular Surgery* 2005;130:234-5.
26. Jenkins KJ, Gauvreau K, Newburger JW, Spray TL, Moller JH, Iezzoni LI. Consensus-based method for risk adjustment for surgery for congenital heart disease. *Journal of Thoracic and Cardiovascular Surgery* 2002;123:110-8.
27. Larsen SH, Pedersen J, Jacobsen J, Johnsen SP, Hansen OK, Hjortdal V. The RACHS-1 risk categories reflect mortality and length of stay in a Danish population of children operated for congenital heart disease. *European Journal of Cardio-Thoracic Surgery* 2005;28:877-81.
28. O'Brien SM, Clarke DR, Jacobs JP, et al. An empirically based tool for analyzing mortality associated with congenital heart surgery. *The Journal of Thoracic and Cardiovascular Surgery* 2009;138:1139-53.
29. Franklin RCG, Jacobs JP, Krogmann ON, et al. Nomenclature for congenital and paediatric cardiac disease: Historical perspectives and The International Pediatric and Congenital Cardiac Code. *Cardiology in the Young* 2008;18:70-80.
30. Olsen J, Basso O, Sorensen HT. What is a population-based registry? *Scand J Public Health* 1999;27:78.
31. Meberg A, Otterstad JE, Froland G, Sorland S, Nitter-Hauge S. Increasing incidence of ventricular septal defects caused by improved detection rate. *Acta Paediatrica, International Journal of Paediatrics* 1994;83:653-7.
32. Sorensen HT, Sabroe S, Olsen J. A framework for evaluation of secondary data sources for epidemiological research. *Int J Epidemiol* 1996;25:435-42.
33. Hoffman JIE, Kaplan S, Liberthson RR. Prevalence of congenital heart disease. *American Heart Journal* 2004;147:425-39.

34. Wren C, O'Sullivan JJ. Survival with congenital heart disease and need for follow up in adult life. *Heart* 2001;85:438-43.
35. Marelli AJ, Mackie AS, Ionescu-Ittu R, Rahme E, Pilote L. Congenital heart disease in the general population: Changing prevalence and age distribution. *Circulation* 2007;115:163-72.
36. Engelfriet P, Boersma E, Oechslin E, et al. The spectrum of adult congenital heart disease in Europe: Morbidity and mortality in a 5 year follow-up period - The Euro Heart Survey on adult congenital heart disease. *Eur Heart J* 2005;26:2325-33.
37. Bouchardy J, Therrien J, Pilote L, et al. Atrial Arrhythmias in Adults With Congenital Heart Disease. *Circulation* 2009;120:1679-86.
38. Opatowsky AR, Siddiqi OK, Webb GD. Trends in Hospitalizations for Adults With Congenital Heart Disease in the U.S. *Journal of the American College of Cardiology* 2009;54:460-7.
39. Kaemmerer H, Bauer U, Pensl U, et al. Management of Emergencies in Adults With Congenital Cardiac Disease. *The American Journal of Cardiology* 2008;101:521-5.
40. The Task Force on the Management of Grown Up Congenital Heart Disease of the European Society of Cardiology, Task Fm, Deanfield J, et al. Management of Grown Up Congenital Heart Disease. *Eur Heart J* 2003;24:1035-84.
41. Silka MJ, Hardy BG, Menashe VD, Morris CD. A population-based prospective evaluation of risk of sudden cardiac death after operation for common congenital heart defects. *Journal of the American College of Cardiology* 1998;32:245-51.
42. Muhll IV, Cumming G, Gatzoulis MA. Risky business: Insuring adults with congenital heart disease. *Eur Heart J* 2003;24:1595-600.
43. Engelfriet P, Meijboom F, Boersma E, Tijssen J, Mulder B. Repaired and open atrial septal defects type II in adulthood: An epidemiological study of a large European cohort. *International Journal of Cardiology* 2008;126:379-85.
44. Verheugt CL, Uiterwaal CSPM, Grobbee DE, Mulder BJM. Long-term prognosis of congenital heart defects: A systematic review. *International Journal of Cardiology* In Press, Corrected Proof.

45. Roos-Hesselink JW, Meijboom FJ, Spitaels SEC, et al. Excellent survival and low incidence of arrhythmias, stroke and heart failure long-term after surgical ASD closure at young age. *Eur Heart J* 2003;24:190-7.
46. Nieminen HP, Jokinen EV, Sairanen HI. Late Results of Pediatric Cardiac Surgery in Finland: A Population-Based Study With 96% Follow-Up. *Circulation* 2001;104:570-5.
47. Gatzoulis MA, Freeman MA, Siu SC, Webb GD, Harris L. Atrial Arrhythmia after Surgical Closure of Atrial Septal Defects in Adults. *N Engl J Med* 1999;340:839-46.
48. M Oliver J, Gallego P, González A, Benito F, Mesa JM, Sobrino JA. Predisposing conditions for atrial fibrillation in atrial septal defect with and without operative closure. *American Journal of Cardiology* 2002;89:39-43.
49. Roos-Hesselink JW, Meijboom FJ, Spitaels SEC, et al. Outcome of patients after surgical closure of ventricular septal defect at young age: Longitudinal follow-up of 22-34 years. *Eur Heart J* 2004;25:1057-62.
50. Roos-Hesselink JW, Meijboom FJ, Spitaels SEC, et al. Long-term outcome after surgery for pulmonary stenosis (a longitudinal study of 22-33 years). *Eur Heart J* 2006;27:482-8.
51. Earing MG, Connolly HM, Dearani JA, Ammass NM, Grogan M, Warnes CA. Long-term Follow-up of Patients After Surgical Treatment for Isolated Pulmonary Valve Stenosis. *Mayo Clinic Proceedings* 2005;80:871-6.
52. Bacha EA, Scheule AM, Zurakowski D, et al. Long-term results after early primary repair of tetralogy of Fallot. *Journal of Thoracic and Cardiovascular Surgery* 2001;122:154-61.
53. Reid GJ, Webb GD, Barzel M, McCrindle BW, Irvine MJ, Siu SC. *Journal of the American College of Cardiology* 2006;48:349-55.
54. Nørgaard MA, Lauridsen P, Helvind M, Pettersson G. Twenty-to-thirty-seven-year follow-up after repair for Tetralogy of Fallot. *European Journal of Cardio-Thoracic Surgery* 1999;16:125-30.
55. Nollert G, Fischlein T, Bouterwek S, Böhm C, Klinner W, Reichart B. Long-Term Survival in Patients With Repair of Tetralogy of Fallot: 36-Year Follow-Up of 490

Survivors of the First Year After Surgical Repair. *Journal of the American College of Cardiology* 1997;30:1374-83.

56. Samanek M, Voriskova M. Congenital heart disease among 815,569 children born between 1980 and 1990 and their 15-year survival: a prospective Bohemia survival study. *Pediatr Cardiol* 1999;20:411-7.
57. Høimyr H, Christensen TD, Emmertsen K, et al. Surgical repair of coarctation of the aorta: up to 40 years of follow-up. *European Journal of Cardio-Thoracic Surgery* 2006;30:910-6.
58. Blalock A, HANLON CR. The surgical treatment of complete transposition of the aorta and the pulmonary artery. *Surg Gynecol Obstet* 1950;90:1-15, illust.
59. Rashkind WJ, Miller WW. Creation of an atrial septal defect without thoracotomy. A palliative approach to complete transposition of the great arteries. *JAMA* 1966;196:991-2.
60. Jatene AD, Fontes VF, Paulista PP, et al. Anatomic correction of transposition of the great vessels. *J Thorac Cardiovasc Surg* 1976;72:364-70.
61. Lange R, Horer J, Kostolny M, et al. Presence of a Ventricular Septal Defect and the Mustard Operation Are Risk Factors for Late Mortality After the Atrial Switch Operation: Thirty Years of Follow-Up in 417 Patients at a Single Center. *Circulation* 2006;114:1905-13.
62. Moons P, Gewillig M, Sluysmans T, et al. Long term outcome up to 30 years after the Mustard or Senning operation: a nationwide multicentre study in Belgium. *Heart* 2004;90:307-13.
63. Boneva RS, Botto LD, Moore CA, Yang Q, Correa A, Erickson JD. Mortality Associated With Congenital Heart Defects in the United States : Trends and Racial Disparities, 1979-1997. *Circulation* 2001;103:2376-81.
64. Pillutla P, Shetty KD, Foster E. Mortality associated with adult congenital heart disease: Trends in the US population from 1979 to 2005. *American Heart Journal* 2009;158:874-9.
65. Tennant PW, Pearce MS, Bythell M, Rankin J. 20-year survival of children born with congenital anomalies: a population-based study. *The Lancet* 2010;375:649-56.

66. Brenner H, Hakulinen T. Implications of incomplete registration of deaths on long-term survival estimates from population-based cancer registries. *Int J Cancer* 2009;125:432-7.
67. Morris CD, Menashe VD. 25-year mortality after surgical repair of congenital heart defect in childhood. A population-based cohort study. *JAMA* 1991;266:3447-52.
68. Ballweg J, Wernovsky G, Gaynor J. Neurodevelopmental Outcomes Following Congenital Heart Surgery. *Pediatric Cardiology* 2007;28:126-33.
69. Kaltman JR, Di H, Tian Z, Rychik J. Impact of congenital heart disease on cerebrovascular blood flow dynamics in the fetus. *Ultrasound Obstet Gynecol* 2005;25:32-6.
70. Limperopoulos C. Disorders of the Fetal Circulation and the Fetal Brain. *Clinics in Perinatology* 2009;36:561-77.
71. Licht DJ, Shera DM, Clancy RR, et al. Brain maturation is delayed in infants with complex congenital heart defects. *The Journal of Thoracic and Cardiovascular Surgery* 2009;137:529-37.
72. Miller SP, McQuillen PS, Hamrick S, et al. Abnormal brain development in newborns with congenital heart disease. *N Engl J Med* 2007;357:1928-38.
73. Chen J, Zimmerman RA, Jarvik GP, et al. Perioperative Stroke in Infants Undergoing Open Heart Operations for Congenital Heart Disease. *The Annals of Thoracic Surgery* 2009;88:823-9.
74. Hsia TY, Gruber PJ. Factors Influencing Neurologic Outcome After Neonatal Cardiopulmonary Bypass: What We Can and Cannot Control. *The Annals of Thoracic Surgery* 2006;81:S2381-S2388.
75. Majnemer A, Limperopoulos C, Shevell MI, Rohlicek C, Rosenblatt B, Tchervenkova C. A New Look at Outcomes of Infants With Congenital Heart Disease. *Pediatric Neurology* 2009;40:197-204.
76. Wernovsky G, Shillingford AJ, Gaynor JW. Central nervous system outcomes in children with complex congenital heart disease. [Miscellaneous]. *Current Opinion in Cardiology* 2005;20:94-9.

77. Forbess JM, Visconti KJ, Hancock-Friesen C, Howe RC, Bellinger DC, Jonas RA. Neurodevelopmental Outcome After Congenital Heart Surgery: Results From an Institutional Registry. *Circulation* 2002;106:I-95.
78. Reiss AL. Childhood developmental disorders: an academic and clinical convergence point for psychiatry, neurology, psychology and pediatrics. *J Child Psychol Psychiatry* 2009;50:87-98.
79. Rutter M, Kim-Cohen J, Maughan B. Continuities and discontinuities in psychopathology between childhood and adult life. *J Child Psychol Psychiatry* 2006;47:276-95.
80. Andrews G, Pine DS, Hobbs MJ, Anderson TM, Sunderland M. Neurodevelopmental disorders: cluster 2 of the proposed meta-structure for DSM-V and ICD-11. *Psychol Med* 2009;39:2013-23.
81. Faraone SV, Sergeant J, Gillberg C, Biederman J. The worldwide prevalence of ADHD: is it an American condition? *World Psychiatry* 2003;2:104-13.
82. Biederman J, Faraone SV. Attention-deficit hyperactivity disorder. *The Lancet* 2005;366:237-48.
83. Gaynor JW, Nord AS, Wernovsky G, et al. Apolipoprotein E genotype modifies the risk of behavior problems after infant cardiac surgery. *Pediatrics* 2009;124:241-50.
84. Levy SE, Mandell DS, Schultz RT. Autism. *The Lancet* 2009;374:1627-38.
85. Murphy KC, Jones LA, Owen MJ. High rates of schizophrenia in adults with velo-cardio-facial syndrome. *Arch Gen Psychiatry* 1999;56:940-5.
86. Gothelf D, Feinstein C, Thompson T, et al. Risk Factors for the Emergence of Psychotic Disorders in Adolescents With 22q11.2 Deletion Syndrome. *Am J Psychiatry* 2007;164:663-9.
87. van Os J, Kapur S. Schizophrenia. *The Lancet* 2009;374:635-45.
88. Tsuang MT, Tohen M. Textbook in psychiatric epidemiology. 2. ed ed. New York: J. Wiley & Sons, 2002.

