FACULTY OF HEALTH SCIENCE, AARHUS UNIVERSITY

Incidence and Mortality of Pulmonary Hypertension in Adults with Congenital Heart Disease: A Nationwide Population-based Cohort Study

Research Year Report

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Preface

This report is based on a study conducted during my research year and was carried out at the Department of Clinical Epidemiology, Aarhus University Hospital, from February 2016 to January 2017.

It has been a pleasure spending a year at KEA, a great working environment with lovely colleagues - hopefully more will follow in the future. Thank you, Nicolas and Russel, for contributing to the project with enthusiasm and your invaluable clinical knowledge. A special thanks to Morten, my supervisor (and mentor of course), for always leaving his door open, laughing at and patiently discussing all of my questions and ideas.

Sara Søndergaard Schwartz, 2017

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Abbreviations

CHD = Congenital Heart Disease

CHD-PH = Congenital Heart Disease with any diagnosis of PH (all forms)

CHD-nonPH = Congenital Heart Disease without any diagnosis of PH (all forms)

CI = Confidence Interval

CPR = Civil Personal Registration

DMBR = Danish Medical Birth Registry

DNPD = Danish National Prescription Database

DNRP = Danish National Registry of Patients

ECD = Extra Cardiac Defects

HR = Hazard Ratio estimated from Cox proportional hazards regression

ICD = International Classification of Diseases

IQR = Interquartile range

PAH = Arterial Pulmonary Hypertension

PH = Pulmonary Hypertension

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ABSTRACT

Background: Reports on pulmonary hypertension (PH) in the aging congenital heart disease (CHD) population are few and often focused patients with systemic-to-pulmonary shunts.
Objectives: Estimate incidence and mortality of PH in CHD adults.
Methods: In Danish nationwide registries, we identified all diagnosed with CHD from 1963-1974 and 1977-2012 and matched them 1:10 by birth year and gender with general population subjects. Adults were followed until PH-diagnosis, death or emigration, whichever came first. We computed cumulative incidences of PH. Using Cox regression, we compared mortality rates between CHD subjects with and without PH.
Results: We identified 14,860 CHD adults. At 70 years of age 7.2% had developed PH (8.3% in those with shunts and 5.3% in those without) compared to 0.4% in the general population. The 1- and 5-year mortality for CHD adults with PH was 24% and 44%, respectively. This represented a 4-fold increase in mortality compared to CHD adults without PH.
Conclusions: The incidence of PH was substantially increased in CHD adults relative to the general population, not only in those with shunts. Among CHD adults PH substantially increased mortality.

DANSK RESUMÉ

Baggrund: Viden om pulmonal hypertension (PH) blandt voksne med medfødte hjertefejl er begrænset og hovedsagligt omhandlende patienter med systemisk-til-pulmonale shunts.
Formål: Vurdere incidens og mortalitet af PH blandt voksne med medfødte hjertefejl.
Metode: I to danske registre identificerede vi alle diagnosticeret med medfødte hjertefejl fra 1963-1974 og 1977-2012 og matchede dem 1:10 på alder og køn med personer fra den generelle population. De blev fulgt indtil PH, død eller emigration. Vi beregnede cumuleret incidens af PH og vha. Cox regressions analyse sammenlignede vi mortalitetsraten blandt hjertefejls patienter med og uden PH.
Resultater: Vi identificerede 14,860 voksne med medfødte hjertefejl. Ved 70 år havde 7.2% udviklet PH (8.3% af patienter med shunts og 5.3% af dem uden), sammenlignet med 0.4% af den generelle population. 1- og 5 års mortaliteten for voksne med hjertefejl var hhv. 24 og 44%, svarende til en 4 gange øget mortalitet sammenlignet med hjertefejlspatienter uden PH.
Konklusion: Incidensen af PH er øget blandt voksne med hjertefejl, ikke kun blandt dem med shunts, sammenlignet med den generelle befolkning.

MANUSCRIPT

Introduction

Congenital heart disease (CHD) is one of the most common birth defects, affecting nearly1% of all live births(1, 2). Over the last four decades the mortality rate of this population has decreased(3), and as a result, the CHD population is growing and aging(4) such that there are now more adults with CHD than children(5). However, several aspects of the long-term morbidity of this unique population require clarification.

One of the potential complications of CHD is pulmonary hypertension (PH), a heterogeneous group of disorders, resulting in limited functional capacity(6), and an increased risk of arrhythmias, heart failure, renal failure, hepatic dysfunction(7), as well as increased mortality(8, 9). PH can both be difficult to diagnose(10) and to classify(11), especially in patients with CHD(12, 13). The World Health Organization has classified PH into five subgroups, based on similarities in etiology, pathophysiological characteristics and treatment(11). Group 1 PH, pulmonary arterial hypertension (PAH), is seen in patients with historical or continued systemic-to-pulmonary shunts and is the most studied type of PH among CHD subjects. However, PH in CHD subjects may also be the consequence of left heart disease, eg. as a result of left heart inflow/outflow obstructive lesions, congenital hypoplasia or left heart failure (group 2). In addition, although less common, PH may also occur with concomitant lung diseases (group 3), pulmonary thromboembolic disease (group 4), or from other uncommon mechanisms (group 5, PH with unclear multifactorial mechanisms).

There are very few data on the occurrence of these other forms of PH in the CHD population. Most previous estimates of the risk of PH in adults with CHD have focused on PAH alone, and therefore only included subjects with historical or continued systemic-to-pulmonary shunts(6, 14, 15). Other studies were further limited by an overrepresentation of

patients treated at tertiary care centres(6), or the consequences of loss to follow-up(16). All previously reported mortality rates of adults with CHD and PH have likewise been limited to PAH.

This nationwide population-based cohort study is the first to evaluate the cumulative incidence and mortality of PH across the entire adult CHD population, not only those with systemic-to-pulmonary shunts, and the first to use a measure of PH that includes all PH sub-types. In addition, this study has the added advantage of an age and gender matched comparison cohort from the general population.

Methods

Setting

This nationwide population-based cohort study was conducted in Denmark, with a current population of approximately 5.6 million individuals. The Danish National Health Service provides tax-supported healthcare, with free access to hospital-based and primary medical care, including care for CHD and PH.

Data linkage

Since 1968, a unique ten-digit civil personal registration (CPR) number has been assigned to all residents of Denmark. CPR numbers are used in all Danish registries, permitting unambiguous individual-level linkage of data from all sources used in this study. This provided us with virtually complete follow up until death, emigration or the outcome under study(17). The Civil Registration System also made it possible to identify a general population comparison cohort.

Congenital Heart Defect Cohort

In two nationwide registries, we identified individuals diagnosed with CHD before 15 years of age in the years 1963-1974 and CHD at any age from 1977-1995. CHD survivors

diagnosed from 1963-1974 were identified based on review of in-patient and out-patient medical records in all Danish pediatric and medical departments by an experienced medical doctor, Henning Bækgaard Laursen(18). Beginning in 1977, the Danish National Registry of Patients (DNRP)(19, 20) contains information on all hospital admissions in Denmark, including dates of admission and discharge, surgical procedures, and up to 20 discharge diagnoses coded by physicians according to the ICD coding of the time (8th edition until the end of 1993 and 10th edition, thereafter). Since 1995, the DNRP also contains information on all emergency room and hospital outpatient clinic contacts. The following ICD codes were used to identify patients with CHD from 1977 and onwards; ICD-8: 746-747 (except for 746.7 and 747.5-747.9, which were not specific to CHD), ICD-10: Q20-Q26 (except for Q26.5-Q26.6, which were not specific to CHD).

General Population Cohort

For each CHD subject, we identified 10 comparison cohort members from the general population using the Civil Registration System(17), matched by gender and birth year.

Pulmonary Hypertension and Covariates

Pulmonary hypertension was identified using the DNRP (see appendix 1).

CHD subjects were categorized in two groups; those with defects resulting in systemic-to-pulmonary shunting (arterial septal defect, ventricular septal defect, atrioventricular septal defect, tetralogy of Fallot, patent ductus arteriosus, common arterial trunc, double inlet ventricle, double outlet right ventricle, aortopulmonary septal defects and other malformations of cardiac septa) and those with all other defects. This was done according to their ICD coding (see appendix 1). Furthermore, subjects were divided according to the CHD complexity: mild (biventricular without any history of surgery or intervention), moderate (biventricular with history of surgery or intervention) or severe (complex biventricular physiology, history of single ventricle diagnoses or palliative surgery such as Norwood,

Glenn, and Fontan), and unclassified. In order to optimize the accuracy of the CHD categorization, we employed a previously described hierarchical algorithm based on the medical facility of the provider issuing the diagnosis(21, 22).

