Faculty of Health, Aarhus University

The Risk of Dementia in Adults with Congenital Heart Disease: A Nationwide Population-Based Cohort Study

Research year report

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PREFACE

The present report is based on a study conducted during my research year at the Department of Clinical Epidemiology, Aarhus University Hospital. I had the privilege to have supervisors and collaborators with very different backgrounds, who shared their extensive knowledge and gave me a great introduction into the world of epidemiologic research.

A special thanks to my main supervisor, Morten Olsen, for providing excellent mentorship, for always leaving the door open, being patient and persistently answering my questions as well as giving friendly encouragements.

During my research year, I had the pleasure of visiting the Heart Institute at Cincinnati Children's Hospital Medical Center for a month. Big thanks to the employees and especially to my co-supervisor, Nicolas L. Madsen, for the warm welcome and endless willingness to help me make the most of my stay.

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ABBREVIATIONS

CHD	Congenital heart disease
CI	Confidence interval
DAG	Direct acyclic graph
DNPR	The Danish National Patient Registry
ECD	Extra cardiac defects
HR	Hazard ratio
ICD	International Classification of Diseases
ICD-8	International Classification of Diseases, 8th edition
ICD-10	International Classification of Diseases, 10th edition
PPV	Positive predictive value

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ABSTRACT

Background: Congenital heart disease (CHD) is associated with several established risk factors for dementia. We compared the risk of dementia in CHD adults to that of the general population.

Methods: In a cohort study, we used medical registries and a medical record review covering all Danish hospitals to identify CHD patients diagnosed between 1963 and 1982. Subjects were followed from January 1st 1981, age 30 years, or date of first CHD registration (index date for matched members of the general population cohort) until hospital-diagnosis of dementia, death, emigration, or end of study (December 2012). For each CHD patient, we identified 10 individuals from the general population utilizing the Danish Civil Registration System, matched on sex and birth year. We computed cumulative incidences and hazard ratios (HRs) of dementia, adjusting for sex and birth year. Analyses were repeated after restricting the comparison cohort to individuals with hospital-diagnosed dementia risk factors (diabetes, stroke, and heart failure).

Results: The cumulative incidence of dementia was 4% by age 80 years in 10,632 adults with CHD (46% male). The overall HR comparing CHD adults with the general population cohort was 1.6 (95% CI: 1.3-2.0). The HR among CHD individuals without extracardiac defects was 1.4 (95% CI: 1.1-1.8). Adults with mild CHD had a HR of 1.6 (95% CI: 1.2-2.2), while the HR was 1.2 (95% CI: 0.7-2.1) and 2.0 (95% CI: 1.1-2.3) for moderate and severe CHD, including univentricular hearts, respectively. The HR for early onset dementia (<65 years of age) was 2.6 (95% CI: 1.8-3.8), whereas late onset demonstrated a HR of 1.3 (95% CI: 1.0-1.8). When comparing CHD adults to individuals (n=8,699) with a dementia related disease, the HR was 0.7 (95% CI: 0.6-1.0).

Conclusions: Congenital heart disease was associated with an increased risk of dementia compared to the general population, in particular for early onset dementia. Subgroup analyses indicated a lower dementia risk for CHD adults than for a cohort of individuals with established risk factors for dementia (diabetes, stroke, and heart failure). Further understanding of dementia risk factors in the CHD population is a potential target for future investigation.

DANSK RESUMÉ

Baggrund: Medfødte hjertefejl er blevet associeret til almindeligt anerkendte risikofaktorer for demens. Derfor undersøgte vi risikoen for demens blandt voksne med medfødte hjertefejl i forhold til den generelle befolkning.

Metode: I dette kohortestudium anvendte vi landsdækkende registre og en tidligere gennemgang af journaler for at identificere personer diagnosticeret med medfødte hjertefejl mellem 1963 og 1982. Alle blev fulgt fra 1. januar 1981, 30 års-alderen eller datoen, hvor den medfødte hjertefejl blev diagnosticeret (indeksdatoen for de matchede medlemmer i sammenligningskohorten), indtil datoen for hospitalsdiagnosticeret demens, død, emigration eller studiets slutdato (december 2012). For hver person med medfødt hjertefejl, identificerede vi 10 personer fra den generelle befolkning vha. det Centrale Personregister, matchet på køn og fødselsår. Vi udregnede kumulerede incidenser og hazard ratioer (HR) for demens justeret for køn og fødselsår. Vi lavede en begrænsning på sammenligningskohorten til dem, som havde en hospitalsdiagnose med risikofaktorer for demens (sukkersyge, slagtilfælde eller hjertesvigt).