89. Linnet KM, Wisborg K, Agerbo E, Secher NJ, Thomsen PH, Henriksen TB. Gestational age, birth weight, and the risk of hyperkinetic disorder. *Archives of Disease in Childhood* 2006;91:655-60.
90. Lindstrom K, Lindblad F, Hjern A. Psychiatric Morbidity in Adolescents and Young Adults Born Preterm: A Swedish National Cohort Study. *Pediatrics* 2009;123:e47-e53.
91. Eaton WW, Mortensen PB, Thomsen PH, Frydenberg M. Obstetric complications and risk for severe psychopathology in childhood. *J Autism Dev Disord* 2001;31:279-85.
92. Hyman SE. Can neuroscience be integrated into the DSM-V? *Nat Rev Neurosci* 2007;8:725-32.
93. Burger H, Neeleman J. A glossary on psychiatric epidemiology. *J Epidemiol Community Health* 2007;61:185-9.
94. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 1995;4. ed.
95. International classification of diseases and related health problems, World Health Organization. The ICD-10 classification of mental and behavioural disorders clinical descriptions and diagnostic guidelines. 1992.
96. Latal B, Helfricht S, Fischer J, Bauersfeld U, Landolt M. Psychological adjustment and quality of life in children and adolescents following open-heart surgery for congenital heart disease: a systematic review. *BMC Pediatrics* 2009;9:6.
97. Spijkerboer AW, Utens EM, Bogers AJ, Verhulst FC, Helbing WA. Long-term behavioural and emotional problems in four cardiac diagnostic groups of children and adolescents after invasive treatment for congenital heart disease. *Int J Cardiol* 2008;125:66-73.
98. Ross L, Johansen C, Dalton SO, et al. Psychiatric Hospitalizations among Survivors of Cancer in Childhood or Adolescence. *N Engl J Med* 2003;349:650-7.
99. Nielsen NM, Rostgaard K, Hjalgrim H, Askgaard D, Skinhoj P, Aaby P. Psychiatric Hospitalizations in a Cohort of Danish Polio Patients. *Am J Epidemiol* 2007;165:319-24.

100. Simonsen E, MÃ,hl B. Grundbog i psykiatri. 1. udgave, 959. 2010. Kbh., Hans Reitzel.
101. Allebeck P. The use of population based registers in psychiatric research. *Acta Psychiatr Scand* 2009;120:386-91.
102. Brandhagen DJ, Feldt RH, Williams DE. Long-term psychologic implications of congenital heart disease: a 25-year follow-up. *Mayo Clin Proc* 1991;66:474-9.
103. Kovacs AH, Saidi AS, Kuhl EA, et al. Depression and anxiety in adult congenital heart disease: Predictors and prevalence. *International Journal of Cardiology* 2009;137:158-64.
104. Miatton M, De WD, Francois K, Thierry E, Vingerhoets G. Neuropsychological performance in school-aged children with surgically corrected congenital heart disease. *J Pediatr* 2007;151:73-8, 78.
105. Hovels-Gurich HH, Konrad K, Skorzinski D, et al. Long-term behavior and quality of life after corrective cardiac surgery in infancy for tetralogy of Fallot or ventricular septal defect. *Pediatr Cardiol* 2007;28:346-54.
106. Majnemer A, Limperopoulos C, Shevell M, Rosenblatt B, Rohlicek C, Tchervenkova C. Long-term neuromotor outcome at school entry of infants with congenital heart defects requiring open-heart surgery. *J Pediatr* 2006;148:72-7.
107. Majnemer A, Limperopoulos C, Shevell M, Rohlicek C, Rosenblatt B, Tchervenkova C. Developmental and functional outcomes at school entry in children with congenital heart defects. *J Pediatr* 2008;153:55-60.
108. Skovgaard AM, Houmann T, Landorph SL, Christiansen E. Assessment and classification of psychopathology in epidemiological research of children 0-3 years of age: a review of the literature. *Eur Child Adolesc Psychiatry* 2004;13:337-46.
109. Skovgaard AM, Houmann T, Christiansen E, et al. The prevalence of mental health problems in children 1(1/2) years of age - the Copenhagen Child Cohort 2000. *J Child Psychol Psychiatry* 2007;48:62-70.
110. Hovels-Gurich HH, Konrad K, Skorzinski D, Herpertz-Dahlmann B, Messmer BJ, Seghaye MC. Attentional dysfunction in children after corrective cardiac surgery in infancy. *Ann Thorac Surg* 2007;83:1425-30.

111. Miatton M, De Wolf D, Frantois K, Thiery E, Vingerhoets G. Neuropsychological Performance in School-Aged Children with Surgically Corrected Congenital Heart Disease. *The Journal of Pediatrics* 2007;151:73-8.
112. van der Rijken R, Hulstijn-Dirkmaat G, Kraaimaat F, et al. Open-heart surgery at school age does not affect neurocognitive functioning. *Eur Heart J* 2008;29:2681-8.
113. van der Rijken R, Hulstijn-Dirkmaat G, Kraaimaat F, Nabuurs-Kohrman L, Daniels O, Maassen B. Evidence of impaired neurocognitive functioning in school-age children awaiting cardiac surgery. *Dev Med Child Neurol* 2010;52:552-8.
114. Fredriksen P, Diseth T, Thaulow E. Children and adolescents with congenital heart disease: assessment of behavioural and emotional problems. *European Child & Adolescent Psychiatry* 2009;18:292-300.
115. Wernovsky G, Shillingford AJ, Gaynor JW. Central nervous system outcomes in children with complex congenital heart disease. *Curr Opin Cardiol* 2005;20:94-9.
116. van Rijen EHM, Utens EMWJ, Roos-Hesselink JW, et al. Longitudinal development of psychopathology in an adult congenital heart disease cohort. *International Journal of Cardiology* 2005;99:315-23.
117. Dittrich H, Buhner C, Grimmer I, Dittrich S, Abdul-Khaliq H, Lange PE. Neurodevelopment at 1 year of age in infants with congenital heart disease. *Heart* 2003;89:436-41.
118. Limperopoulos C, Majnemer A, Shevell MI, et al. Predictors of developmental disabilities after open heart surgery in young children with congenital heart defects. *J Pediatr* 2002;141:51-8.
119. Wray J, Sensky T. Controlled study of preschool development after surgery for congenital heart disease. *Arch Dis Child* 1999;80:511-6.
120. Utens EM, Versluis-Den Bieman HJ, Verhulst FC, Meijboom FJ, Erdman RA, Hess J. Psychopathology in young adults with congenital heart disease. Follow-up results. *Eur Heart J* 1998;19:647-51.
121. Limperopoulos C, Majnemer A, Shevell MI, et al. Functional Limitations in Young Children With Congenital Heart Defects After Cardiac Surgery. *Pediatrics* 2001;108:1325-31.

122. Mitchell ME, Ittenbach RF, Gaynor JW, Wernovsky G, Nicolson S, Spray TL. Intermediate outcomes after the Fontan procedure in the current era. *The Journal of Thoracic and Cardiovascular Surgery* 2006;131:172-80.
123. Shillingford AJ, Glanzman MM, Ittenbach RF, Clancy RR, Gaynor JW, Wernovsky G. Inattention, hyperactivity, and school performance in a population of school-age children with complex congenital heart disease. *Pediatrics* 2008;121:e759-e767.
124. Kirshbom PM, Myung RJ, Gaynor JW, et al. Preoperative pulmonary venous obstruction affects long-term outcome for survivors of total anomalous pulmonary venous connection repair. *Ann Thorac Surg* 2002;74:1616-20.
125. Nieminen H, Sairanen H, Tikanoja T, et al. Long-term results of pediatric cardiac surgery in Finland: education, employment, marital status, and parenthood. *Pediatrics* 2003;112:1345-50.
126. Ternstedt M, Wall K, Oddsson H, Riesenfeld T, Groth I, Schollin J. Quality of Life 20 and 30 Years After Surgery in Patients Operated on for Tetralogy of Fallot and for Atrial Septal Defect. *Pediatric Cardiology* 2001;22:128-32.
127. van Rijen EH, Utens EM, Roos-Hesselink JW, et al. Psychosocial functioning of the adult with congenital heart disease: a 20-33 years follow-up. *Eur Heart J* 2003;24:673-83.
128. Kokkonen J, Paavilainen T. Social adaptation of young adults with congenital heart disease. *Int J Cardiol* 1992;36:23-9.
129. Nuutinen M, Koivu M, Rantakallio P. Long-term outcome for children with congenital heart defects. A study from 1 year birth cohort born in 1966 in northern Finland. *Arctic Med Res* 1989;48:175-84.
130. Frank L. EPIDEMIOLOGY: When an Entire Country Is a Cohort. *Science* 2000;287:2398-9.
131. Pedersen CB, Gøtzsche H, Møller JI, Mortensen PB. The Danish Civil Registration System. A cohort of eight million persons. *Danish Medical Bulletin* 2006;53:441-9.
132. Andersen TF, Madsen M, Jorgensen J, Mellemkjoer L, Olsen JH. The Danish National Hospital Register. A valuable source of data for modern health sciences. *Dan Med Bull* 1999;46:263-8.

133. <http://www.dst.dk/TilSalg/Forskningservice/Databaser/IDA.aspx>. 2010.
134. Munk-Jorgensen P, Mortensen PB. The Danish Psychiatric Central Register. *Dan Med Bull* 1997;44:82-4.
135. Knudsen LB, Olsen J. The Danish Medical Birth Registry. *Danish Medical Bulletin* 1998;45:320-3.
136. European Surveillance of Congenital Anomalies. Guide 1.3 - Instructions for the Registration and Surveillance of Congenital Anomalies. 2009. 27-5-2009.
137. www.unesco.org. Accessed 8-11-2009.
138. Larsen H, Nielsen GL, Bendsen J, Flint C, Olsen J, Sorensen HT. Predictive value and completeness of the registration of congenital abnormalities in three Danish population-based registries. *Scand J Public Health* 2003;31:12-6.
139. Welke KF, Ungerleider RM. Mortality as an outcome parameter for pediatric heart surgery. *ASAIO Journal* 2006;52:552-5.
140. (2008) *Health care in Denmark*.
http://www.sum.dk/publikationer/healthcare_in_dk_2008/index.htm. 2008.
141. Koch SV, Kejs AM, Engholm G, Johansen C, Schmiegelow K. Educational attainment among survivors of childhood cancer: a population-based cohort study in Denmark. *Br J Cancer* 2004;91:923-8.
142. Gooley TA, Leisenring W, Crowley J, Storer BE. Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. *Stat Med* 1999;18:695-706.
143. ROTHMAN KJ. *Epidemiology an introduction*. Oxford: Oxford University Press, 2002.

144. Billett J, Majeed A, Gatzoulis M, Cowie M. Trends in hospital admissions, in-hospital case fatality and population mortality from congenital heart disease in England, 1994 to 2004. *Heart* 2008;94:342-8.
145. Kristensen P. Bias from nondifferential but dependent misclassification of exposure and outcome. *Epidemiology* 1992;3:210-5.
146. Jepsen B, Jepsen P, Johnsen SP, Espersen GT, Sørensen HT. Validity of diagnoses of cardiac malformations in a Danish population-based hospital-discharge registry. *International Journal of Risk and Safety in Medicine* 2006;18:77-81.
147. Kessing LV, Olsen EW, Mortensen PB, Andersen PK. Dementia in affective disorder: a case-register study. *Acta Psychiatr Scand* 1999;100:176-85.
148. Lauritsen MB, Jorgensen M, Madsen KM, et al. Validity of childhood autism in the Danish Psychiatric Central Register: findings from a cohort sample born 1990-1999. *J Autism Dev Disord* 2010;40:139-48.
149. Toren P, Horesh N. Psychiatric morbidity in adolescents operated in childhood for congenital cyanotic heart disease. *J Paediatr Child Health* 2007;43:662-6.
150. Bromberg JI, Beasley PJ, D'Angelo EJ, Landzberg M, DeMaso DR. Depression and anxiety in adults with congenital heart disease: A pilot study. *Heart and Lung: Journal of Acute and Critical Care* 2003;32:105-10.
151. Nieminen HP, Jokinen EV, Sairanen HI. Causes of late deaths after pediatric cardiac surgery: a population-based study. *J Am Coll Cardiol* 2007;50:1263-71.
152. Indredavik MS, Skranes JS, Vik T, et al. Low-Birth-Weight Adolescents: Psychiatric Symptoms and Cerebral MRI Abnormalities. *Pediatric Neurology* 2005;33:259-66.
153. Stump DA. Embolic Factors Associated with Cardiac Surgery. *Seminars in Cardiothoracic and Vascular Anesthesia* 2005;9:151-2.
154. McCusker CG, Doherty NN, Molloy B, et al. Determinants of neuropsychological and behavioural outcomes in early childhood survivors of congenital heart disease. *Arch Dis Child* 2007;92:137-41.