We included information on extra-cardiac defects (ECDs) and chromosomal abnormalities (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, excluding the codes mentioned above for CHD) given at any time after birth. 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 ears(23). We also included information on congestive heart failure and left ventricular dysfunction (ICD-8: 427.09-19, 428.99, 782.49 and ICD-10: I11.0, I13.0, I13.2, I42, I50.0-1, I50.9, see appendix 1).

Statistical analysis

Adults over 18 years were followed from January 1st 1977 and continued until death, emigration, onset of PH or end of study (January 1, 2013), whichever came first.

We made cumulative incidence curves by age in years with death as a competing risk and computed 70-year cumulative incidence of PH for the CHD cohort and the comparison cohort overall, as well as for several subgroups of CHD (subjects with or without systemic-to-pulmonary shunt lesions, subjects with mild, moderate or severe lesions, and those born with and without ECD). We computed incidence rates for the above mentioned subgroups, and using Cox proportional hazards regression, we computed hazard ratios to estimate the relative risk of PH among adults with CHD compared to the general population cohort. All analyses were adjusted for gender and birth year unless the covariate was used for stratification.

The prevalences of PH were calculated as the ratio between the number of CHD subjects diagnosed with PH during the study period who were alive and ≥18 years of age at January 1st 2013 and the total number of CHD subjects alive and ≥18 years of age in January 2013. Confidence intervals were calculated with a confidence level of 95%.

We computed 1, 5 and 10 year all-cause mortality rates for adults with CHD diagnosed with PH (CHD-PH) during the study period and for a control group of CHD adults without PH (CHD-nonPH), with two control subjects per CHD-PH adult matched on gender and birth year (±2 years). All CHD-nonPH controls were given an index date equivalent to the time of the PH diagnosis of the matching CHD-PH adult. Utilizing Cox regression analyses we compared the all-cause mortality between CHD-PH adults and CHD-nonPH controls. In addition, within the CHD-PH adults, we computed HRs for men and women and between adults with shunt lesions and those with other defect types. These analyses were adjusted for gender, birth year, CHD severity and the presence of ECD.

Analyses were performed using Stata® 14 package (StataCorp LP, Texas, US).

Results

We identified 14,594 CHD subjects, with a median follow-up period of 22.3 years (interquartile range 8.9-34.5 years). Of the total, 47% were male and 65% had a diagnosis of a systemic-to-pulmonary shunt (Table 1).

Risk of Pulmonary Hypertension

During the study period, 266 were diagnosed with PH, with a median age at the time of diagnosis of 51 years (interquartile range 36-67 years). Adults with CHD-PH compared to CHD-nonPH were more often female (64% vs. 52%), more likely to have a history of a systemic-to-pulmonary shunt lesion (75% vs. 65%), older (56% vs. 20% were born prior to 1955), more likely to have a diagnosis of congestive heart failure at any time (50% vs. 11%),

and more likely to have a diagnosis of congestive heart failure before the diagnosis of PH (28% vs. 11%) (Table 2). The cumulative incidence of adult onset PH by 70 years of age in the CHD population was 7.2% (95% CI 6.2-8.4) compared to 0.4% (95% CI 0.4-0.5) in the general population cohort (see Figure 1 and Table 3). The majority of those with PH were women (64% by 70 years of age), and the cumulative incidence was higher in women than men (8.7%, 95% CI 7.2-10.4 compared to 5.7%, 95% CI 4.4-7.2). The overall incidence rate of PH in adults with CHD was 1.3 (1.1-1.4) per 1,000 person-years. Incidence rates per 1,000 patient-years increased with age from 0.5 (95% CI 0.4-0.7) in young adults (18-29 years) to 6.3 (95% CI 5.0-7.5) in those greater than 60 years of age. The overall hazard ratio of developing PH was 23.6 (95% CI 18.7-29.6) when comparing adults with CHD to their age and gender matched general population cohort members. When excluding subjects with ECD, the hazard ratio was 21.6 (95% CI 16.8-27.6).

Although the cumulative incidence of PH was highest among CHD adults with severe lesions (13.4%, 95%CI 10.7-16.3), the cumulative incidence at 70 years of age was roughly 6% in both those with mild (5.8%, 95% CI 4.4-7.5) and moderate (5.7%, 95% CI 3.8-8.3) CHD defects.

For CHD adults with systemic-to-pulmonary shunts, the cumulative incidence of PH was 8.3% (95% CI 7.0-9.8) compared to 5.3% (95% CI 3.9-7.1) noted in those CHD adults with other CHD defect types. We did not find a difference between CHD adults with and without shunt lesions in the proportion of subjects who had a diagnosis of congestive heart failure or left ventricular dysfunction. This was true both in the entire CHD study population (12% vs. 11%, respectively), and among CHD adults who had developed PH (30% vs. 24%, respectively when only including those with a diagnoses of congestive heart failure prior to the PH diagnosis, and 51% vs. 47%, respectively when including those with a diagnosis of congestive heart failure diagnosed after PH) (Table 1 and 2).

Compared to the age and gender matched general population cohort, the hazard ratio for PH was 26.8 (95% CI 20.3-35.4) and 17.4 (95% CI 11.5-26.2) for CHD adults with and without systemic-to-pulmonary shunts, respectively. The overall incidence of CHD-PH was 1.5 (1.2 in men and 1.7 in women) per 1,000 person-years in CHD subjects with a history of systemic-to-pulmonary shunts and 0.9 (0.6 in men and 1.2 in women) per 1,000 person-years within the population of adults with CHD with other cardiac defects.

Prevalence

Of 11,343adults with CHD alive and ≥18 years of age on January 1st 2013, 126 had been diagnosed with PH during the study period, equivalent to a prevalence of 1.1% (95%CI 0.9%-1.3%). The prevalence of PH did not differ between those with and without a history of systemic-to-pulmonary shunts (1.2%, 95%CI 0.9-1.4% and 1.0%, 95%CI 0.7-1.4, respectively). The prevalence of PH in CHD adults with mild, moderate and severe defects was 0.6% (95%CI 0.4-0.9), 1.2% (95%CI 0.8-1.7) and 2.3% (95%CI 1.8-2.9), respectively. Among all 11,343 adults with CHD, 65% had a systemic-to-pulmonary shunt, compared to 68% among the 126 CHD-PH adults (see table 4).

Mortality

Cumulative mortality curves for CHD-PH adults and CHD-nonPH controls are displayed in Figure 2. The 1-, 5- and 10-year mortality for CHD-PH subjects was 24%, 44% and 52% , respectively (Table 5). CHD adults with PH had a more than 4 times higher mortality compared to CHD-nonPH controls after adjustment for gender, birth year, CHD severity and presence of ECD (HR=4.3, 95% CI 3.3-5.6).

We found no difference in mortality between men and women with CHD-PH [HR 0.9 (0.6-1.3)]. The estimates did not change when adjusting for birth year, CHD severity and the presence of ECD. When comparing all-cause mortality for CHD-PH adults with a specific history of systemic-to-pulmonary shunts to those CHD-PH adults with other CHD defects,

the HR was 1.8 (95% CI 1.1-2.9) after adjusting for gender, birth year, CHD severity and presence of ECD.

Discussion

The incidence of PH in adults with CHD is increased relative to the general population, and it is not limited to those with a history of systemic-to-pulmonary shunts or with severe defects. In addition, PH increased the risk of mortality substantially among CHD adults. Our study indicates that the risk for PH in adults with CHD is broadly distributed across the entire population.

Risk and Prevalence of Pulmonary Hypertension

We are the first to evaluate the incidence of PH in a well-defined CHD population with complete follow-up. Only two studies have previously estimated the incidence of PH in the CHD population(25, 26), but since their main focus were all types of PAH and not CHD, incidence rates of CHD-PAH were reported per million population-years (0.3 and 2.2 cases per million population-years in a French(26) and Scottish(25) study, respectively) and comparison of the estimates were therefore not readily done.