Resultater: Den kumulerede incidens for demens ved 80 år var 4% blandt 10.632 voksne med medfødte hjertefejl (46% mænd). Den overordnede HR for demens blandt voksne med medfødt hjertefejl sammenlignet med den generelle befolkningskohorte var 1,6 (95% CI: 1,3-2,0). For voksne med medfødte hjertefejl uden ekstrakardielle defekter var HR 1,4 (95% CI: 1,1-1,8). HR for personer med milde hjertefejl var 1,6 (95% CI: 1,2-2,2), mens den var henholdsvis 1,2 (95% CI: 0,7-2,1) og 2,0 (95% CI: 1,1-2,3) for grupperne med moderate og svære hjertefejl, inklusiv univentrikulære hjerter. HR for tidlig debut af demens (<65 år) var 2,6 (95% CI: 1,8-3,8), mens den var 1,3 (95% CI: 1,0-1,8) for sen debut. Ved sammenligning mellem voksne med medfødte hjertefejl og personer fra sammenligningskohorten med risikofaktorer for demens (n=8.699) var HR 0,7 (95% CI: 0,6-1,0).

Konklusioner: Risikoen for demens var øget blandt voksne med medfødte hjertefejl sammenlignet med en generelle befolkning, især for tidlig debut af demens. Subgruppeanalysen demonstrerede en lavere risiko for demens blandt voksne med medfødte hjertefejl sammenlignet med kohorten bestående af individer med risikofaktorer for demens (sukkersyge, slagtilfælde og hjertesvigt). Et potentielt mål for fremtidige studier er en bedre forståelse af risikofaktorer for demens hos personer med medfødte hjertefejl.

MANUSCRIPT

Introduction

Congenital heart disease (CHD) is prevalent in 6 to 10 per 1,000 live births and represents the most common group of congenital malformations[1-3]. Due to recent advances in CHD management and an overall reduction in mortality, there is increased attention to the potential for acquired morbidities in the aging CHD population[4,5].

Neurodevelopmental deficits among CHD infants and children are well-described[6-8]. However, research on long-term neurologic outcomes in adults with CHD is more limited. Dementia is among the most important late-life neurologic diseases in the general population. The prevalence of dementia is growing dramatically as a result of increased life expectancy. In the Danish population, 6.6% of those above 65 years of age have been diagnosed with dementia[9], and prevalence estimates are similar in other countries[10]. Dementia is the fifth most common cause of death in Denmark[11] and the sixth most common in the United States[12].

Previous studies have reported an increased incidence of established risk factors for dementia in the CHD population[13,14]. These include genetic disorders such as Down syndrome, and cardiovascular diseases such as ischemic and hemorrhagic stroke, hypertension, heart failure, atrial fibrillation, and diabetes mellitus[15-21]. In addition, some CHD adults have poor exercise tolerance[22], which is a reported dementia risk factor[23].

In the absence of a disease-modifying treatment for most forms of dementia, the identification of factors with the potential to delay dementia onset is crucial. Based on the increased incidence of neurodevelopmental impairments and risk factors for dementia in the CHD population, we hypothesized that the risk of dementia is higher in individuals with CHD than in the general population.

Methods

Study design and settings

This nationwide population-based cohort study was conducted in Denmark using linked medical registry databases. Denmark has a current population of 5.6 million individuals. The healthcare system is tax-supported. It provides free and universal access to hospital-based and

primary medical care, including care for individuals with CHD or dementia. No informed written consent or permission from the Scientific Ethical Committee is required for register-based studies in Denmark. The study was approved by the Danish Data Protection Agency (Journal number: 2013-41-1754).

Data linkage

The study was based on an unambiguous individual-level record linkage across healthcare registries using the Civil Personal Registration number, an assigned unique ten-digit identifier, and the Danish Civil Registration System, which contains data on all Danish residents since 1968[24]. The Danish Civil Registration System is updated daily and has electronic records on dates of birth, emigration and death[24].

Congenital heart disease cohort

We utilized two nationwide data sources to identify all adults who received a diagnosis of CHD between 1963 and 1974 (before 15 years of age) and between 1977 and 1982 (at any age). The identification of CHD survivors diagnosed between 1963 and 1974 was based on medical record review and has been described elsewhere[25]. The Danish National Patient Registry (DNPR) contains information on dates of admission and discharge, discharge diagnoses and surgical procedures in Denmark since 1977, as well as clinical care by emergency departments and outpatient clinics since 1995[26]. Diagnoses were coded according to the 8th edition of the International Classification of Diseases (ICD) until the end of 1993 and the 10th edition thereafter. The individuals diagnosed with CHD during the two-year gap (1975 and 1976) between the medical record review and the DNPR without any subsequent medical record data points were not captured in this study. The ICD-codes utilized are provided in Supplemental Table 1.