155. Otterstad JE, Tjore I, Sundby P. Social function of adults with isolated ventricular septal defects. Possible negative effects of surgical repair? *Scand J Soc Med* 1986;14:15-23.
156. Wright M, Nolan T. Impact of cyanotic heart disease on school performance. *Arch Dis Child* 1994;71:64-70.
157. Ballweg JA, Wernovsky G, Gaynor JW. Neurodevelopmental outcomes following congenital heart surgery. *Pediatr Cardiol* 2007;28:126-33.

Appendix

Study I

Late Mortality Among Danish Patients With Congenital Heart Defect

Morten Olsen, MD^{a,b,c,*}, Thomas Decker Christensen, PhD^{a,b}, Lars Pedersen, PhD^c, Søren Paaske Johnsen, PhD^c, and Vibeke Elisabeth Hjortdal, DMSc^{a,b}

To examine long-term mortality in Danish patients with congenital heart defect (CHD), we performed a population-based follow-up study using nationwide registries. We identified all children born in Denmark from January 1, 1977 to January 1, 2006 from the Danish Civil Registration System. Children with a primary diagnosis of CHD, diagnosed before 1 year of age, were then identified in the National Registry of Patients. We computed cumulative mortality of patients and the background population according to birth period (1977 to 1986, 1987 to 1996, and 1997 to 2005). We identified 6,646 patients with CHDs. Overall cumulative mortality estimates in patients with CHDs at 1 year and 10 and 25 years of age were 20% (95% confidence interval [CI] 19 to 21), 25% (95% CI 24 to 26), and 28% (95% CI 27 to 30). In Danes born in the same period equivalent mortality estimates were 0.6% (95% CI 0.56 to 0.58), 0.8% (95% CI 0.74 to 0.77), and 1.3% (95% CI 1.26 to 1.31). Mortality differed substantially according to heart defect type and mortality at 10 years of age ranged from 9% (95% CI 6 to 12) in patients with atrial septal defects (n = 361) to 55% (95% CI 45 to 66) in patients with common arterial trunk (n = 78). Mortality decreased during the study period; 1-year mortality was 28% (95% CI 26 to 31) for patients born from 1977 to 1986 (n = 2,907) compared to 13% (95% CI 12 to 15) for patients born from 1997 to 2005 (n = 2,741). Mortality decreased in all heart defect type categories. In conclusion, mortality in patients with CHD was high compared to the general population, especially in infancy, but also after 10 years of age, emphasizing the need for long-term medical follow up. Mortality at 1 year of age has decreased substantially during recent decades. © 2010 Published by Elsevier Inc. (Am J Cardiol 2010;xx:xxx)

More knowledge on mortality from birth to adulthood of the growing population of patients with congenital heart defect (CHD)¹ is important to evaluate treatment results beyond in-hospital mortality,² to evaluate the need for additional long-term medical follow-up,^{3–5} and to provide information to patients and their parents. We therefore examined the mortality of Danish patients diagnosed with CHD before the age of 1 year and compared it to the mortality of the general population using nationwide databases with up to 30 years of follow-up from birth.

Methods

We used the civil registration system to identify the 1,795,298 subjects born in Denmark from January 1, 1977 to January 1, 2006 and followed them until January 1, 2007. The study period started on the date of initial availability of data from the Danish National Registry of Patients. The 10-digit unique civil registration number assigned to every Danish resident since 1968 allows for valid individual-level linkage between Danish public registries.⁶ The Danish National Health Service provides tax-supported health care for

all inhabitants, guarantees free access to general practitioners and hospitals, and refunds a variable proportion of the prescription medication costs. Patients with CHD are exclusively treated at public hospitals (http://www.sum.dk/publikationer/healthcare_in_dk_2008/index.htm).

Using computerized data from the Danish National Registry of Patients we identified all patients in the study population with a primary discharge diagnosis of CHD before 1 year of age from January 1, 1977 to January 1, 2007. The registry is updated daily and contains information on patient civil registration number, dates of admission and discharge, and surgical procedures coded exclusively by doctors according to the International Classification of Diseases (ICD). The eighth edition of the ICD (ICD-8) was used until the end of 1993 and the 10th edition (ICD-10) thereafter. ICD-8 codes used to identify patients with CHD were 746 to 747 (except for 746.7 and 747.5 to 747.9, which were not specific to CHD) and ICD-10 codes were Q20 to Q26 (except for Q26.5 to Q26.6, which were not specific to CHD). Diagnoses of patent ductus arteriosus were considered only for mature infants (gestational age ≥ 37 weeks). We assigned each patient 1 CHD diagnostic code, namely the primary diagnosis from the first admission with CHD as the primary diagnosis. We grouped ICD-10 diagnostic codes according to the corresponding ICD-8 diagnostic codes to provide a uniform categorization of the study cohort during the study period (Table 1).

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Table 1
Categories of congenital heart defects

Diagnostic Category	ICD-8 Codes	ICD-10 Codes
Common arterial trunk	7460	Q200
Transposition of great vessels	7461	Q203, Q205
Tetralogy of Fallot	7462	Q213
Ventricular septal defect	7463	Q210
Atrial septal defect	7464	Q211
Atrioventricular septal defect	7465, 74641	Q212, Q218B
Anomalies of heart valve	7466	Q220-Q229, Q230-Q239
Other heart anomalies	7468, 7469	Q201, Q202, Q204, Q206, Q208, Q209, Q214, Q218, Q219, Q240-Q248, Q249
Patent ductus arteriosus	7470	Q250
Coarctation of aorta	7471	Q251
Other anomalies of great arteries	7472, 7473	Q252-Q254, Q255-Q256, Q257-Q259
Malformations of great veins	7474	Q260-Q264, Q268-Q269

Table 2
Characteristics of 6,646 patients with congenital heart defect

	Patients	ECD or Chromosomal Abnormality (%)	Preterm Birth (%)	First Therapeutic Procedure Before 1 Year of Age (%)	First Therapeutic Procedure After 1 Year of Age (%) (median age at first intervention)	Patients Undergoing Therapeutic Intervention According to Birth Period (%)		
						1977-1986	1987-1996	1997-2005
All patients with congenital heart defect	6,646	22%	11%	40%	12% (2.0years)	751 (43%)	1,259 (49%)	1,443 (63%)
Diagnostic category								
Common arterial trunk	78	19%	22%	58%	3% (1.4years)	6 (38%)	17 (53%)	24 (80%)
Transposition of great arteries*	461	11%	8%	64%	16% (1.2years)	87 (70%)	131 (82%)	154 (88%)
Tetralogy of Fallot	381	27%	15%	65%	23% (1.7years)	60 (79%)	116 (87%)	161 (94%)
Ventricular septal defect	1,559	20%	11%	29%	13% (2.1years)	164 (43%)	244 (40%)	252 (45%)
Atrial septal defect	361	28%	20%	23%	14% (3.3years)	25 (42%)	51 (37%)	58 (36%)
Atrioventricular septal defect	354	69%	13%	70%	11% (1.6years)	47 (68%)	104 (79%)	136 (88%)
Anomalies of heart valve	510	13%	14%	53%	7% (2.7years)	12 (46%)	100 (52%)	194 (67%)
Other anomalies of heart	2,092	19%	9%	25%	11% (2.6years)	265 (31%)	283 (32%)	196 (54%)
Patent ductus arteriosus	300	21%	—	45%	5% (1.5years)	31 (62%)	52 (44%)	65 (49%)
Coarctation of aorta	334	16%	15%	78%	7% (3.2years)	35 (61%)	117 (89%)	132 (90%)
Other anomalies of great arteries	177	25%	15%	57%	6% (2.2years)	19 (44%)	39 (66%)	53 (71%)
Malformations of great veins	39	26%	13%	56%	3% (1.0 year)	0 (0%)	5 (56%)	18 (67%)
Extracardiac defect or chromosomal anomalies†								
No	5,191	—	10%	37%	11 (2.0years)	559 (40%)	895 (44%)	1,053 (60%)
Yes	1,455	—	15%	51%	14 (1.8years)	192 (51%)	364 (65%)	390 (75%)

* Complete and congenitally corrected transposition.

† Diagnosed at any time during follow-up.

We categorized patients into 2 main groups according to treatment (surgery or catheter-based treatment) or no treatment. We used the following codes to identify diagnoses of extracardiac defect (ECD) and chromosomal abnormalities in the Danish National Hospital Registry: ICD-8 codes 740.99 to 759.99 and ICD-10 codes Q0.00 to Q99.9, except for CHD-related codes. According to a guideline from the European Surveillance of Congenital Anomalies (EUROCAT), we disregarded isolated minor defects such as torticollis (Q68.0) or protuberant ears (Q17.3).⁷ We obtained data on gestational age from the Danish Medical Birth Registry that contains computerized data on all newborns in Denmark from 1973 onward⁸ and defined preterm birth as a gestational age <37

weeks. We retrieved data on vital status for the entire cohort through linkage with the civil registration system that has kept daily updated electronic records on date of birth, date of emigration, and exact date of death for all Danish residents since 1968.

We computed the proportion of patients who had ECDs or chromosomal abnormalities, the proportion who were born before term, and the proportion who underwent therapeutic interventions at any time during the study period, before 30 days of age, or before 1 year of age. Based on the Kaplan-Meier estimator, we computed cumulative mortality 1 year and 10 and 25 years from birth for overall patients with CHD and in subgroups according to defect type and

Table 3

Proportion of patients undergoing cardiac intervention and their mortality according to period of birth

Birth Period (Patients)	Proportion Who Underwent Therapeutic Cardiac Intervention Before 30 Days or 1 Year of Age (95% CI)*		CMPs at Specified Times From Discharge After First Intervention (95% CI) [†]		
	30 Days	1 Year	30 Days	1 Year	5 Years
1977–1986 (1,767)	4% (3–4)	21% (19–23)	25% (21–30)	34% (29–39)	42% (37–47)
1987–1996 (2,591)	13% (12–14)	37% (35–38)	15% (13–17)	23% (20–25)	27% (24–30)
1997–2005 (2,288)	22% (20–24)	60% (58–62)	7% (6–8)	13% (11–15)	14% (12–16)

CMP = cumulative mortality proportion.

* Denominators are all patients born in the same period.

[†] Mortality in patients who underwent a therapeutic intervention before 1 year of age.

presence of ECDs or chromosomal abnormalities and for the remaining Danish population. We computed cumulative mortality curves for patients with CHD by period of birth (1977 to 1986, 1987 to 1996, and 1997 to 2005).

Using Cox regression analysis we computed the hazard ratio as an estimate of the relative risk in patients with CHD of dying during the first year of life in the most recent birth period compared to the earliest birth period, adjusting for gender. We computed overall and type-specific hazard ratios. In patients undergoing therapeutic procedures we computed the cumulative mortality at 30 days, 1 year, and 5 years from discharge after the first therapeutic procedure. We computed hazard ratios to compare mortality during 1 year from discharge in the recent and early birth periods in those undergoing surgery before 1 year of age. We adjusted for gender and age at surgery (<30 or ≥30 days of age). Analyses were performed using STATA 10.1 (STATA Corp. LP, College Station, Texas).

Results

We identified 6,646 patients with CHD diagnosed before 1 year of age, corresponding to a prevalence at birth of 3.7 per 1,000 live births. Overall, approximately 1 of 5 had ECDs or chromosomal anomalies and 11% were born before term (Table 2).

One-half of patients with CHD received invasive treatment (surgery and/or catheter-based procedure; Table 2) and as expected the proportion of treated patients was closely associated with type of CHD. The highest treatment rates were found in patients diagnosed with tetralogy of Fallot, coarctation of the aorta, atrioventricular septal defect, and transposition of the great arteries. The proportion of patients undergoing treatment in infancy increased during the study period; approximately 20% of patients born from 1977 to 1986 received invasive treatment in infancy compared to 60% of patients born from 1997 to 2005 (Table 3).

In this cohort of patients diagnosed with CHD before 1 year of age, 1/5 died within the first year of life. Mortality remained high throughout the follow-up period; an additional 5% died before 10 years of age and another 3% died from 10 to 25 years of age. In the comparison cohort (the remaining Danish population) only 0.6% died as infants and an additional 0.7% had died by 25 years of age. Mortality varied by type of CHD and presence of ECD or chromosomal abnormalities (Ta-

ble 4). During the study period overall cumulative mortality at 1 year of age decreased from 28% (95% confidence interval [CI] 26 to 31) in the early period to 13% (95% CI 12 to 15) in the most recent period (Figure 1). The corresponding overall mortality rate ratio was 0.42 (95% CI 37 to 49) when comparing patients from the most recent birth period to patients born from 1977 to 1986. Lower mortality rate ratios were also consistently found in the defect-specific analyses (Table 5). Of patients born in the early period (1977 to 1986) who underwent a cardiac therapeutic intervention before 1 year of age, 34% (95% CI 29 to 39) died within 1 year after the first intervention. In comparison, only 13% (95% CI 11 to 15) died within 1 year after the first intervention in the late period (1997 to 2005; Table 3). This corresponded to an overall mortality rate ratio of 0.25 (95% CI 0.20 to 0.32).