The only other previous study to examine all types of PH was a cross-sectional study that found that at least 20% of CHD-PH patients did not have a history of a shunt lesion(24), which is in line with our results showing that a third of prevalent CHD-PH adults did not have a shunt lesion. Unfortunately, 40% of the CHD-PH adults in their study had an unspecified CHD-type(24).

As left heart failure is one of the most common causes of pulmonary venous hypertension, we designed our study to determine the proportion of subjects with diagnoses for congestive heart failure and left ventricular dysfunction. We did find that the proportion of left heart failure was higher among CHD-PH adults compared to CHD-nonPH adults. This

highlights the idea that preventing congestive heart failure in the CHD population is an important step in preventing PH, and given the associated mortality of PH, this is a finding of clinical significance.

We found that more women than men developed PH by 70 years of age, and that the highest cumulative incidences of PH were found in CHD survivors with severe lesions and extra cardiac defects. However, the cumulative incidence of PH at 70 years of age were over 5% for both mild and moderate CHD and almost 7% for CHD adults without ECD, again underlining the need to embrace a wider focus when evaluating which CHD patients might be at risk for PH.

Most previous studies have been cross-sectional, inherently based on survivors and might therefore be missing the most severe cases of PH. In addition, high mortality following PH could result in a low prevalence estimate, even if the incidence is high. Our point prevalence estimate (1.1%) was substantially lower than what previous studies have reported. A Canadian registry study(24), found the prevalence of PH to be 5,8% in 38,430 CHD adults alive and >18 years in 2005. However, in contrast to our study, they included PH-diagnoses made before 18 years of age, which likely explains part of the difference. Since many cases of pediatric PH in CHD patients are transient(27), and because these patients typically survive into adulthood, they might incorrectly contribute to the overall adult PH prevalence estimate. In addition, both the median age (42: IQR 28-63 compared to 38: IQR 25-50) and the percentage of women (56 % compared to 52%) were higher in the Canadian prevalence cohort than in ours, which could also explain some of the difference.

A Dutch study(28) found the prevalence of PAH to be 4.2% among 5,970 CHD adults in 2005. This registry included adults with CHD who have been identified from 86 tertiary centres and regional hospitals since 2001, and therefore only included patients who have had contact with the health care system after age 18 years. This could limit the cohort to CHD

adults at increased risk for PH because of a higher severity of disease. Unfortunately, no baseline characteristics were listed to allow for comparison with our study population.

The true cumulative incidence proportions and the incidence rates of PH might be even higher than what we have observed. There is both a possibility of under-coding and underdiagnosing. The symptoms of PH are non-specific and not uncommon in patients with CHD and some cases might go unrecognized. One study found that around 20% of patients with PAH experienced symptoms more than two years prior to diagnosis(10), and another study found an average time from symptoms to diagnosis of PH in patients with CHD to be 52.0 ± 62.8 months(29). This delay and the potential absence of diagnosis can have severe clinical implications, especially considering that we found a 1 year mortality rate of 24%.

Mortality

We found PH to be associated with an increase in mortality for all CHD-PH adults. Our 44% 5-year mortality estimate was higher than the 20-28% range demonstrated by previous studies(24, 30). Our higher mortality rates cannot readily be explained by the inclusion of other types of PH in our cohort, as CHD-PH adults with a history of systemic-to-pulmonary shunts did not demonstrate a lower mortality rate than those with other heart defect types. Comparing CHD-PH subjects with CHD-non-PH controls we found a 4-fold increase in mortality, which is in line with previous results(24, 32).

Study strengths and limitations

The Danish civil registration system allows a population-based study design with virtually complete long-term follow-up of vital status, emigration and hospital admissions, substantially reducing selection bias. However, some limitations should be acknowledged. The validity of our design is dependent on the accuracy of coding of the CHD and PH diagnoses, and while we did not have access to individual medical records, the positive predictive value of CHD according to the DNRP is known to be nearly 90%(33).

Additionally, utilizing the criteria developed by the Danish Registry of Congenital Heart Defects, it is likely even higher(34). Furthermore, any misclassification of overall CHD status is small and independent of future development of PH. There remains a risk for misclassification of shunt-status among CHD subtypes, and we specifically did not include the approximately one hundred CHD adults with surgically created shunts in this category. However, sub-analyses showed that including those subjects did not change the main results (data not shown).

The validity of the various PH diagnosis in the Danish registries have not previously been examined; however, one previous registry study using ICD-9 diagnostic codes for PH performed a sensitivity analysis based on information from diagnostic procedures and supported the validity of the PH diagnoses(24). Specifically, excluding patients whose PH diagnoses were not made during hospitalization by cardiologist or pulmonologists familiar with PH did not change their main results(24).

The fact that having a diagnosis coding of PH was associated with increased mortality also supports the validity of the diagnosis in the DNPR. As mentioned, diagnosis of PH is often delayed and the diagnostic dates do not necessarily represent the true onset of the disease, which should be taken into account when evaluating the mortality estimates.

Unfortunately, the WHO classification of PH has not been translated into useful ICD-categories and ICD does not differentiate between the five clinical subgroups of PH. Although subjects with systemic-to-pulmonary shunt lesions are suspected to be at higher risk for group 1 PH (pulmonary arterial hypertension) and those with non-shunt lesions are most likely to develop group 2 PH (pulmonary venous hypertension due to left heart disease), we cannot assert anything conclusive about the type of PH and its associated incidence and mortality. This is an area of potential future research. Several studies have found misclassification between subtypes of PH, especially pulmonary venous hypertension

misclassified as being arterial, likely a result of methodology(35, 36) and limitations/changes in the ICD coding(37). However, none of these studies invalidate the conclusion that these individuals have some form of PH. Since we included all cases of PH, this potential misclassification between subtypes does not affect our results.

The high proportion of CHD-PH adults with systemic-to-pulmonary shunt lesions who had a diagnosis of congestive heart failure might call attention to the fact that these individuals have venous and not arterial PH. Although the congestive heart failure diagnosis has been found to have a high specificity and positive predictive value (95% and 84%, respectively), the sensitivity is only 63%(23). In addition, there may be a high degree of underreporting, and further research is needed to say anything conclusive about the relationship between congestive heart failure and PH in the CHD population.

Another potential limitation to address in the comparative analysis is surveillance bias. Adults with CHD could be more likely to receive a diagnosis of PH relative to the general population-based controls given their potential for more frequent contact with the medical establishment. By the same logic, there could be a bias towards diagnosing adults with more severe CHD defects relative to those with mild defects. However, we expect the surveillance bias to be minimal in our study for two reasons. One, PH is not routinely screened for in most CHD types, and this is especially true of those with mild disease. And two, Danish health care is free and universal for the population, which presumably results in adults seeking medical help when necessary as opposed to only those with chronic disease.

Due to the continuous development of both CHD and PH treatment and management strategies, results from different eras cannot be readily compared. However, while the methods and interventions that preceded and potentially led to PH in our population may have been modified or even become obsolete, PH remains hugely important today for all the

adults with CHD across all eras. Studying these eras helps us understand how we need to care for these populations and how to determine predictors of poor health.

Conclusion

This nationwide study demonstrates that PH in the aging CHD population is a common and morbid long-term complication. Our results indicate that PH is more ubiquitous in the CHD population that previously described, and that the risk is not isolated to those with systemic-to-pulmonary shunts or severe CHD type. We believe future efforts should be targeted at increasing the long-term attention to both the diagnosis, as well as the associated management, in order to improve the health of those with CHD.

SUPPLEMENTARY

The following sections contain additional background information on pulmonary hypertension, methodological and statistical considerations and discussions concerning strengths and limitations, including reflections on bias and confounding. Furthermore, additional analyses and results on the effect of premature birth and the presence of extra cardiac defects on the risk of PH not included in the manuscript are presented.

Extended Background

Pulmonary hypertension; pathophysiology and classification

Pulmonary hypertension (PH) is an increase of blood pressure in the pulmonary vascular system. The cardinal symptoms include shortness of breath, fainting, light-headedness in activity, fatigue, and chest pain. All symptoms are unspecific and PH is not routinely examined for in patients with CHD. In addition the pressure of the pulmonary circulation is not easily measured, further complicating PH diagnosis. This is of particular concern because delay in diagnosis may worsen the prognosis.

Previously, studies on PH in patients with CHD have focused on pulmonary arterial hypertension (PAH), but WHO's most recent classification scheme (see supplementary table 1) acknowledges that PH in adult patients with CHD can be related to pulmonary venous hypertension (WHO group 2, PH due to left heart disease)(12).

The pathogeneses of pulmonary arterial and venous hypertension are very different. For patients with systemic-to-pulmonary shunt lesions the pathophysiological mechanisms include increased pulmonary blood flow that lead to increased pulmonary pressure and shear stress, that in time may lead to progressive vascular remodelling and ultimately pulmonary arterial hypertension (PAH)(38). In patients with left heart inflow/outflow obstructions, congenital cardiomyopathy or left heart failure the inefficient pumping of blood can result in

back pressure and pooling of blood in the lungs and thereby an increased pulmonary venous pressure. Although the latter is not specific for patients with CHD, it is still important as CHD is associated with heart failure(39).We wish to address the fact that all CHD adults, and not only those with a history of systemic-to-pulmonary shunts may be at risk of PH.

CHD subjects are known to be at risk for neonatal PH(27), but there is still limited knowledge about PH in the adult CHD population. This is becoming ever more important as the CHD population is aging(40). Therefore, and because most cases of pediatric PH is transient(27), we choose to focus on adult-onset PH only and only considered PH-diagnoses made after 18 years of age.

Methodological considerations

Additional information on exclusion and inclusion criteria for CHD

More detailed description of the diagnostic codes and exclusion criteria used for identifying CHD subjects in DNPR has previously been published(41). For instance, diagnoses of isolated atrial septum defect, ventricular septum defect or patent ductus arteriosus were excluded if the age at diagnosis was less than 2 months, given that the diagnosis was not repeated later in life, and no therapeutic cardiac procedure was recorded within the first two months of age(41).

Study design and statistical analyses

Our primary aim was to investigate the risk of PH in all adult patients with CHD, compared to the general population. Second, we wanted to estimate the mortality rate for CHD adults after PH-diagnosis and compare it to CHD patients without PH.

For both purposes we designed observational registry-based cohort studies using data from registries, as registry-based cohort studies are able to demonstrate the temporal relationship between exposure and outcome in a highly cost-effective way.

A cohort is a group of subjects that share certain characteristics and are followed for a period of time. For both study purposes we included a matched cohort. For our primary aim we used the Civil Registration System to identify a comparison cohort from the general population matched 10:1 on gender and birth year. The matching was without replacement, meaning that subjects lost in the comparison cohort would not be replaced. In comparative analyses we also adjusted for gender and birth year, because potentially differential loss to follow-up, especially with the long follow-up period of our study, may lead to an unsustainable matching.

For our second aim, the study cohort consisted of those CHD adults diagnosed with PH (CHD-PH) identified in our first study and the comparison cohort consisted of CHD adults without PH (CHD-nonPH) matched on gender and birth year ($\pm$2 years). Instead of matching a comparison cohort we also considered analysing mortality by using PH as a time dependent variable (see 'Time dependent variables' for explanatory comments). In that way we could use the entire CHD population as basis for comparison, but we found that the rates between the two groups were non-proportional, so we could not perform a cox regression analysis. Furthermore, because this would not allow us to have an index date for CHD adults without PH, we would not have been able to compare 1, 5 and 10 year mortality rates between CHD adults with and without PH.

Competing events and other assumptions

To compute cumulative incidences, incidence rates, and hazard ratios comparing the rate of PH in CHD adults and subgroups hereof to the general population we used time to event methodology (time to first event). We wished to assess adult onset PH and each subject were considered at risk and follow-up time began from CHD diagnosis, 18 year birthday or study start (January 1st 1977), whatever came last, which is known as delayed or staggered entry. They were then followed until the first event of our study outcome, PH, loss to follow-

up eg. because of emigration or death. We needed to take loss to follow-up into account, as a criterion for being a cohort member is to be at risk and therefore able to experience the outcome. Cumulative incidence proportions is defined as the probability that an event has occurred by a given time(42) and is calculated using by the number of new events during a period divided by the number of subjects at risk in the population, and if a subjects dies he or she is of course no longer at risk(43). Therefore it would not be appropriate to censor study subjects in the event of death when calculating cumulative incidence, such as it is done in the Kaplan Meier estimator, as censored subjects are assumed to have the same probability of experiencing the outcome as uncensored subjects (independent censoring, see below), and death was therefore included as a competing event when calculating cumulative incidence proportions(44). To illustrate, we found a cumulative risk of 7.2% at 70 years of age in CHD subjects, but if more CHD adults had died, then fewer would have developed PH and the cumulative incidence would therefore have been lower.

Both incidence rates and hazard ratios derived from Cox regression analyses are based on rates, and absence of competing risks is not a required assumption. There are, however, several important basic assumptions for the cox regression analysis that needs to be met, including that the time of outcome must be either right censored or observed exactly and that censoring must be independent given the co-variates (in order for the study population to be representative of the real population (see 'External validity') censoring should occur independent of the outcome, so that censored subjects, had they not been censored, would have the same course as subjects who were not censored). Because we have delayed entry and subjects therefore enter into the study at different ages and/or time points and because we have administrative censoring at January 1st 2013, independent censoring is equivalent of assuming there is no time trend of the event incidence over calendar time(45). Calendar time trends is present if the risk of the outcome is affected by the time of study entry, and with

administrative censoring, individuals with different entry periods will have different length of follow-up. We checked for the presence of time trends by an analysis stratified by entry-date groups. In addition, the cox regression model assumes proportional hazards, meaning that the hazard ratio between the two cohort compared remain constant over the entire follow-up period. This assumption was checked visually using log-minus-log plots. Because our outcome of interest (PH) is uncommon (<15%), the hazard ratios are reasonable estimates of the relative risk.

Definition of systemic-to-pulmonary shunts

Previous studies on PH in CHD adults have centred on PAH and most have therefore been limited to CHD patients with systemic-to-pulmonary shunts. Based on the hypothesis that all patients with CHD and not only those with shunt lesions were at increased risk for PH compared with the general population, we divided our cohort into two groups; those with a history of systemic-to-pulmonary shunts and those with non-shunt lesions. This was done in collaboration with an expert cardiologist. Diagnoses included in the shunt category included arterial septal defect, ventricular septal defect, atrioventricular septal defect, tetralogy of Fallot, patent ductus arteriosus, common arterial trunc, double inlet ventricle, double outlet right ventricle, aortopulmonary septal defects and other malformations of cardiac septa and diagnostic codes can be seen in appendix 1.

All patients with a diagnostic code for a systemic-to-pulmonary shunt were included in the shunt group, regardless of whether the shunt was closed spontaneously, surgically or was persistent. We did not include patients with surgically created shunts in our main analysis. 122 CHD patients in our CHD cohort had a procedure code for a surgically created shunt (see supplementary table 2 for included procedure codes) and including this subgroup of patients as having a shunt lesion did not change the main results. It is important to note, that we did not have information on surgical procedure codes before 1977.

Additional analyses and results

Premature birth

The lungs are the last organ to mature and subjects born premature may therefore have underdeveloped lungs. This has been shown to increase not only the risk of paediatric PH, but also adult PH(46).

Our dataset included information on premature birth, gestational age and gestational weight, obtained from the Danish Medical Birth Registry(47). Those data were categorized as <37 (preterm) and ≥37 (term). Unfortunately, data were missing for a large proportion of CHD cohort members.

Despite the limitations of data missing for 49% of CHD adults in our study cohort, we choose to perform a cox regression analysis estimating the association between preterm birth and PH within the CHD population. Of those with information on gestational age, 15% (N=1155) were born preterm. This proportion was 15% (N=1145) among CHD-nonPH adults and 21% (N=10) among CHD-PH adults, and using a cox regression analysis we could not find any conclusive difference in the risk of PH among CHD adults born at term or premature (HR=1.4, 95%CI 0.7-2.8). Adjusting for gender, birth year, CHD severity and the presence of ECD did not change the estimate. A previous study not specific for CHD found that adult PH was associated with premature birth with an odds ratio of 3.08 (95% CI 1.21-7.87)(46). Premature birth might be an important intermediate step between CHD and PH it would be interesting to investigate this in future studies.