Discussion

In this nationwide follow-up study we found a marked decrease during 30 years in early postoperative and long-term mortality of patients diagnosed with CHD. However, mortality in patients with CHD remained high compared to the general population.

In a population-based Czech study that, equivalent to our study, included all patients with CHD with and without surgery or catheter-based intervention, Samanek and Voriskova⁹ classified complex CHDs according to the malformation that dominated in the pathologic hemodynamics. Overall 1- and 10-year mortalities of patients with CHD in the study population born from 1980 to 1990 (20% and 23%) were comparable to our findings. However, 1-year mortality rates for specific defects such as transposition of the great arteries (38.4%), atrioventricular septal defect (37.8%), and coarctation of the aorta (32.0%) were higher than our estimates. However, despite the similarities, the study is not directly comparable to ours due to differences in study period and age at diagnosis of CHD. Thus, Samanek and Voriskova⁹ included all patients diagnosed at any age up to 15 years, which may explain that the proportion of patients with ventricular and atrial septal defects was higher (41.6% and 8.7%, respectively) compared to our study. Nieminen et al¹⁰ found that the overall late survival of patients with CHD who had undergone surgery decreased from the 1950s to the 1980s because more children with complicated CHDs

Table 4
Cumulative mortality proportion at one year and 10 and 25 years of age based on Kaplan-Meier estimator

	CMP (95% CI)		
	1 Year*	10 Years	25 Years
Danish population	0.6% (0.6–0.6)	0.8% (0.7–0.8)	1.3% (1.3–1.3)
All congenital heart defects	20% (19–21)	25% (24–26)	28% (27–30)
	13% (12–15) [†]		
Diagnostic category			
Common arterial trunk	55% (45–66)	55% (45–66)	55% (45–66)
	27% (14–46) [†]		
Transposition of great arteries [‡]	26% (22–30)	38% (33–42)	50% (41–59)
	19% (14–25) [†]		
Tetralogy of Fallot	17% (13–21)	30% (26–35)	33% (26–42)
	9% (6–15) [†]		
Ventricular septal defect	6% (5–7)	10% (8.3–11)	11% (9.0–13)
	3% (2–5) [†]		
Atrial septal defect	7% (4.7–10)	9% (6.4–12)	16% (8.8–28)
	4% (2–8) [†]		
Atrioventricular septal defect	25% (21–30)	35% (30–41)	41% (35–49)
	21% (16–29) [†]		
Anomalies of heart valve	34% (30–38)	38% (34–42)	60% (31–89)
	32% (27–38) [†]		
Other anomalies of heart	27% (26–29)	32% (30–34)	35% (33–37)
	24% (16–35) [†]		
Patent ductus arteriosus	6% (4–10)	10% (6.8–14)	10% (6.8–14)
	2% (1–7) [†]		
Coarctation of aorta	16% (13–21)	18% (15–23)	27% (18–39)
	4% (2–9) [†]		
Other anomalies of great arteries	32% (25–39)	37% (30–44)	37% (30–44)
	17% (14–22) [†]		
Malformations of great veins	36% (23–53)	36% (23–53)	—
	26% (13–47) [†]		
Extracardiac defect or chromosomal anomalies [§]			
No	20% (18–21)	24% (23–25)	27% (26–28)
	13% (11–14) [†]		
Yes	21% (19–24)	31% (28–34)	36% (32–41)
	16% (13–19) [†]		

Abbreviation as in Table 3.

* Mortality proportions at 1 year of age are presented for the entire study population (born 1977 to 2005).

[†] Mortality proportions at 1 year of age are presented for patients born from 1997 to 2005.

[‡] Complete and congenitally corrected transposition.

[§] Diagnosed at or before date of diagnosis of congenital heart defect.

underwent surgery in the latter decades and were operated at a younger age. In contrast, we observed an increase in survival in patients undergoing therapeutic interventions from 1977 to 2007, including survival specific to patients with transposition of the great arteries, tetralogy of Fallot,

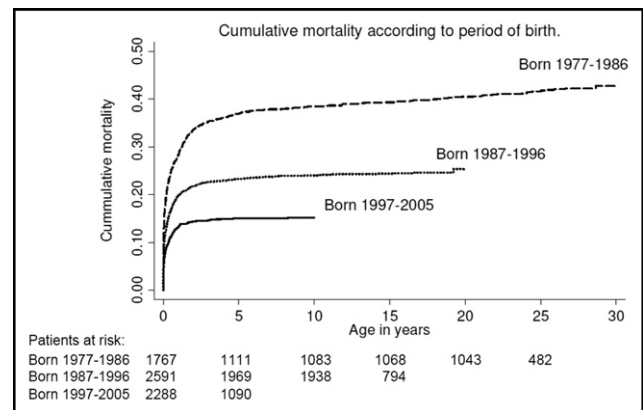


Figure 1. Cumulative mortality of patients with congenital heart defect according to period of birth.

Table 5

Overall and defect type-specific mortality rate ratios comparing one-year mortality of patients born in most recent birth period (1997 to 2005) to one-year mortality of patients born in early period (1977 to 1986)

Diagnostic Category	MRR (95% CI)*
All congenital heart defects	0.42 (0.37–0.49)
Common arterial trunk	0.19 (0.08–0.47)
Transposition of great arteries [†]	0.47 (0.30–0.73)
Tetralogy of Fallot	0.23 (0.12–0.42)
Ventricular septal defect	0.30 (0.17–0.55)
Atrial septal defect	0.20 (0.07–0.56)
Atrioventricular septal defect	0.69 (0.40–1.20)
Anomalies of heart valve	0.60 (0.34–1.08)
Other anomalies of heart	0.44 (0.33–0.58)
Patent ductus arteriosus	0.12 (0.03–0.47)
Coarctation of aorta	0.09 (0.04–0.22)
Other anomalies of great arteries	0.39 (0.21–0.75)
Malformations of great veins	0.25 (0.06–1.00)

MRR = mortality rate ratio.

* Complete and congenitally corrected transposition.

[†] Adjusted for gender.

and atrioventricular septal defect (data not shown). This difference may reflect that we covered a later calendar period in our study and thus more experience regarding surgery for complex CHD had been gained. Eskedal et al¹¹ found a 5-year from birth mortality of patients with CHD and ECD, including syndromes other than Down syndrome, born from 1990 to 1999 of approximately 25%. This corresponds with our mortality estimates for patients with ECD or chromosomal anomalies, including births from 1977 to 2005.

When interpreting our results the following issues should be considered. We used data from public registers and some misclassification with regard to CHD diagnoses may have occurred. However, the overall positive predictive value of the Danish National Registry of Patients with regard to presence of CHD is high (89%).^{12,13} The ICD-8 did not provide as detailed subcategories as the ICD-10; however, the most prevalent CHD diagnoses were accounted for. The proportion of patients with ECD or chromosomal abnormalities is in accordance with other studies,^{11,14} indicating a high quality of our data.

Study strengths also include the population-based design, the prospective data collection, and the complete follow-up across 3 decades regarding mortality of patients with CHD and the entire remaining Danish population born from January 1, 1977 to January 1, 2006.

We focused on patients with CHD who required hospital admission primarily due to their CHD and therefore we did not include outpatients or patients receiving a CHD diagnosis as an additional diagnosis only. This probably limited the bias in the comparison of mortality in different birth periods because of improved detection of mild septal defects with better ultrasound techniques.¹⁵ Furthermore, all type-specific mortality estimates decreased during the study period. Nevertheless, higher detection rates of mild defects probably still explain some of the improved survival observed during the study period.

1. Wren C, O'Sullivan JJ. Survival with congenital heart disease and need for follow up in adult life. *Heart* 2001;85:438–443.
2. Billett J, Majeed A, Gatzoulis M, Cowie M. Trends in hospital admissions, in-hospital case fatality and population mortality from congenital heart disease in England, 1994 to 2004. *Heart* 2008;94:342–348.
3. Engelfriet P, Boersma E, Oechslin E, Tijssen J, Gatzoulis MA, Thilen U, Kaemmerer H, Moons P, Meijboom F, Popelova J, Laforest V, Hirsch R, Daliento L, Thaulow E, Mulder B. The spectrum of adult congenital heart disease in Europe: morbidity and mortality in a 5 year follow-up period—the Euro Heart Survey on adult congenital heart disease. *Eur Heart J* 2005;26:2325–2333.
4. Hoimyr H, Christensen TD, Emmertsen K, Johnsen SP, Riis A, Hansen OK, Hjortdal VE. Surgical repair of coarctation of the aorta: up to 40 years of follow-up. *Eur J Cardiothorac Surg* 2006;30:910–916.

5. Opatowsky AR, Siddiqi OK, Webb GD. Trends in hospitalizations for adults with congenital heart disease in the U.S. *J Am Coll Cardiol* 2009;54:460–467.
6. Pedersen CB, Gøtzsche H, Møller J, Mortensen PB. The Danish Civil Registration System. A cohort of eight million persons. *Dan Med Bull* 2006;53:441–449.
7. European Surveillance of Congenital Anomalies. Guide 1.3—Instructions for the Registration and Surveillance of Congenital Anomalies. 2009.
8. Knudsen LB, Olsen J. The Danish Medical Birth Registry. *Dan Med Bull* 1998;45:320–323.
9. Samanek M, Voriskova M. Congenital heart disease among 815,569 children born between 1980 and 1990 and their 15-year survival: a prospective Bohemia survival study. *Pediatr Cardiol* 1999;20:411–417.
10. Nieminen HP, Jokinen EV, Sairanen HI. Causes of late deaths after pediatric cardiac surgery: a population-based study. *J Am Coll Cardiol* 2007;50:1263–1271.
11. Eskedal L, P, Hagemo A, Eskild G, Aamodt KS, Seiler E, Thaulow A. A population-based study of extra-cardiac anomalies in children with congenital cardiac malformations. *Cardiol Young* 2004;14:600–607.
12. Jepsen B, Jepsen P, Johnsen SP, Espersen GT, Sørensen HT. Validity of diagnoses of cardiac malformations in a Danish population-based hospital-discharge registry. *Int J Risk Saf Med* 2006;18:77–81.
13. Larsen H, Nielsen GL, Bendtsen J, Flint C, Olsen J, Sørensen HT. Predictive value and completeness of the registration of congenital abnormalities in three Danish population-based registries. *Scand J Public Health* 2003;31:12–16.
14. Pradat P. Noncardiac malformations at major congenital heart defects. *Pediatr Cardiol* 1997;18:11–18.
15. Meberg A, Otterstad JE, Froland G, Sorland S, Nitter-Hauge S. Increasing incidence of ventricular septal defects caused by improved detection rate. *Acta Paediatr* 1994;83:653–657.

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Study II

Title: Congenital heart defects and psychiatric in- or outpatient admissions: A nationwide cohort study

Brief title: Congenital heart defects and psychiatric disorders

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Abstract:

Objectives: To examine the risk of psychiatric in- or outpatient admissions among Danish patients with congenital heart defects (CHD).

Background: CHD have been associated with neurodevelopmental impairment, but the risk of clinically-verified psychiatric disorders is unknown.

Methods: We used The National Patient Registry to identify CHD patients born 1/1/1977- 1/1/2002. For each patient we identified 10 population control cohort members in the Civil Registration System, matched for sex and birth year. These data were linked with the Danish Psychiatric Central Registry. We computed cumulative incidence and Cox proportional hazard ratios of time to first psychiatric in- or outpatient admission overall and according to age group (<15 and 15-30 years), gender, and surgical or catheter-based therapeutic intervention, adjusted for parents' educational level and psychiatric morbidity.

Results: We identified 6,927 CHD patients, 49% male. At 15 years of age the cumulative incidence of psychiatric admission was 5.85% (95%CI: 5.15-6.61) among CHD patients. The hazard ratios for CHD patients and control cohort members under 15 years of age were: males: 1.76 (95%CI: 1.48-2.09), females: 2.49 (95%CI: 2.00-3.11). At age 15-30 years, males: 1.57 (95%CI: 1.22-2.00), females: 1.04 (95%CI: 0.84–1.30). Patients both with and without therapeutic interventions had higher risk of psychiatric admission compared with the control cohort. Exclusion of patients and controls born preterm or with extracardiac defects or syndromes did not substantially change the estimates.

Conclusion: CHD patients with or without therapeutic interventions are at increased risk of psychiatric disorders.

Keywords: Congenital heart defects, psychiatric disorders, prognosis, population based.