Congestive heart failure and left ventricular dysfunction

Left heart failure is one of the most common causes of pulmonary venous hypertension and we wanted to investigate if congestive heart failure and left ventricular dysfunction (see supplementary table 2 for diagnostic codes) was a risk factor for PH, as we expected this to be the case, especially among those with other defects than systemic-to-pulmonary shunts.

For this analysis we used the same study cohort of 14,860 CHD adults identified in our primary analysis and as with all previous cox regression analysis, the assumption of proportional rates was verified graphically using log minus log plots. We followed patients from 18 years of age, date of CHD diagnosis or January 1st 1977, whatever came last. During the study period we identified those who received a diagnosis for congestive heart failure or left ventricular dysfunction, and because CHD adults could change exposure-group (having or not having congestive heart failure) during the study period, the variable was time dependent; patients who received a diagnosis of congestive heart failure therefore contributed to both cohorts, first with risk time as 'unexposed' before their diagnosis and then as 'exposed' after their diagnosis.

We found that CHD adults with congestive heart failure had a 3.1 (95%CI 2.3-4.2) times higher risk of developing PH after adjusting for gender, birth year, CHD severity and the presence of ECD (Unadjusted HR=3.7, 95%CI 2.7-4.9). This effect of congestive heart failure on the risk of PH was the same in CHD adults with and without a history of shunt lesions (adjusted HR=3.2 (95%CI 2.3-4.5) and 2.5 (95%CI 1.2-5.2), respectively).

The positive predictive value of congestive heart failure in DNPR is found to be 84%(48). This is supported by an American study that found both high specificity and positive predictive value (95.4% and 83.5%, respectively)(37). The sensitivity, however, was found to be only 62.8%(37), and there may be a high degree of underreporting, and further research is needed to say anything conclusive about the relationship between congestive heart failure and PH in the CHD population.

Strengths and limitations

Several potential limitations of observational studies must be addressed. Observational errors can be divided into two components; random and systematic error. Random error

happens when variability in the data is present by change, results in inconsistent and unpredictable measurement variations and is therefore reduced if the study if sufficiently large. To help describe the statistical variation and thereby the random error that underlie our point estimates we used 95 % confidence intervals, meaning that if the data collection and analysis were replicated again and again and given the study were free of bias, the true value of the measure would be within the confidence interval 95% of the time(49). Wide confidence intervals therefore indicate low precision. Systematic errors are, in contrast, predictable and typically constant and would not be reduced by increasing the study size. There are several sources of systematic error, including selection bias, information bias and confounding.

Selection bias

Selection bias arises if the study population is not representative of the population you are intending to say something about. This can occur if eg. subjects who do not participate in the study differ from those that do in ways that can affect the outcome. Three main factors substantially reduced the risk of selection bias in our study; 1. The Danish registries used cover the entire population, 2. Free access to high quality health care in Denmark ensured a well distributed cohort, and 3. We had virtually complete follow-up provided by the Civil Registration System and DNPR regarding our outcomes, PH, death and emigration, and selection bias due to loss of follow-up were therefore not expected to affect our results. An algorithm developed by experienced cardiac surgeons, cardiologists, and epidemiologists and based on extensive medical record review enabled inclusion of all patients with valid CHD diagnoses(41), so despite the potential limitations of underdiagnosing and -reporting of CHD (see 'Information bias') and the fact that the two registries used to identify CHD subjects did not include patients diagnosed with CHD from January 1st 1974 to December 31st 1976 who

did not have any subsequent medical record data points in DNPR, we expected the study population to be representative of all CHD subjects in Denmark.

Information bias

Information bias occurs if information collected about participant is erroneous(49). It is often referred to as misclassification if the variable (exposure, outcome or covariates) is categorical and the error leads to participants being categorized incorrectly. Misclassification can be either non-differential, if it is unrelated to other variables and the misclassification is the same in all subjects or it can be differential, if it is related to other variables and the risk of misclassification therefore differs between groups. The risk of differential misclassification is minimized by our retrospective registry-based study design because data collection and registration have been prospective and mandatory and therefore independent of our study outcome. However, the fact that data were not collected with the research questions in mind could affect both the type and quality of the data.

As previously stated, the positive predictive value of CHD is expected to be at least 90%(32, 33) and we expect the potential misclassification of our exposure, CHD, to be low and non-differential as diagnosis of CHD is performed without knowledge of later development of PH. It could be hypothesized that mild cases of CHD are more likely to go undiagnosed and therefore be misclassified and that mild cases of CHD are less likely to develop PH than more severe cases, resulting in differential misclassification. We do not have information on the sensitivity of the CHD diagnosis and therefore cannot estimate the scope of potential under-diagnosis.

There is, however, a risk for differential misclassification of our outcome, PH. I have addressed the validity of the PH diagnosis earlier, but another potential source for misclassification of PH is surveillance bias. Our exposure group, CHD adults, are expected to have a higher degree of contact with the medical establishment than our general population

comparison cohort. PH might therefore be more likely to be detected among CHD adults than the general population. The same surveillance bias might be present between CHD adults with severe lesions compared to those with milder defects. As previously stated there are two reasons we expect the risk of surveillance bias to be minimized in our study; First, because PH is not routinely screened for in CHD adults and second, Danish health care is free and universal for the population, presumably resulting in all adults seeking medical help when necessary. In addition, our follow-up period was long and PH is a severe disease resulting in limited functional capacity which could increase the chance of PH being detected during the follow-up period. However, the combination of high 1-year mortality and the fact that PH diagnosis often is delayed(10), increases the risk of not detecting PH, especially in those without contact with the medical establishment.

CHD vary immensely in severity, and for all CHD subjects we included information on CHD severity degree (Mild: biventricular without any history of surgery or intervention; Moderate: biventricular with history of surgery or intervention; Severe: complex biventricular physiology, history of single ventricle diagnoses or palliative surgery such as Norwood, Glenn, and Fontan; Unclassified). Neither the 8^{th} nor the 10^{th} versions of the ICD provide sufficient specificity to allow complete stratification on CHD complexity. In case of misclassification, we expect higher severity degree to be misclassified as lower severity more often than the other way around, as it seems more likely that pathology have been overlooked, especially in the past with less advanced medical equipment and screening protocols. In patients identified from 1963-1974 using manual review of patient records it is also likely that some surgical procedures have been unnoticed, increasing the risk of subjects being misclassified from moderate to mild severity degree.

Our sub-analyses based on shunt status (see ‘Definition of Systemic-to-pulmonary Shunts’) are also dependent on the classification of type of CHD defect. CHD subjects with

multiple CHD diagnoses were categorized according to the CHD type judged to have the greatest haemodynamic effect(33). A validation study on CHD diagnoses is undergoing and will hopefully support the diagnostic validity.

Confounding

Confounding is an important point of concern in most observational epidemiological studies. Confounding is bias in the estimation of the effect of the exposure on the outcome due to a lack of comparability between exposed and unexposed, in such a way that the risk of outcome would be different in the two groups even if they were both exposed. Thereby the risk of the outcome could falsely be attributed to the exposure despite the real cause being the confounding variable. In other words, a confounding variable is an extraneous variable that wholly or partially accounts for the observed effect of a risk factor on the outcome. To be a confounder, the variable must, be 1. associated with the exposure, 2. associated with the risk of the outcome independently of the exposure and 3. not be a causal pathway between the exposure and the outcome, an intermediate step. Typically a confounding variable is a co-variable like gender, age or comorbidity and it can be controlled in both the study design eg. through randomization, restriction and matching and in analysis by stratification, standardization and by adjusting in multivariable regression analyses(42).

An increased risk of PH for CHD patients compared with the general population could arguably be caused by other factors than the CHD itself, such as congestive heart failure, arrhythmias or premature birth and associated complications such as incomplete lung maturation. These factors, however, may be regarded as intermediate steps in a potential causal pathway between CHD and PH and were therefore not included as confounding variables in statistical analyses, as this would lead us to underestimate any potential association between CHD and PH.

Lifestyle factors such as exercise, diet and smoking might also be confounders, but we did not have information on these and therefore could not adjust for them.

External validity

Another point of concern is external validity, which refers to the transferability of the results from one population to another, eg. to other populations, time periods and geographical places. In other words, external validity concerns whether results can be validly generalized. Our study population of CHD subjects was population-based and we therefore expected our study population to be representative of the entire CHD population in Denmark (See 'Selection bias'). The retrospective study design with the use of administrative data also adds to the representativeness of the results. When evaluating the transferability of both our PH incidence and mortality estimates to different time eras and geographical places it is, however, important to bear in mind that it is dependent on factors like available medical treatments and management strategies in the population of concern. We included information on CHD complexity and birth year categories which hopefully increases the potential for transferability of our results.

Clinical perspectives and future studies

Unfortunately, we did not have information about type or severity of PH, which would be highly relevant to include in future studies. As mentioned, management of arterial and venous PH are very different, and any potential misclassification of PH type is therefore of clinical importance. The recent decades have entailed substantial advances in targeted therapy for PAH, but the development of treatment strategies for pulmonary venous hypertension have not improved as much, and treatment efforts for primarily been focused on treating the underlying cause of PH, such as heart failure and have included blood pressure control and fluid management. Promising research on new treatments is ongoing, but patients of course

need to be identified and diagnosed appropriately in order to receive optimal treatment, and focus on not only diagnosing but also classifying PH is therefore highly important, especially among CHD adults, where classification can be particularly challenging(11), because pathologic processes can overlap and lead to ambiguous phenotypes of PH, which is of particular relevance in CHD subjects with more than one heart defect and/or other congenital and acquired diseases(12).

For future studies, a validation study of PH diagnoses is warranted. To increase the sensitivity of detecting PH patients future studies could consider including data on filled prescriptions for PH medications. Some medication used in PAH-treatment is also used for other conditions as well but aside from diuretics, the alternative indications for these (such as erectile dysfunction and finger wounds in patients with systemic sclerosis and mb. Bürger) are less prevalent conditions. Including prescription data as an outcome measure could therefore increase sensitivity without expectedly decreasing specificity substantially compared to hospital diagnosis of PH.

As expected, we found that the incidence rate of PH increased substantially with increasing age in the CHD population, highlighting the need for complete and lifetime surveillance of PH. Optimally future studies on PH in the CHD population would be able to include more elaborate clinical data such as information on and results from diagnostic procedures, and have a longer follow-up period. Studies on potential risk factors for PH such as cardiac arrhythmias and high systemic blood pressure and an investigation on the effect of surgical closure of systemic-to-pulmonary shunt lesions in different age groups could potentially improve both prevention and management strategies.

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MANUSCRIPT TABLES AND FIGURES

Figure 1. Cumulative incidence of adult onset pulmonary hypertension (PH) in congenital heart disease (CHD) subjects and subgroups, and in a general population comparison cohort**.**

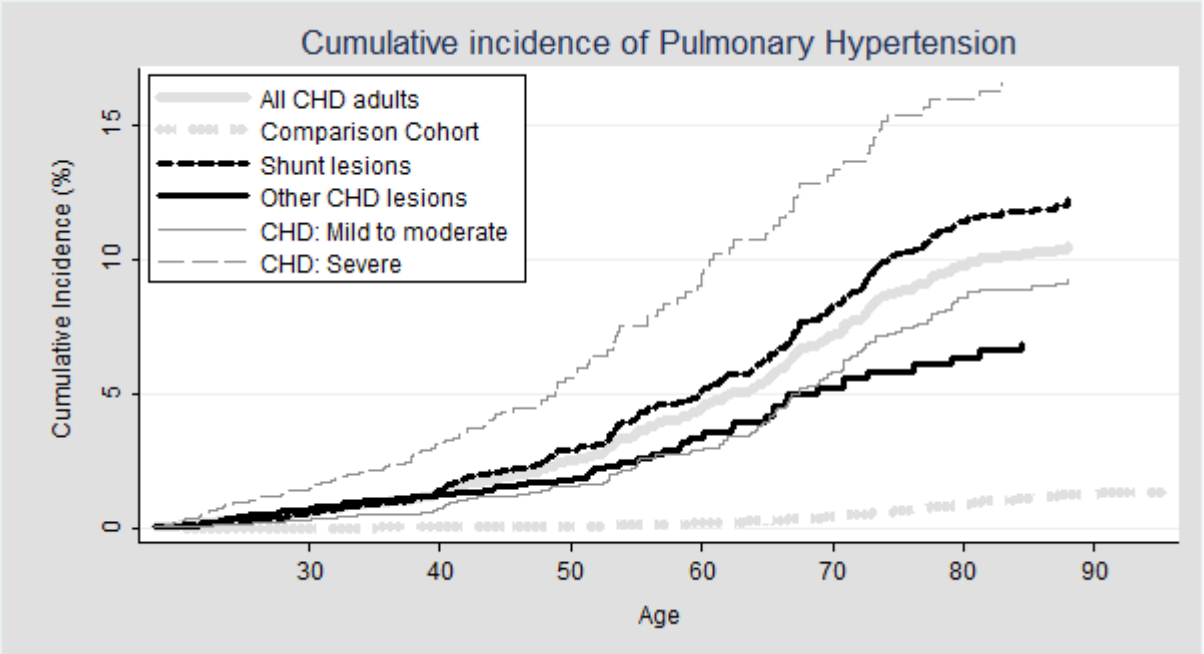

Figure 2. Mortality rates following the diagnosis of pulmonary hypertension (PH), or a corresponding index date, for adults with congenital heart disease (CHD) and PH, as well as for adults with congenital heart disease but without PH.

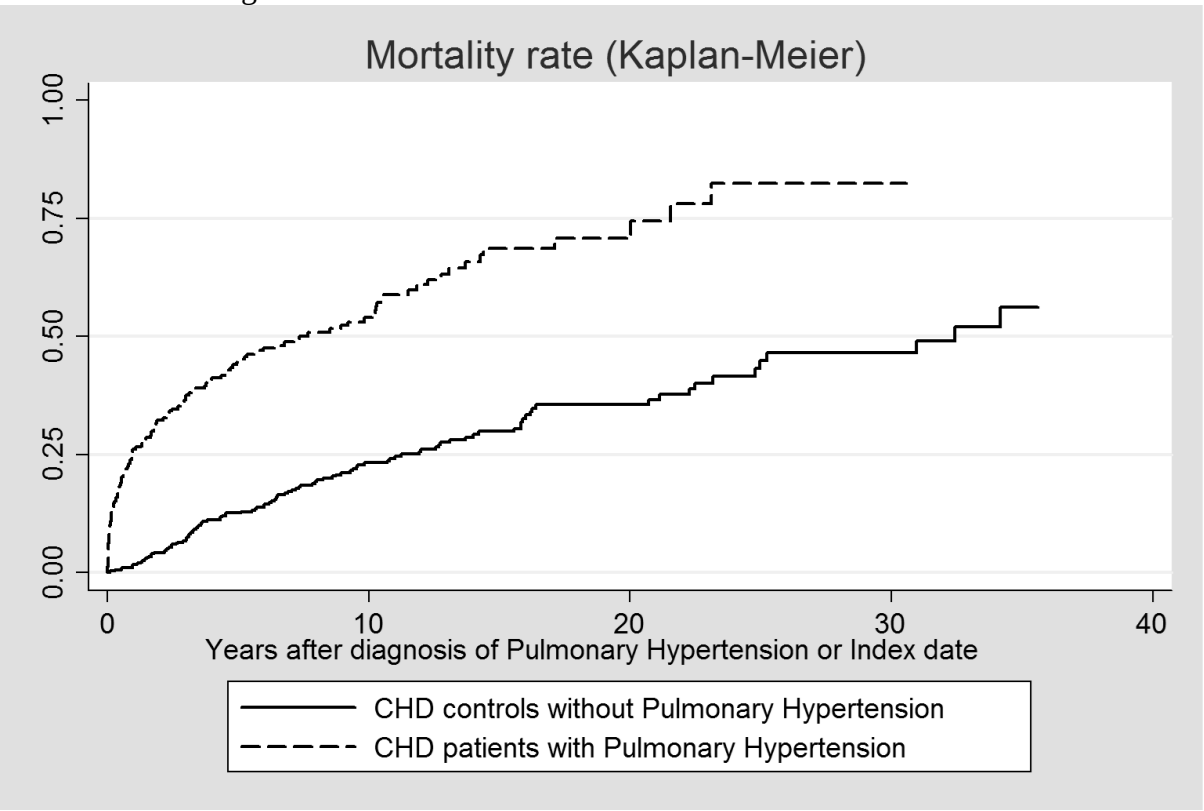

Table 1. Baseline characteristics of patients with congenital heart defects (CHD) and a general population comparison cohort matched for gender and birth year