Abbreviations:

ADHD = Attention Deficit Hyperactivity Disorder

CI = Confidence interval

CHD = Congenital heart defect

CRS = Danish Civil Registration System

DPCR = Danish Psychiatric Central Registry

ECD = Extracardiac defect

HR = Hazard ratio

ICD = International Classification of Diseases

NPR = The National Patient Registry

Introduction:

The prevalence of congenital heart defects (CHD) at birth is approximately 6-10 per 1,000 live births ^{1;2}. Survival has improved markedly during recent decades, making outcome data other than mortality important. Such data are needed to understand the clinical course of CHD and to potentially prevent later complications.

Studies including a wide range of CHD types have reported associations between CHD and attention deficit hyperactivity disorder (ADHD), pervasive developmental disorders (e.g. autism) and other neurodevelopmental, behavioural and emotional problems ³⁻⁸. These studies have mainly focused on patients undergoing heart surgery. Factors identified as affecting the mental health of CHD patients in this context include coexisting syndromes, *e.g.*, Down's and DiGeorge syndromes ^{9;10}, and familial processes (parenting styles, maternal mental health and worry) ¹¹. Few published data exist on the mental health of CHD patients who have not undergone surgery or catheter-based intervention, even though risk factors for psychiatric disorders unrelated to surgical treatment, such as preterm birth ^{12;13}, occur more often than expected among CHD patients ¹⁴.

To our knowledge, no studies have been published regarding the incidence of psychiatric hospitalization or outpatient psychiatric care among patients with CHD. We therefore conducted a nationwide population-based cohort study examining the incidence of psychiatric hospitalization or outpatient visits among Danish patients with CHD, compared with a population-based control cohort.

Methods:

Study cohorts and design

We based this cohort study on data from nationwide registries. We used The National Patient Registry (NPR) to identify all infants born from January 1, 1977 to January 1, 2002 who received a primary diagnosis of CHD. The NPR contains information on all hospital admissions in Denmark, encompassing patients' civil registration numbers, dates of admission and discharge, surgical procedures, and up to 20 discharge diagnoses coded by physicians according to the *International Classification of Diseases* (ICD). The 8th edition of ICD was used until the end of 1993 and the 10th edition thereafter. ICD-8 codes used to identify CHD patients were 746-747 (except for 746.7 and 747.5-747.9, which are not specific to CHD) and ICD-10 codes Q20-Q26 (except for Q26.5-Q26.6, also not specific to CHD). ICD-10 codes were categorized according to corresponding ICD-8 codes. Patients were grouped according to the first main CHD diagnosis. Diagnoses of patent ductus arteriosus were only considered for infants whose gestational age was ≥ 37 completed weeks according to the National Medical Birth Registry ¹⁵.

For each patient we identified 10 persons as a population control cohort from the Danish Civil Registration System (CRS) matched for sex and birth year. The CRS has kept electronic records on date of birth, date of emigration, and date of death for all Danish residents since 1968 ¹⁶, based on a unique personal identifier assigned to every Danish citizen. This identifier allowed us to assess the educational level of the parents via linkage to the Integrated Database for Labour Market Research ¹⁷. The parents' highest educational level recorded during the study period was categorized as basic education, youth education, or higher education. We used the following codes to

identify diagnoses of extracardiac defects (ECD) and chromosomal abnormalities in the NPR, except for the CHD codes: ICD-8: 310.40-310.41, 310.5, 311.40-311.41, 311.5, 312.40-312.41, 312.5, 313.40-313.41, 313.5, 314.40-314.41, 314.5, 315.40-315.41, 315.5, 740.99-759.99 and ICD-10: DQ00.0-DQ99.9. We considered diagnoses given at all ages. In accordance with a guideline from the European Surveillance of Congenital Anomalies (Eurocat), we disregarded isolated minor defects such as subluxation or unstable hip, cryptorchidism, torticollis, or protuberant ears¹⁸. We obtained data on gestational age from the National Medical Birth Registry and defined preterm birth as gestational length < 37 weeks.

Psychiatric morbidity

We linked the CHD and comparison cohorts to the Danish Psychiatric Central Registry (DPCR)¹⁹, which consists of electronic records on all inpatient admissions to Danish psychiatric hospitals since 1970, and on outpatient admissions since 1995. We then established the outcome variables and indicators of maternal or paternal psychiatric morbidity¹³. Psychiatric diseases have been coded in DPCR according to ICD-8 and, since January 1 1994, ICD-10. Parental psychiatric morbidity was defined by the presence of any psychiatric diagnosis (ICD-8: 290-315, ICD-10: F.00-F.99) before the birth date of the CHD patient or control individual. We restricted this indicator to diagnoses occurring before the birth of a child with CHD because having a critically ill child is likely to increase parental risk of psychiatric morbidity.

Patient follow-up for psychiatric health care contacts began on January 1, 1995, as a result of availability of outpatient contact data (a substantial part of Danish psychiatric health care is provided in outpatient clinics)^{20;21}. Outcomes included any

psychiatric diagnosis (F.00-F.99) and specific psychiatric disorders of special interest in the CHD population: psychotic disorders (F.20-F.29) ²², pervasive developmental disorders (F.84) ⁴, specific developmental disorders of speech, motor function and learning (F.80-F.83) ⁵, ADHD (F.90) ⁴, and mental retardation of any degree (F.70-F79) ^{6;23}. The study was approved by the Danish Data Protection Agency, whose role is to ensure the protection of the privacy and integrity of the individuals recorded in the registries. No informed consent was required for this study.

Data analysis

Follow-up began on the date of CHD diagnosis or on January 1, 1995, whichever came later, and continued until a first psychiatric diagnosis, emigration, death, or January 1, 2007. The delayed entry on January 1, 1995 was chosen to restrict the analysis to a period when outpatient contacts were included in the DPCR. Patients hospitalized for psychiatric disorders before the start of follow-up were excluded, to avoid prevalent disease. The cumulative incidence of psychiatric admissions at 15 years of age was computed assuming death to be a competing risk ²⁴.

We used Cox proportional regression analysis to compute hazard ratios (HR) of time to first psychiatric diagnosis among CHD patients compared with the population control cohort, with age as the underlying time scale. We adjusted for parents' educational level and presence of psychiatric morbidity. Analyses were performed according to gender and surgical or catheter-based therapeutic intervention, and repeated after the exclusion of patients and controls born preterm or with ECDs, including syndromes or chromosomal anomalies. Individuals with missing data on parental educational level were excluded from the analyses. We graphically assessed the

assumption of proportional hazards. Analyses were performed using the Stata® 10.1 package (StataCorp LP, Texas, US).

Results

We identified 6,927 CHD patients, 49% male, who were born between January 1, 1977 and January 1, 2002, and were alive on January 1, 1995 or later. The most frequent types of CHD diagnoses were ventricular septal defect and atrial septal defect. ECD or syndromes were present in 19.5% of the CHD patients and in 3.3% of the control cohort members. Among CHD patients, 9.1% were born preterm, compared with 5.0% of control cohort members (Table 1).

The overall cumulative incidence of psychiatric admission or outpatient clinic visit of CHD patients at age 15 years was 5.85% (95% CI: 5.15-6.61). The overall HR for psychiatric admission or outpatient clinic visit among CHD patients compared with the control cohort was 1.60(95% CI: 1.44-1.77) and the risk of admissions for both psychotic disorders, developmental disorders, ADHD, and mental retardation of any degree was also increased among CHD patient (Table 2)

The risk of psychiatric disorders was increased for CHD patients compared with the control cohort in the younger age group (0-14 years) independent of the need for surgery or catheter-based intervention (Table 3). Patients who did not undergo surgery or catheter-based intervention were at increased risk in the older age group as well, compared with the control cohort [HR: 1.34(95% CI: (1.08-1.66))]. Both male and female CHD patients under age 15 were at increased risk of psychiatric disorders [male HR: 1.76 (95% CI: 1.48-2.09), female HR: 2.49 (95% CI: 2.00-3.11)].

Male CHD patients aged 15-30 years were also at increased risk of psychiatric disorders [HR: 1.57 (95% CI: 1.22-2.01)]. In contrast, we did not observe an elevated risk of psychiatric disorders in female patients aged 15-30 years, compared with the control cohort [HR: 1.04 (95% CI: 0.84-1.30)]. When patients and controls with ECD or syndromes, and those born preterm, were excluded from the analysis, the estimates were not substantially changed, although some reduction of risk was seen in the younger age group below 15 years (Table 3).

Discussion

To our knowledge, this population based study is the first to examine clinically-verified psychiatric disorders among CHD patients. It extends the findings of previous studies that reported an increased risk of neurodevelopmental impairment and behavioral problems among patients with CHD followed at treatment centers.

Multiple studies have reported findings of neurodevelopmental impairment in terms of slightly impaired cognitive function, speech and language difficulties, and impaired motor skills^{5,25}. In accordance with this we found an increased risk for CHD patients, compared with the control cohort of hospital admission or outpatient clinic visits with mental retardation and specific developmental disorders of motor, speech and learning. The cumulative incidence in our CHD population of these disorders at 15 years of age was about 1% (Table 2). Recently there have been reports of increased risk of ADHD among CHD patients. Thus, in a follow up study of 380 preschool age children having undergone cardiac surgery of a wide range of complexity, Gaynor et al⁴ reported that of the entire cohort 30% scored in the clinically significant range for inattention and 22% for impulsivity on the ADHD Rating Scale-

IV, Preschool Version. This was compared with the 4% to 7% reported in the Diagnostic and Statistical Manual of Mental disorders; Fourth Edition (DSM-IV). We also found an increased risk of ADHD among the CHD patients, compared with the control cohort, yet the cumulative incidence of approximately 1% at 15 years of age may seem low, compared with the DSM-IV estimates. There may at least be two possible explanations to this, one being that ICD-10 criteria for the ADHD diagnosis are stricter than DSM-IV criteria ²⁶. The other that the high mortality of the CHD cohort compared with the control cohort will lead to a lower cumulative incidence of ADHD admissions, because death is a competing risk. We found a higher occurrence of pervasive developmental disorders among CHD patients compared with the control cohort (Table 2). This is in line with the findings of Gaynor et al who found worse problem scores for pervasive developmental problems, compared with normative data in a follow up study of preschool children having undergone cardiac surgery ⁴. The increased occurrence of psychotic disorders that we found among CHD patients compared with the control cohort may at least in part be due to the 22q11.2 deletion syndrome, also known as velocardiofacial syndrome or DiGeorge syndrome, that is associated with CHD ²⁷. One-third of all individuals with 22q11.2 deletion syndrome develop schizophrenia-like psychotic disorders ²².

We did not identify an increased risk of hospital admissions for psychiatric care, nor for attendance at outpatient psychiatric clinics, among female patients in the older age group (15-30 years, Table 2). Van Rijen et al ⁸ assessed emotional and behavioral problems in adults with CHD using the Young Adult Self Report, reporting an increased proportion of female CHD patients (age 20-27 years) scoring in the psychopathological range compared with normative data. In contrast to

this finding, Utens et al ²⁸, using the same assessment instrument, found that more male CHD patients (aged 22-25 years), but not female patients, scored in the psychopathological range compared with normative data. However, these contrasting findings are not readily comparable to ours, as they reflect the prevalence of psychiatric morbidity in a certain age group, and not the incident cases that we report.

Possible mechanisms underlying risk of psychopathology among CHD patients include patient-related factors such as genetic syndromes ²⁹ and preterm birth ¹². However, we also identified an association between CHD and psychiatric disorders after excluding patients with these characteristics. Abnormal intrauterine blood flow among patients with complex CHD ³⁰, as well as white matter lesions ³¹ or cerebral hypoxia, may also impair neurological development and increase the risk of psychiatric disorders ^{32;33}. Treatment-related factors that may cause neurological damage include cerebral embolization ³⁴ or reduced cerebral blood flow due to inadequate cardiopulmonary bypass technique ³⁵. These factors do not, however, explain the increased risk of psychiatric disorders found among CHD patients who did not undergo surgical treatment. As need for surgery is related to CHD severity, this finding also indicates that severity of CHD is not strongly related to the risk of psychiatric disorders. Accordingly, Hövels-Gürich et al noted that children with Tetralogy of Fallot are not at increased risk of behavioral problems compared with children with ventricular septal defects, in a study of children undergoing cardiac surgery ³⁶. The results from a study of children with a range of cyanotic and acyanotic defects, who underwent either corrective or palliative surgery, highlight the sometimes greater relevance of family processes (e.g. parenting style, maternal mental health and worry), rather than disease or

surgical factors, in predicting behavioral outcomes in particular in this context ¹¹. Thus, interactions among several biological and psychological risk factors are likely.

The validity of our estimates depends on the accurate coding of CHD and psychiatric diagnoses. The positive predictive value of CHD diagnoses in the NPR is reported to be high ³⁷, and any misclassification of overall CHD status is small and independent of future psychiatric morbidity. The CRS allowed a population-based design with complete long-term follow-up of vital status and linkage to the DPCR. The validity of the DPCR is high, reflected in validation studies regarding diagnoses such as schizophrenia, affective psychoses, and childhood autism ^{38;39}.

If CHD patients were more likely to be referred to psychiatric treatment because they were already in contact with the health care system, we would overestimate their relative risk of psychiatric disorders compared with controls. However, given previous research demonstrating an increased risk of neurodevelopmental disorders ^{3;5;6} and psychological maladjustment ^{40;41}, as well as the strength of the associations in our study, we do not believe that this potential bias can explain our results. Psychiatric hospitalisation is a recognized outcome measure in research on psychiatric disorders ⁴².

We lacked information on clinical detail, such as detailed information on the severity of CHD. Yet, our data indicated an elevated risk of psychiatric admission that was independent of whether surgical or catheter-based interventions had taken place, and therefore possibly also independent of defect severity. This is in line with the findings of others ¹¹.

Although our data may reflect sufficient medical follow-up of this patient population regarding mental health problems, more patients may benefit from increased

attention to this matter. The symptoms of the developmental disorders examined in this study may cross many clinical disciplines including Neurology, Pediatrics, and Psychiatry. Therefore the optimal clinical evaluation and treatment of childhood developmental disorders may involve an interdisciplinary approach ⁴³.

In conclusion, we identified increased risks of psychiatric disorders among male and female CHD patients below 15 years of age, and among male patients aged over 15 years, compared with a population control cohort. Patients who did not undergo surgery or catheter-based interventions were also at increased risk. When patients and controls with ECD or chromosomal abnormalities and those born preterm were excluded, the risk was still elevated. Nonetheless, the majority of CHD patients appear to have a favorable mental health prognosis.

Table 1. Characteristics of patients with congenital heart defects (CHD) and the matched population control cohort.

	Patients with CHD N (%)	Comparison cohort N (%)
All	6,927(100)	68,185(100)
Male	3,392(49.0)	33,417(49.0)
Year of birth		
1977-1982	1,115(16.1)	10,861(16.0)
1983-1986	1,038(15.0)	10,124(14.9)
1987-1992	1,334(19.3)	13,093(19.2)
1993-1996	1,738(25.1)	17,214(25.3)
1997-2002	1,702(24.6)	16,893(24.8)
Preterm birth	629(9.1)	3,418(5.0)
Extracardiac defect*	1,352(19.5)	2,264(3.3)
Maternal psychiatric diagnosis†	215(3.1)	1,657(2.4)
Paternal psychiatric diagnosis†	195(2.8)	1,554(2.3)
Maternal highest educational level		
Basic education	2,014(29.1)	16,757(24.6)
Youth education	2,772(40.0)	28,480(41.8)
Higher education	1,964(28.4)	21,723(31.9)
Data missing	177(2.6)	1,225(1.8)
Paternal highest educational level		
Basic education	1,847(26.7)	15,979(23.4)
Youth education	3,136(45.3)	31,081(45.6)
Higher education	1,733(25.0)	19,054(27.9)
Data missing	211(3.1)	2,071(3.0)
Diagnostic categories		
Common arterial trunk	35(0.5)	-
Transposition of great vessels‡	277(4.0)	-
Tetralogy of Fallot	288(4.2)	-
Ventricular septal defect	1,617(23.3)	-
Atrial septal defect	828(12.0)	-
Atrioventricular septal defect	310(4.5)	-
Anomalies of heart valve	567(8.2)	-
Other anomalies of heart	1,845(26.6)	-
Patent ductus arteriosus	548(7.9)	-
Coarctation of aorta	392(5.7)	-
Other malformations of great arteries	184(2.7)	-
Malformation of great veins	36(0.5)	-
Surgery or catheter-based intervention	3867(55.8)	-

*Including syndromes and chromosomal anomalies. †Diagnosed before the birth of the CHD patient or control. ‡Complete and congenitally corrected transposition.

Table 2. Cumulative incidence and hazard ratios of psychiatric in- or outpatient admission for specific psychiatric disorders among congenital heart defect patients compared with the population control cohort. Data are presented for all study subjects and for a subgroup of patients and control cohort members born at term without extracardiac defects.

	Hazard ratio (95% confidence interval)*		15-year cumulative incidence, % (95% confidence interval)
	All	No extracardiac defect [†] and born at term	All
Any psychiatric disorder	1.60(1.44-1.77)	1.41(1.24-1.60)	5.85(5.15-6.61)
Psychotic disorders (e.g. schizophrenia)	1.44(0.99-2.11)	1.57(1.04-2.37)	0.09(0.03-0.24)
Pervasive developmental disorders (e.g. autism spectrum disorders)	2.01(1.49-2.72)	1.66(1.13-2.45)	0.96(0.71-1.29)
Specific developmental disorders (speech, motor and learning disorders)	1.47(0.93-2.33)	1.17(0.65-2.11)	0.47(0.30-0.72)
Attention deficit hyperactivity disorder	1.80(1.31-2.48)	1.64(1.11-2.42)	0.91(0.67-1.22)
Mental retardation (mild to severe)	6.18(4.54-8.40)	4.25(2.78-6.50)	1.17(0.89-1.53)

*Adjusted for: paternal psychiatric disorder, maternal psychiatric disorder, paternal educational level, and maternal educational level. †Including syndromes and chromosomal anomalies.

Table 3. Hazard ratios of psychiatric in- or outpatient admission among congenital heart defect patients compared with the population control cohort by age, gender, and surgery or catheter-based intervention. Data are presented for all study subjects and for a subgroup of patients and control cohort members born at term without extracardiac defects.

Hazard ratio by age group in years (95% confidence interval)*				
	All		No extracardiac defect [†] and born at term	
	<15 years	15-30 years	<15 years	15-30 years
All	1.99(1.73-2.27)	1.22(1.04-1.44)	1.61(1.35-1.91)	1.21(1.00-1.46)
Gender				
Male	1.76(1.48-2.03)	1.57(1.22-2.01)	1.47(1.19-1.83)	1.54(1.15-2.06)
Female	2.49(2.00-3.10)	1.04(0.84-1.30)	1.89(1.42-2.51)	1.06(0.83-1.35)
Surgery or catheter-based intervention				
Yes	2.22(1.86-2.65)	1.15(0.90-1.48)	1.64(1.29-2.08)	1.05(0.78-1.41)
No	1.72(1.41-2.10)	1.34(1.08-1.66)	1.55(1.22-1.98)	1.41(1.11-1.78)

*Adjusted for: paternal psychiatric disorder, maternal psychiatric disorder, paternal educational level, and maternal educational level. [†]Including syndromes and chromosomal anomalies.

Reference List

- (1) Hoffman JIE, Kaplan S. The incidence of congenital heart disease. *Journal of the American College of Cardiology* 2002;39:1890-1900.
- (2) Garne E. Congenital heart defects -- occurrence, surgery and prognosis in a Danish County. *Scand Cardiovasc J* 2004;38:357-362.
- (3) Gaynor JW, Gerdes M, Zackai EH et al. Apolipoprotein E genotype and neurodevelopmental sequelae of infant cardiac surgery. *Journal of Thoracic and Cardiovascular Surgery* 2003;126:1736-1745.
- (4) Gaynor JW, Nord AS, Wernovsky G et al. Apolipoprotein E genotype modifies the risk of behavior problems after infant cardiac surgery. *Pediatrics* 2009;124:241-250.
- (5) Miatton M, De Wolf D, Frantois K, Thiery E, Vingerhoets G. Neuropsychological Performance in School-Aged Children with Surgically Corrected Congenital Heart Disease. *The Journal of Pediatrics* 2007;151:73-78.
- (6) Majnemer A, Limperopoulos C, Shevell M, Rohlicek C, Rosenblatt B, Tchervenkova C. Developmental and functional outcomes at school entry in children with congenital heart defects. *J Pediatr* 2008;153:55-60.
- (7) Spijkerboer AW, Utens EM, Bogers AJ, Verhulst FC, Helbing WA. Long-term behavioural and emotional problems in four cardiac diagnostic groups of children and adolescents after invasive treatment for congenital heart disease. *Int J Cardiol* 2008;125:66-73.
- (8) van Rijen EHM, Utens EMWJ, Roos-Hesselink JW et al. Longitudinal development of psychopathology in an adult congenital heart disease cohort. *International Journal of Cardiology* 2005;99:315-323.
- (9) Gaynor JW, Wernovsky G, Jarvik GP et al. Patient characteristics are important determinants of neurodevelopmental outcome at one year of age after neonatal and infant cardiac surgery. *The Journal of Thoracic and Cardiovascular Surgery* 2007;133:1344-1353.
- (10) Amelsvoort Tv, Henry J, Morris R et al. Cognitive deficits associated with schizophrenia in velo-cardio-facial syndrome. *Schizophrenia Research* 2004;70:223-232.
- (11) McCusker CG, Doherty NN, Molloy B et al. Determinants of neuropsychological and behavioural outcomes in early childhood survivors of congenital heart disease. *Arch Dis Child* 2007;92:137-141.

- (12) Lindstrom K, Lindblad F, Hjern A. Psychiatric Morbidity in Adolescents and Young Adults Born Preterm: A Swedish National Cohort Study. *Pediatrics* 2009;123:e47-e53.
- (13) Linnet KM, Wisborg K, Agerbo E, Secher NJ, Thomsen PH, Henriksen TB. Gestational age, birth weight, and the risk of hyperkinetic disorder. *Archives of Disease in Childhood* 2006;91:655-660.
- (14) Tanner K, Sabine N, Wren C. Cardiovascular malformations among preterm infants. *Pediatrics* 2005;116:e833-e838.
- (15) Knudsen LB, Olsen J. The Danish Medical Birth Registry. *Danish Medical Bulletin* 1998;45:320-323.
- (16) Pedersen CB, G^otzsche H, M^oller J^l, Mortensen PB. The Danish Civil Registration System. A cohort of eight million persons. *Danish Medical Bulletin* 2006;53:441-449.
- (17) <http://www.dst.dk/TilSalg/Forskningsservice/Databaser/IDA.aspx>. 2010.
- (18) European Surveillance of Congenital Anomalies. Guide 1.3 - Instructions for the Registration and Surveillance of Congenital Anomalies. 2009. 27-5-2009.
- (19) Munk-Jorgensen P, Mortensen PB. The Danish Psychiatric Central Register. *Dan Med Bull* 1997;44:82-84.
- (20) Kistrup M, Madsen J, Aggernaes KH, Wang AG. [Intersectorial co-operation in psychiatry]. *Ugeskr Laeger* 2009;171:3514-3518.
- (21) Allebeck P. The use of population based registers in psychiatric research. *Acta Psychiatr Scand* 2009;120:386-391.
- (22) Gothelf D, Feinstein C, Thompson T et al. Risk Factors for the Emergence of Psychotic Disorders in Adolescents With 22q11.2 Deletion Syndrome. *Am J Psychiatry* 2007;164:663-669.
- (23) Majnemer A, Limperopoulos C, Shevell M, Rohlicek C, Rosenblatt B, Tchervenkov C. Developmental and functional outcomes at school entry in children with congenital heart defects. *J Pediatr* 2008;153:55-60.
- (24) Gooley TA, Leisenring W, Crowley J, Storer BE. Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. *Stat Med* 1999;18:695-706.
- (25) Snookes SH, Gunn JK, Eldridge BJ et al. A Systematic Review of Motor and Cognitive Outcomes After Early Surgery for Congenital Heart Disease. *Pediatrics* 2010;125:e818-e827.