Characteristic	Comparison cohort, N (%)	All patients with CHD, N (%)	CHD with shunt*, N (%)	CHD without shunt, N (%)
All	146,787	14,860	9,712	5,148
Male	69424 (47)	7,035 (47)	4166 (43)	2869 (56)
Year of birth				
<1955	30,293 (21)	3,036 (20)	2084 (21)	952 (18)
1955-1964	24,620 (16)	2,482 (17)	1573 (16)	909 (18)
1965-1974	30,970 (21)	3,139 (21)	2077 (21)	1062 (21)
1975-1984	24,579 (17)	2,492 (17)	1653 (17)	839 (16)
≥1985	36,325 (25)	3,711 (25)	2325 (24)	1386 (27)
Severity**				
Mild	-	6,315 (43)	5684 (59)	631 (12)
Moderate	-	3,006 (20)	2445 (25)	561 (11)
Severe	-	3,438 (23)	1544 (16)	1894 (37)
Unclassified	-	2,101 (14)	39 (1)	2062 (40)
Congenital defects***	5,537 (4)	2,564 (17)	1574 (16)	990 (19)
Down Syndrome	84 (0.05)	494 (3)	367 (4)	39 (1)
Congestive heart failure****	2,846 (2)	1,701 (11)	1157 (12)	544 (11)

*Includes atrial septal defect, ventricular septal defect, atrioventricular septal defect, tetralogy of fallot, persistent ductus arteriosus, common arterial trunc, double inlet left ventricle, double outlet right ventricle, aortopulmonary septal defects and other congenital malformations of cardiac septa

**Mild: biventricular without any history of surgery or intervention, Moderate: biventricular with history of surgery or intervention, Severe: complex biventricular physiology, history of single ventricle diagnoses or palliative surgery such as Norwood, Glenn, and Fontan.

***Including syndromes and chromosomal anomalies. Complete data on extra cardiac defects in comparison cohort are not readily available given that routine collection in DNRP did not begin until 1977.

****Including left ventricular dysfunction and diagnosed any time during the study period.

Table 2. Characteristics of adults with congenital heart defects (CHD) with and without pulmonary hypertension (PH)

Characteristic	CHD-PH N (%)	CHD-nonPH N (%)	CHD-PH with shunt*	CHD-PH without shunt
All	266	14,594	200	66
Male	95 (36)	6,940 (48)	67 (34)	28 (42)
Median age at diagnosis (interquartile range)	50.6 years (35.8-66.6)	-	52.9 years (39.3-67.5)	43.7 years (27.8-59.1)
Year of birth				
<1955	150 (56)	2,886 (20)	118 (59)	32 (49)
1955-1964	49 (18)	2,443 (17)	40 (20)	≤10 (~15)
1965-1974	37 (14)	3,102 (21)	25 (12.5)	≤15 (~15)
1975-1984	21 (8)	2,471 (17)	11 (5.5)	≤10 (~15)
≥1985	9 (3)	3,702 (25)	6 (3)	≤5 = (~5)
Severity**				
Mild	90 (34)	6,225 (43)	85 (43)	5 (8)
Moderate	39 (15)	2,967 (20)	≤35 (~15)	7 (11)
Severe	114 (43)	3,324 (23)	79 (40)	35 (53)
Unclassified	23 (9)	2,078 (14)	≤5 (~2)	19 (29)
Extra cardiac defects***	51 (19)	2,513 (17)	35 (18)	16 (24)
Congestive heart failure****				
Any time	133 (50)	1,568 (11)	102 (51)	31 (47)
Before potential PH	75 (28)	1,568 (11)	59 (30)	16 (24)

*Includes atrial septal defect, ventricular septal defect, atrioventricular septal defect, tetralogy of Fallot, persistent ductus arteriosus, common arterial trunc, double inlet left ventricle, double outlet right ventricle, aortopulmonary septal defects and other congenital malformations of cardiac septa

**Mild: biventricular without any history of surgery or intervention, Moderate: biventricular with history of surgery or intervention, Severe: complex biventricular physiology, history of single ventricle diagnoses or palliative surgery such as Norwood, Glenn, and Fontan.

***Including syndromes and chromosomal anomalies. Complete data on extra cardiac defects in comparison cohort are not readily available given that routine collection in DNRP did not begin until 1977.

****Including left ventricular dysfunction. Results are subdivided in diagnoses given at any time during the study period and diagnoses given before a potential diagnosis of PH.

Table 3. Cumulative Incidence, Incidence rates per 1,000 person years and Hazard Ratios for adult onset pulmonary hypertension (PH) among adults with congenital heart disease (CHD) compared with a general population cohort, according to gender, year of birth, type of heart defect, CHD severity and the presence of extra cardiac defects.

	No. of PH cases		Cumulative incidence at 70 years of age in patients with CHD (95% CI) Comparison 0.4 (0.4-0.5)	Incidence rate per 1,000 person-years		HR (95% CI)
	CHD cohort	General population comparison cohort		CHD cohort (208,403 person-years)	Comparison cohort (3,069,249 person-years)	
Overall±	266	217	7.2 (6.2-8.4)	1.28 (1.13-1.44)	0.07 (0.06-0.08)	22.9 (19.1-27.4)
Gender±						
Male	95	100	5.7% (4.4-7.2)	0.97 (0.79-1.19)	0.07 (0.06-0.09)	17.7 (13.3-23.5)
Female	171	117	8.7% (7.2-10.4)	1.55 (1.33-1.80)	0.07 (0.06-0.09)	27.2 (21.4-34.5)
Year of birth±						
>1955	150	185	-	3.75 (3.20-4.40)	0.19 (0.16-0.22)	18.0 (14.5-22.4)
1955-1964	49	19	-	0.88 (0.66-1.16)	0.02 (0.02-0.04)	34.9 (20.5-59.3)
1965-1974	37	8	-	0.58 (0.42-0.79)	0.01 (0.01-.02)	53.1 (24.7-114.0)
>1975	30	5	-	0.62 (0.44-0.90)	0.00 (0.00-0.00)	65.1 (25.3-167.9)
Age period±*						
18-29	43	5	-	0.49 (0.36-0.65)	0.00 (0.00-0.01)	111.6 (44.1-283.3)
30-44	69	22	-	0.93 (0.74-1.18)	0.02 (0.01-0.03)	47.5 (29.2-77.3)
45-59	60	49	-	1.96 (1.52-2.53)	0.09 (0.07-0.11)	24.0 (16.4-35.2)
≥60	94	141	-	6.3 (5.01-7.50)	0.44 (0.37-0.52)	14.3 (11.0-18.6)
Type of heart defect$^{\gamma}$						
Shunt**	200	-	8.3% (7.0-9.8)	1.49 (1.30-1.71)	-	26.8 (20.3-35.4)
Other	66	-	5.3% (3.9-7.1)	0.89 (0.70-1.13)	-	17.4 (11.5-26.2)
Severity$^{\gamma}$***						
Mild	90	-	5.8% (4.4-7.5)	1.08 (0.88-1.33)	-	18.0 (12.5-25.8)
Moderate	39	-	5.7 (3.8-8.3)	0.81 (0.59-1.11)	-	17.5 (10.2-30.1)
Severe	114	-	13.4% (10.7-16.3)	2.50 (2.08-3.01)	-	51.6 (32.0-83.0)
Unclassified	23	-	3.6% (2.0-5.8)	0.74 (0.49-1.11)	-	12.3 (6.5-23.0)
Extra cardiac defects$^{\gamma}$****						
Yes	51	-	10.8% (7.2-15.2)	1.53 (1.16-2.02)	-	38.5 (20.5-72.3)
No	215	-	6.8% (5.7-8.0)	1.23 (1.07-1.40)	-	21.6 (16.8-27.6)

±Adjusted for gender and birth year categories, unless the covariate was used for stratification

$^{\gamma}$ Patients with CHD were compared with their age and gender matched comparison cohort members.