- (26) Biederman J, Faraone SV. Attention-deficit hyperactivity disorder. *Lancet* 2005;366:237-248.
- (27) Momma K. Cardiovascular Anomalies Associated With Chromosome 22q11.2 Deletion Syndrome. *The American Journal of Cardiology* 2010;105:1617-1624.
- (28) Utens EM, Versluis-Den Bieman HJ, Verhulst FC, Meijboom FJ, Erdman RA, Hess J. Psychopathology in young adults with congenital heart disease. Follow-up results. *Eur Heart J* 1998;19:647-651.
- (29) Murphy KC, Jones LA, Owen MJ. High rates of schizophrenia in adults with velo-cardio-facial syndrome. *Arch Gen Psychiatry* 1999;56:940-945.
- (30) Kaltman JR, Di H, Tian Z, Rychik J. Impact of congenital heart disease on cerebrovascular blood flow dynamics in the fetus. *Ultrasound in Obstetrics and Gynecology* 2005;25:32-36.
- (31) Miller SP, McQuillen PS, Hamrick S et al. Abnormal brain development in newborns with congenital heart disease. *N Engl J Med* 2007;357:1928-1938.
- (32) Indredavik MS, Skranes JS, Vik T et al. Low-Birth-Weight Adolescents: Psychiatric Symptoms and Cerebral MRI Abnormalities. *Pediatric Neurology* 2005;33:259-266.
- (33) Eaton WW, Mortensen PB, Thomsen PH, Frydenberg M. Obstetric complications and risk for severe psychopathology in childhood. *J Autism Dev Disord* 2001;31:279-285.
- (34) Stump DA. Embolic Factors Associated with Cardiac Surgery. *Seminars in Cardiothoracic and Vascular Anesthesia* 2005;9:151-152.
- (35) Hsia TY, Gruber PJ. Factors Influencing Neurologic Outcome After Neonatal Cardiopulmonary Bypass: What We Can and Cannot Control. *The Annals of Thoracic Surgery* 2006;81:S2381-S2388.
- (36) Hovels-Gurich HH, Konrad K, Skorzewski D et al. Long-term behavior and quality of life after corrective cardiac surgery in infancy for tetralogy of Fallot or ventricular septal defect. *Pediatr Cardiol* 2007;28:346-354.
- (37) Jepsen B, Jepsen P, Johnsen SP, Espersen GT, Sørensen HT. Validity of diagnoses of cardiac malformations in a Danish population-based hospital-discharge registry. *International Journal of Risk and Safety in Medicine* 2006;18:77-81.
- (38) Kessing LV, Olsen EW, Mortensen PB, Andersen PK. Dementia in affective disorder: a case-register study. *Acta Psychiatr Scand* 1999;100:176-185.

- (39) Lauritsen MB, Jorgensen M, Madsen KM et al. Validity of childhood autism in the Danish Psychiatric Central Register: findings from a cohort sample born 1990-1999. *J Autism Dev Disord* 2010;40:139-148.**
- (40) Toren P, Horesh N. Psychiatric morbidity in adolescents operated in childhood for congenital cyanotic heart disease. *J Paediatr Child Health* 2007;43:662-666.**
- (41) Bromberg JI, Beasley PJ, D'Angelo EJ, Landzberg M, DeMaso DR. Depression and anxiety in adults with congenital heart disease: A pilot study. *Heart and Lung: Journal of Acute and Critical Care* 2003;32:105-110.**
- (42) Ross L, Johansen C, Dalton SO et al. Psychiatric Hospitalizations among Survivors of Cancer in Childhood or Adolescence. *N Engl J Med* 2003;349:650-657.**
- (43) Reiss AL. Childhood developmental disorders: an academic and clinical convergence point for psychiatry, neurology, psychology and pediatrics. *J Child Psychol Psychiatry* 2009;50:87-98.**

Study III

Educational achievement among long-term survivors of congenital heart defects:

A Danish population-based follow-up study

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Keywords: Congenital heart defects, Educational status, Population based, Prognosis

Abstract:

Background: Congenital heart defect patients may experience neurodevelopmental impairment. We investigated their educational attainments, from basic schooling to higher education.

Patients and Methods: Using administrative databases, we identified all Danish patients with a heart defect diagnosis born from January 1, 1977 to January 1, 1991 alive at age 13 years. As a comparison cohort, we randomly sampled 10 persons per patient. We obtained information on educational attainment from Denmark's Database for Labour Market Research. The study population was followed until achievement of educational levels, death, emigration or January 1, 2006. We estimated the hazard ratio of attaining given educational levels, conditional on completing preceding levels, using discrete time Cox regression and adjusting for socioeconomic factors. Analyses were repeated for a subcohort of patients and controls born at term and without extracardiac defects or chromosomal anomalies.

Results: We identified 2,986 patients. Their probability of completing compulsory basic schooling was approximately 10% lower than control individuals' [adjusted hazard ratio = 0.79(95 % CI: 0.75-0.82)]. Their subsequent probability of completing secondary school was lower than controls', both for all patients [adjusted hazard ratio = 0.74 (95 % CI: 0.69-0.80)] and for the subcohort [adjusted hazard ratio = 0.80 (95 % CI: 0.73-0.86)]. The probability of attaining a higher degree, conditional on completion of youth education, was affected both for all patients [adjusted hazard ratio = 0.88 (95 % CI: 0.76-1.01)] and for the subcohort [adjusted hazard ratio = 0.92 (95 % CI: 0.79-1.07)].

Conclusion: The probability of educational attainment was reduced among long-term congenital heart defect survivors.

Introduction

The prevalence of congenital heart defects is more than 6 per 1,000 live births and is one of the most frequent congenital defects.¹ Most congenital heart defects are diagnosed during the first year of life, but age at diagnosis varies according to defect type and severity.² Survival of congenital heart defect patients has improved markedly during recent decades³ and the prevalence of adults living with severe congenital heart defects is increasing.⁴ The current goal is to ensure these patients' broad well being, including prevention of comorbidity and promotion of educational attainment.

Several factors affect congenital heart defect patients' educational level. Hospital stays may interfere with school attendance or motivation may be lacking due to emotional difficulties, social isolation, and restricted physical activity.⁵⁻⁷ Perhaps most importantly, neurodevelopmental impairment may affect these patients' ability to pursue an education, due to e.g. chromosomal abnormalities, preterm birth, or treatment-related factors.^{8, 9}

More information on long-term educational outcomes among the growing population of adults with congenital heart defects is needed to counsel patients and their parents, to provide appropriate care and follow up, and to better understand the effect of congenital heart defects on the brain.¹⁰

Interpretation of existing studies is hampered by the following factors: use of self-reported educational data, low participation rates,^{11, 12} inclusion of selected congenital heart defect types,¹³⁻¹⁵ follow up ending after basic schooling,¹⁶ and failure to control for socioeconomic factors related to educational attainment.

We therefore undertook a nationwide study to compare the educational attainments of congenital heart defect patients, from basic schooling to higher education, with that of a population-based comparison cohort.

Patients and methods.

Data on congenital heart defects

We conducted this population-based follow-up study using electronic data from the Danish National Registry of Patients to identify all Danish patients born between January 1, 1977 and January 1, 1991 who received a primary discharge diagnosis of congenital heart defect before the age of 13 years. These patients were followed until January 1, 2006. The Danish National Registry of Patients contains information on all hospital admissions in Denmark, including patients' civil registration number, dates of admission and discharge, surgical procedures, and up to 20 discharge diagnosis coded exclusively by physicians according to the International Classification of Diseases. The 8th edition of the International Classification of Diseases was used until the end of 1993 and the 10th edition thereafter. International Classification of Diseases 8th revision codes used to identify congenital heart defect patients were 746-747 (except for 746.7 and 747.5-747.9, which were not specific to congenital heart defects) and International Classification of Diseases 10th revision codes Q20-Q26 (except for Q26.5-Q26.6 which were not specific to congenital heart defects). Diagnoses of patent ductus arteriosus were only considered for infants with gestational age ≥ 37 weeks. For study purposes each patient was assigned one congenital heart defect diagnostic code, based on the first primary discharge diagnosis of congenital heart defect. We subsequently grouped International Classification of Diseases 10th revision codes according to the corresponding International Classification of Diseases 8th revision codes, to uniformly categorize the study cohort during the study period (Table 1).

We used Denmark's Civil Registration System to sample a comparison cohort of 10 persons per congenital heart defect patient, frequency matched on sex and year of birth.¹⁷ The Civil Registration System also allowed us to identify the parents of all study subjects. The 10-digit

unique civil registration number assigned to every Danish resident since 1968 allows for valid linkage between Danish national registries. In Denmark all persons with congenital heart defects receive public health care free of charge.¹⁸

Data on educational attainment

We used Denmark's Integrated Database for Labour Market Research to obtain annually updated information on the educational level of each study subject and his/her parents, family structure, and parental income. Completion of the following educational levels was ascertained (with the corresponding International Standard Classification of Education level¹⁹): Basic schooling (9 or 10 years of compulsory education) (International Standard Classification of Education level 2); Youth education (International Standard Classification of Education level 3), including upper secondary school and vocational education (the latter leading to jobs such as skilled craftsman or assistant nurse); Higher education, designated as short cycle (International Standard Classification of Education level 4), leading to jobs such as programmer or laboratory technician, medium cycle (International Standard Classification of Education level 5), leading to jobs such as primary school teacher or nurse, and long cycle (International Standard Classification of Education level 5), leading to jobs such as attorney or physician.

Data on extracardiac defects, chromosomal abnormalities, and preterm birth

We used the following codes to identify diagnoses of extracardiac defects and chromosomal abnormalities in the Danish National Registry of Patients: International Classification of Diseases 8th revision: 310.40-310.41, 310.5, 311.40-311.41, 311.5, 312.40-312.41, 312.5, 313.40-313.41, 313.5, 314.40-314.41, 314.5, 315.40-315.41, 315.5, 740.99-759.99 and International Classification of Diseases 10th revision: DQ00.0-DQ99.9. We considered diagnoses given at all ages. According to

a guideline from the European Surveillance of Congenital Anomalies (Eurocat), we disregarded isolated minor defects such as torticollis (Q68.0) or protuberant ears (Q17.3).²⁰ We obtained data on gestational age from the National Medical Birth Registry and defined preterm birth as gestational age < 37 weeks.

Data on mortality

We obtained data on vital status for the entire cohort through linkage with the Civil Registration System, which has kept electronic records on date of birth, date of emigration, and exact date of death for all Danish residents since 1968.¹⁷

Data analyses

Person-years at risk were calculated based on a prespecified age preceding the earliest age at which each educational level could be completed: 13 years of age for basic schooling, 16 years of age for youth education, 18 years of age for short-, medium-, and long-cycle higher education. Persons were followed until the level of education under investigation was attained or until death, emigration or the end of the study period, whichever came first. We estimated the hazard ratio of attaining each educational level using discrete-time Cox regression analysis, with calendar time as the underlying time scale, conditional on attainment of the foregoing level. This method was adapted from Koch *et al.*²¹ We report estimates adjusted for current age, sex, parental income, number of siblings, presence of only a single parent, and parents' highest educational level. The adjusted and unadjusted estimates were not substantially different. We repeated the analysis after excluding individuals in both cohorts who were born preterm or with extracardiac defects or chromosomal abnormalities.

Results

Descriptive data

Of the congenital heart defect patients born between 1977 and 1991, 2,986 were alive at the age of 13 years. The proportion of patients born with extracardiac defects or chromosomal abnormalities (19%) or born preterm (8%) was higher in the congenital heart defect cohort than in the comparison cohort (4% and 4%, respectively) (Table 2).

Educational attainment

The proportion of all congenital heart defect patients who completed basic schooling (85.0%) was lower than the corresponding proportion in the comparison cohort (87.5%) (adjusted hazard ratio = 0.79(95% CI: 0.75-0.82). Also in the subcohort, after excluding persons born with extracardiac defects or chromosomal abnormalities or born preterm, the probability of attaining basic school education among congenital heart defect patients was lower than that for the comparison cohort [hazard ratio = 0.87 (95% CI: 0.83-0.92)]. We repeated this analysis after grouping some of the patients as severe congenital heart defects (including common arterial trunk, transposition of great vessels, tetralogy of Fallot, atrioventricular septal defect, anomalies of heart valve, other malformations of great arteries, and malformations of great veins) and as minor to moderate severity congenital heart defects (ventricular septal defect, atrial septal defect, patent ductus arteriosus, and coarctation of aorta). Congenital heart defect patients in both subgroups had a lower probability of attaining basic schooling than controls and the estimates did not differ according to severity (severe congenital heart defects: hazard ratio = 0.87 (95% CI: 0.76-1.00), moderate severity congenital heart defects: hazard ratio = 0.92 (95% CI:0.85-1.00)). Estimates did not differ according

to gender either (female hazard ratio = 0.86 (95% CI: 0.79-0.93), male hazard ratio = 0.89 (95% CI: 0.83-0.96)).

Among patients who completed a basic schooling, the proportion then completing a youth education was lower among congenital heart defect patients (57.8%) than in the comparison cohort (67.4%) [hazard ratio = 0.76 (95% CI: 0.72-0.81)]. The lower probability of attaining a youth education held in the subcohort analysis, due to differences in attainment of upper secondary school education [hazard ratio: 0.80(95% CI: 0.73-0.86)] but not vocational education [hazard ratio: 1.03(95% CI: 0.87-1.25)]. Among subcohort patients completing youth education, the probability of then attaining a higher education was lower overall than that for the comparison subcohort [hazard ratio = 0.92 (95% CI: 0.79-1.07)].

Discussion

In this population-based follow-up study, we found a lower probability of completing basic and upper secondary school among congenital heart defect patients compared with a population-based control cohort. For all congenital heart defect patients who had completed youth education, the likelihood of completing a medium or long cycle higher education was also lower than that for population controls.

Our study findings extend previous research on this topic.¹¹⁻¹⁶ In line with our results, van Rijen *et al.* found lower than expected educational achievement in a study among adult Dutch patients with a wide range of congenital heart defect diagnostic categories, after exclusion of mentally retarded patients.¹² In contrast to our findings, Nieminen *et al.* found that the educational level among congenital heart defect patients was comparable to that of the general population in a Finnish nationwide study encompassing all congenital heart defect diagnostic categories.¹¹ However, this study was based on self-reports from congenital heart defect patients, with a response rate of 76%,

using data from Statistics Finland on the educational level of the general population as a comparison. It was thus susceptible to both information and selection biases and did not control for socioeconomic variables.

Several factors affect the interpretation of our findings. The congenital heart defect cohort was defined as individuals with a discharge diagnosis of congenital heart defect according to the Danish National Registry of Patients, and misclassification of exposure status may have occurred.

However, the positive predictive value of congenital heart defect diagnoses in the Danish National Registry of Patients is reported to be high,²² and any misclassification is most likely independent of future educational level. A study strength is its population-based design. The Civil Registration System allowed complete long-term follow up of vital status and linkage to complete and accurate data on educational level, reducing selection and information bias. The public and freely accessible nature of the Danish education system reduced the potential for confounding from differences in socioeconomic status among the congenital heart defect patients and the comparison cohort. Furthermore, we were able to adjust for socioeconomic and familial factors that influence educational attainment.

As expected, our analysis indicate that presence of extracardiac defects, chromosomal abnormalities, or preterm birth influence the educational attainments of congenital heart defect patients relative to the comparison cohort as these conditions are more prevalent among congenital heart defect patients and are associated with decreased educational levels.²³⁻²⁵

However in this study we can only speculate on the mechanisms explaining the decreased educational attainments of congenital heart defect patients without these conditions. Most likely multiple factors interact depending on diagnostic subcategories of congenital heart defects, including abnormal brain development²⁶ and brain injury potentially occurring in fetal life,²⁷ during

cardiopulmonary bypass,²⁸ or postoperatively in the intensive care unit²⁹ as well as psychosocial factors.⁷

Conclusion

We found an association between congenital heart defects and a reduced probability of completing basic and upper secondary school as well as medium and long cycle higher education. Attainment of vocational and short cycle higher education did not differ among congenital heart defect patients and their controls.

Reference List

1. Øyen N, Poulsen G, Boyd HA, Wohlfahrt J, Jensen PKA, Melbye M. National time trends in congenital heart defects, Denmark, 1977-2005. *Am Heart J.* 2009; 157:467-73.
2. Hoffman JIE, Kaplan S. The incidence of congenital heart disease. *J Am Coll Cardiol.* 2002; 39:1890-900.
3. Nieminen HP, Jokinen EV, Sairanen HI. Causes of late deaths after pediatric cardiac surgery: a population-based study. *J Am Coll Cardiol.* 2007; 50:1263-71.
4. Marelli AJ, Mackie AS, Ionescu-Ittu R, Rahme E, Pilote L. Congenital heart disease in the general population: Changing prevalence and age distribution. *Circulation.* 2007; 115:163-72.
5. Bruto VC, Harrison DA, Fedak PW, Rockert W, Siu SC. Determinants of health-related quality of life in adults with congenital heart disease. *Congenit Heart Dis.* 2007; 2:301-13.
6. Brandhagen DJ, Feldt RH, Williams DE. Long-term psychologic implications of congenital heart disease: a 25-year follow-up. *Mayo Clin Proc.* 1991; 66:474-9.
7. Kovacs AH, Sears SF, Saidi AS. Biopsychosocial experiences of adults with congenital heart disease: Review of the literature. *Am Heart J.* 2005; 150:193-201.
8. Miatton M, De Wolf D, Frantois K, Thiery E, Vingerhoets G. Neuropsychological Performance in School-Aged Children with Surgically Corrected Congenital Heart Disease. *J Pediatr.* 2007; 151:73-8.

9. Shillingford AJ, Glanzman MM, Ittenbach RF, Clancy RR, Gaynor JW, Wernovsky G. Inattention, hyperactivity, and school performance in a population of school-age children with complex congenital heart disease. *Pediatrics*. 2008; 121: 759-767.
10. Altman DG. Systematic reviews in health care: Systematic reviews of evaluations of prognostic variables. *BMJ*. 2001; 323:224-8.
11. Nieminen H, Sairanen H, Tikanoja T, Leskinen M, Ekblad H, Galambosi P, Jokinen E. Long-Term Results of Pediatric Cardiac Surgery in Finland: Education, Employment, Marital Status, and Parenthood. *Pediatrics*. 2003;112:1345-50.
12. van Rijen EH, Utens EM, Roos-Hesselink JW, Meijboom FJ, van Domburg RT, Roelandt JR, Bogers AJ, Verhulst FC. Psychosocial functioning of the adult with congenital heart disease: a 20-33 years follow-up. *Eur Heart J*. 2003; 24:673-83.
13. Ternstedt M, Wall K, Oddsson H, Riesenfeld T, Groth I, Schollin J. Quality of Life 20 and 30 Years After Surgery in Patients Operated on for Tetralogy of Fallot and for Atrial Septal Defect. *Pediatr Cardiol*. 2001; 22:128-32.
14. Otterstad JE, Tjore I, Sundby P. Social function of adults with isolated ventricular septal defects. Possible negative effects of surgical repair? *Scand J Soc Med*. 1986; 14:15-23.
15. Wright M, Nolan T. Impact of cyanotic heart disease on school performance. *Arch Dis Child*. 1994; 71:64-70.
16. Nuutinen M, Koivu M, Rantakallio P. Long-term outcome for children with congenital heart defects. A study from 1 year birth cohort born in 1966 in northern Finland. *Arctic Med Res*. 1989; 48:175-84.

17. Pedersen CB, Gøtzsche H, Møller JO, Mortensen PB. The Danish Civil Registration System. A cohort of eight million persons. *Dan Med Bull.* 2006; 53: 441-9.
18. Health care in Denmark. http://www.sum.dk/publikationer/healthcare_in_dk_2008/index.htm.
19. ISCED 1997. http://www.unesco.org/education/information/nfsunesco/doc/isced_1997.htm.
20. European Surveillance of Congenital Anomalies. Guide 1.3 - Instructions for the Registration and Surveillance of Congenital Anomalies. 2009.
21. Koch SV, Kejs AM, Engholm G, Johansen C, Schmiegelow K. Educational attainment among survivors of childhood cancer: a population-based cohort study in Denmark. *Br J Cancer.* 2004; 91:923-8.
22. Jepsen B, Jepsen P, Johnsen SP, Espersen GT, Sørensen HT. Validity of diagnoses of cardiac malformations in a Danish population-based hospital-discharge registry. *International Journal of Risk and Safety in Medicine.* 2006; 18:77-81.
23. Moster D, Lie RT, Markestad T. Long-term medical and social consequences of preterm birth. *N Engl J Med.* 2008; 359:262-73.
24. Grech V, Gatt M. Syndromes and malformations associated with congenital heart disease in a population-based study. *Int J Cardiol.* 1999; 68:151-6.
25. Tanner K, Sabrine N, Wren C. Cardiovascular malformations among preterm infants. *Pediatrics.* 2005;116:833-838.

26. Miller SP, McQuillen PS, Hamrick S, Xu D, Glidden DV, Charlton N, Karl T, Azakie A, Ferriero DM, Barkovich AJ, Vigneron DB. Abnormal brain development in newborns with congenital heart disease. *N Engl J Med*. 2007; 357:1928-38.
27. Kaltman JR, Di H, Tian Z, Rychik J. Impact of congenital heart disease on cerebrovascular blood flow dynamics in the fetus. *Ultrasound Obstet Gynecol*. 2005; 25:32-6.
28. Hsia TY, Gruber PJ. Factors Influencing Neurologic Outcome After Neonatal Cardiopulmonary Bypass: What We Can and Cannot Control. *Ann Thorac Surg*. 2006; 81: 2381-2388.
29. Newburger JW, Wypij D, Bellinger DC et al. Length of stay after infant heart surgery is related to cognitive outcome at age 8 years. *J Pediatr* 2003; 143: 67-73.

Table 1. Diagnostic categories with corresponding ICD-8 and ICD-10 codes.

Diagnostic category		ICD-8 codes	ICD-10 codes
Common arterial trunk		7460	Q200
Transposition of great vessels		7461	Q203, Q205
Tetralogy of Fallot		7462	Q213
Ventricular septal defect		7463	Q210
Atrial septal defect		7464	Q211
Atrioventricular septal defect		7465, 74641	Q212, Q218B
Anomalies of heart valve		7466	Q220-Q229, Q230-Q239
Other	Other specified anomalies of heart	7468	Q201, Q202, Q204, Q206, Q208, Q209, Q214, Q218, Q219, Q240-Q248
	Unspecified anomalies of heart	7469	Q249
Patent ductus arteriosus		7470	Q250
Coarctation of aorta		7471	Q251
Other anomalies of great arteries	Other anomalies of aorta	7472	Q252-Q254
	Stenosis or atresia of pulmonary artery	7473	Q255-Q256
			Q257-Q259
Malformations of great veins		7474	Q260-Q264, Q268-Q269

ICD: International Classification of Diseases.

Table 2. Characteristics of congenital heart defect patients > 13 years of age and the comparison cohort.

	Patients with CHD. Frequency, N (%)	Comparison cohort. Frequency, N (%)
All	2,986	29,246
Preterm birth	232 (8 %)	1234 (4 %)
ECD or chromosomal abnormality	558 (19 %)	1177 (4 %)
Diagnostic categories		
Common arterial trunk	6	-
Transposition of great vessels *	72	-
Tetralogy of Fallot	89	-
Ventricular septal defect	727	-
Atrial septal defect	312	-
Atrioventricular septal defect	111	-
Anomalies of heart valve	151	-
Other anomalies of heart	1069	-
Patent ductus arteriosus	231	-
Coarctation of aorta	140	-
Other malformations of great arteries	76	-
Malformation of great veins	2	-

ECD: Extra cardiac defect.

CHD: congenital heart defect

*Complete and congenitally corrected transposition.

Table 3. Educational attainment of all congenital heart defect patients and the subcohort excluding patients born preterm or with extracardiac defects.

Educational level		All patients				After exclusion of individuals born preterm or with ECD or chromosomal anomalies			
		Number at risk (n)*	Proportion who completed education (%)	Median age at completion (Years)	Hazard ratio, adjusted (95% CI) [§]	Number at risk (n)*	Proportion who completed education (%)	Median age at completion (Years)	Hazard ratio, adjusted (95% CI) [§]
Basic school (Born before 1991) [†]	Comparison cohort	29,246	87.5	16.5	1	26,904	87.6	16.5	1
	CHD patients	2,986	85.0	16.6	0.79(0.75-0.82)	2,260	86.6	16.6	0.87(0.83-0.92)
Youth education (Born before 1987) [†]									
<i>Overall</i>	Comparison cohort	20,531	67.4	20.4	1	18,923	68.0	20.4	1
	CHD patients	2,072	57.8	20.6	0.76(0.72-0.81)	1,617	62.3	20.6	0.83(0.78-0.89)
<i>Upper sec.</i>	Comparison cohort	20,531	48.1	20.1	1	18,923	48.7	20.1	1
	CHD patients	2,072	38.8	20.3	0.74(0.69-0.80)	1,617	41.8	20.2	0.80(0.73-0.86)
<i>Vocational</i>	Comparison cohort	20,531	24.7	22.1	1	18,923	24.8	22.1	1
	CHD patients	2,072	24.1	22.2	0.94(0.79-1.12)	1,617	26.6	22.3	1.03(0.87-1.25)
Higher education (Born before 1982) [†]									
<i>Overall</i>	Comparison cohort	8,554	31.1	25.3	1	7,982	31.3	25.3	1
	CHD patients	770	26.9	25.1	0.88(0.76-1.01)	657	28.3	25.1	0.92(0.79-1.07)
<i>Short cycle</i>	Comparison cohort	8,554	6.46	24.5	1	7,982	6.5	24.5	1
	CHD patients	770	6.10	23.8	0.98(0.72-1.32)	657	6.7	23.8	1.08(0.79-1.48)
<i>Medium cycle</i>	Comparison cohort	8,554	11.2	25.8	1	7,982	11.2	25.8	1
	CHD patients	770	8.8	25.8	0.82(0.64-1.05)	657	9.3	25.8	0.82(0.64-1.05)
<i>Long cycle</i>	Comparison cohort	8,554	14.1	25.1	1	7,982	14.3	25.1	1
	CHD patients	770	12.3	24.9	0.89(0.72-1.11)	657	12.8	25.1	0.91(0.73-1.14)

*Conditional on being alive at age 13. Results are also conditional on completion of basic school before youth education and completion of youth education before higher education. † Restrictions based on birth year were made to enable attainment of educational level within the study period. § Adjusted for current age, sex, parental income, number of siblings, having a single parent, and parents' highest educational level. CHD: congenital heart defect, CI: Confidence interval, ECD: Extra cardiac defect.

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