*Age was treated as a time dependent variable
**Includes atrial septal defect, ventricular septal defect, atrioventricular septal defect, tetralogy of fallot, persistent ductus arteriosus, common arterial trunc, double inlet left ventricle, double outlet right ventricle, aortopulmonary septal defects and other congenital malformations of cardiac septa
***Mild: biventricular without any history of surgery or intervention, Moderate: biventricular with history of surgery or intervention, Severe: complex biventricular physiology, history of single ventricle diagnoses or palliative surgery such as Norwood, Glenn, and Fontan.
****Including syndromes and chromosomal anomalies.

Table 4. Characteristics of adult Congenital Heart Disease (CHD) Prevalence Cohort, January 1st 2013

Characteristic	Comparison Cohort, N (%)	All adults with CHD; N (%)	CHD-nonPH, N (%)	CHD-PH, N (%)	CHD-PH With shunt*, N (%)	CHD-PH without shunt, N (%)
All	93,931	11,343	11,217	126	86	40
Pulmonary Hypertension (PH)	45 (0.05)	126 (1.1)	-	-	-	-
Male	44,839 (48)	5,414 (48)	5,366 (48)	48 (38)	29 (34)	19 (48)
Shunt*	60 (0.1)	7,359 (65)	7,273 (65)	86 (68)	-	-
Median age (interquartile range)	37.9 (24.5-49.9)	38.0 (24.5-49.9)	38.0 (24.5-49.9)	55.9 (45.0-70.4)	54.9 (44.2-68.2)	49.4 (38.5-65.8)
Severity**						
Mild	-		4,732 (42)	29 (23)	≤30 (~30)	≤5 (~5)
Moderate	-		2,308 (21)	27 (21)	≤20 (~20)	≤10 (~20)
Severe	-		2,593 (23)	60 (48)	≤40 (~45)	≤25 (~55)
Unclassified	-		1,584 (14)	10 (8)	≤5 (~5)	≤10 (~20)
Extra cardiac defects***	3,833 (4)	2,076 (18)	2,052 (18)	24 (19)	15 (17)	9 (23)
Down Syndrome	49 (0.1)	294 (3)	287 (3)	7 (6)	7 (8)	0 (0)

* Includes atrial septal defect, ventricular septal defect, atrioventricular septal defect, tetralogy of fallot, persistent ductus arteriosus, common arterial trunc, double inlet left ventricle, double outlet right ventricle, aortopulmonary septal defects and other congenital malformations of cardiac septa
**Mild: biventricular without any history of surgery or intervention, Moderate: biventricular with history of surgery or intervention, Severe: complex biventricular physiology, history of single ventricle diagnoses or palliative surgery such as Norwood, Glenn, and Fontan.
***Including syndromes and chromosomal anomalies. Complete data on extra cardiac defects in comparison cohort are not readily available given that routine collection in DNRP did not begin until 1977.

Table 5. 1, 5 and 10-Year Mortality of Pulmonary Hypertension and Hazard Ratios of all-cause mortality between CHD adults with PH and CHD controls without PH matched on gender and birth year (± 2 years)

Characteristic	CHD-nonPH controls*	All CHD-PH patients	CHD-PH patients with shunts	CHD-PH without shunts
All, N	532	266	200	66
Men, N (%)	190 (36)	95 (36)	67 (34)	28 (42)
Median age at PH-diagnosis in years (IQR)	-	50.6 (35.8-66.6)	52.9 (39.3-67.5)	43.7 (27.8-59.1)
Mortality rates (95% CI)				
1 year mortality	2 (1-3)	24 (19-30)	24 (18-31)	26 (17-36)
5 year mortality	13 (10-17)	44 (37-50)	46 (39-55)	37 (28-49)
10 year mortality	21 (17-26)	52 (46-59)	52 (44-60)	53 (41-66)
Hazard Ratio (HR) comparing mortality between patients in the groups above (95% CI)				
Crude	1 (ref)	3.5 (2.7-4.5)	1.7 (1.1-2.6)	1 (ref)
Adjusted*	1 (ref)	4.3 (3.3-5.6)	1.8 (1.1-2.9)	1 (ref)

*Adjusted for gender, birth year, CHD severity and the presence of extra cardiac defects
IQR: Interquartile Range, CI: Confidence Interval

Appendix 1. Diagnostic Codes

ICD-8		ICD-10	
Pulmonary Hypertension			
426	Pulmonary Heart Disease	DI27.0	Primary Pulmonary Hypertension
		DI27.1	Kyphoscoliotic heart disease
		DI27.2	Secondary PH??
		DI27.8	Other specified pulmonary heart disease.
		DI27.9	Chronic cardiopulmonary disease, unspecified
Systemic-to-pulmonary shunts			
746.0	Common truncus	Q20.0	Common arterial trunk
746.2	Tetralogy of Fallot	Q20.1	Double outlet right ventricle
746.3	Ventricular septal defect	Q20.4	Double inlet ventricle
746.4	Atrial septal defect	Q21.0	Ventricular septal defect
746.5	Ostium atrioventriculare commune	Q21.1	Atrial septal defect
		Q21.2	Atrioventricular septal defect
747.0	Patent ductus arteriosus	Q21.3	Tetralogy of Fallot
		Q21.4	Aortopulmonary septal defect
		Q21.8	Other congenital malformations of cardiac septa
		Q21.9	Congenital malformation of cardiac septum, unspecified
		Q25.0	Patent ductus arteriosus
Congestive heart failure and left ventricular dysfunction			
427.09	Congestive heart failure	I11.0	Hypertensive heart disease with congestive heart failure
427.10	Left ventricular failure		
427.11	Acute left heart failure	I13.0	Hypertensive heart and renal disease with congestive heart failure
427.19	Left heart failure		
428.99	Other myocardial insufficiency	I13.2	Hypertensive heart and renal disease with both congestive heart failure and renal failure
782.49	Acute heart failure, undefined		
		I42	Cardiomyopathy
		I50.0	Congestive heart failure
		I50.1	Left ventricular failure
		I50.9	Heart failure, unspecified

SUPPLEMENTARY TABLES AND FIGURES

Supplementary table 1. Classification of Pulmonary Hypertension. From Simonneau et al 2013(11)

1. Pulmonary arterial hypertension
1.1 Idiopathic PAH
1.2 Heritable PAH
1.2.1 BMPR2 1.2.2 ALK-1, ENG, SMAD9, CAV1, KCNK3
1.2.3 Unknown
1.3 Drug and toxin induced
1.4 Associated with:
1.4.1 Connective tissue disease
1.4.2 HIV infection
1.4.3 Portal hypertension
1.4.4 Congenital heart diseases
1.4.5 Schistosomiasis
1′ Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis
1″. Persistent pulmonary hypertension of the new-born (PPHN)
2. Pulmonary hypertension due to left heart disease
2.1 Left ventricular systolic dysfunction
2.2 Left ventricular diastolic dysfunction
2.3 Valvular disease
2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
3. Pulmonary hypertension due to lung diseases and/or hypoxia
3.1 Chronic obstructive pulmonary disease
3.2 Interstitial lung disease
3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
3.4 Sleep-disordered breathing
3.5 Alveolar hypoventilation disorders
3.6 Chronic exposure to high altitude
3.7 Developmental lung diseases
4. Chronic thromboembolic pulmonary hypertension (CTEPH)
5. Pulmonary hypertension with unclear multifactorial mechanisms
5.1 Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy
5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
5.4 Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH

*BMPR = bone morphogenic protein receptor type II; CAV1 = caveolin-1; ENG = endoglin; HIV = human immunodeficiency virus; PAH = pulmonary arterial hypertension.

Supplementary table 2. Diagnostic and Procedure Codes

ICD-8		ICD-10	
Surgically created shunts			
304.00	Anastomosis Aortico-Pulmonalis (Waterson)	KFDN	Created passage in ductus arteriosus
304.40	Anastomosis arteriae subclav. Ad arteriam pulm (Blalock)	KFFE	Construction or expansion of atrial septal defect
304.50	Arterial Septotomi	KFHH	Ventricular Septostomi or expansion of ventricular septal defect
305.20	Anastomosis aortico-pulmonalis (Pott)		
306.20	Septotomia interatriorum (Blalock-Hanlon)		
308.20	Ventricular Septotomi		
312.10	Anastomosis (A.m. Blalock)		
314.20	Operatio Pro canale atrioventriculare communi		
316.65	Anastomosis aortico-pulmonalis		
316.69	Anastomosis art. Subclaviae ad art pulmonale (Blalock)		

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