The patients were grouped according to a hierarchy of physiologic complexity: Univentricular (history of single ventricle diagnoses or palliative surgery such as Norwood, Glenn and/or Fontan) > severe (complex biventricular physiology including tetralogy of Fallot, transposition of the great arteries, and atrioventricular canal defect) > moderate (simple biventricular physiology with a history of any surgery or catheter-based intervention for atrial septal defect, ventricular septal defect, isolated coarctation of the aorta, and patent ductus arteriosus) >

mild (simple biventricular physiology without any history of surgery or catheter-based intervention), or unclassified.

The CHD cohort was subdivided according to cyanotic potential to examine the potential impact on the development of dementia. Due to the inability to directly identify duration and severity of cyanosis exposure based on the ICD-coding, the analysis was limited to individuals having lesions with the highest certainty of being cyanotic for some period of time. Specifically, the defects selected to have cyanotic potential included tetralogy of Fallot, transposition of the great arteries, truncus arteriosus/common arterial trunk, and univentricular physiology. The lesions selected as representative of acyanotic physiology were atrial septal defect, ventricular septal defect, coartation of the aorta, and patent ductus arteriosus. All individuals who fell outside this categorization were defined as "unclassified" in this particular analysis. Those with Eisenmenger's physiology were excluded.

General population comparison cohort

For each CHD adult, 10 individuals from the general population without a CHD diagnosis at study entry were randomly sampled through the Danish Civil Registration System, matched on sex and birth year[24]. To provide perspective to the results, we performed a subgroup analysis where we restricted the general population comparison cohort to adults with a hospital-diagnosed disease associated to cognitive decline and dementia (diabetes, stroke, and heart failure)[13,14,20,21]. The risk factors of dementia were recorded in the DNPR.

Dementia

The outcome of interest was a first-time hospital-diagnosis of any dementia in the inpatient or outpatient clinic setting obtained from the DNPR. Individuals, who received a dementia diagnosis before the index date, were excluded. As the age of dementia onset is rarely below 30 years of age[27], we restricted the analysis to those older than 30 years of age. Dementia onset was divided into early and late onset by use of the conventional threshold of 65 years of age[28].

Covariates

Information on the highest completed educational level by 30 years of age in both cohorts was available from Statistics Denmark and categorized as basic (completion of primary education), moderate (completion of 3 years of secondary education known as 'gymnasium' or completion of 3-4 year vocational programs after primary education), or advanced (completion of university education). By means of the DNPR, extracardiac defects (ECD) and chromosomal abnormalities diagnosed at any time after birth were identified. In accordance with the guideline from the European Surveillance of Congenital Anomalies, minor isolated defects such as subluxation and unstable hip, torticollis, cryptorchidism, or protuberant ears were disregarded[29]. Information on hospital-diagnosed cardiovascular diseases (atrial fibrillation or flutter, heart failure, stroke and hypertension) and diabetes at any time was also obtained utilizing the DNPR.

Statistical analyses

All adults with CHD were followed from 30 years of age, initiation of Statistics Denmark's database on education in 1981, or the date of first CHD registration (index date for the matched comparison cohort members), whichever came last. Follow-up continued until the date of dementia diagnosis, emigration, death or end of the study period (December 31, 2012), whichever came first.

We computed the cumulative incidence of dementia in both cohorts by using the Aalen-Johansen estimator, considering death as a competing risk. All-cause mortality was estimated using the Kaplan-Meier estimator. The incidence rates of dementia were computed as the count of dementia diagnoses divided by the total person-time at risk. The hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) of time to dementia diagnosis were estimated by means of Cox proportional hazard regression. We compared CHD subjects to the general population cohort using age as a time scale and adjusted for sex and birth year. Follow-up of matched members from the general population cohort, who subsequent to entry were diagnosed with CHD (n=874), was not discontinued in the comparison cohort.

Analyses were stratified by sex and birth year. Subgroup analyses comparing the CHD adults with their matched members from the general population cohort were performed by severity of the CHD, cyanosis potential, age at first CHD diagnosis, CHD diagnosis type, educational attainment, and presence of ECD. Furthermore, we did separate analyses for follow-up peri-

ods below and above age 65 years to differentiate early and late onset dementia, as well as before and after the year 1994, when ICD-10 superseded ICD-8. To investigate the role of cardiovascular diseases (atrial fibrillation or flutter, heart failure, stroke, and hypertension) and diabetes, we evaluated the HRs during time at risk before and after potential diagnosis in the CHD cohort (index date for matched comparison cohort members). Lastly, we performed a subgroup analysis using the general population cohort restricted to individuals with a hospital diagnosed dementia risk factor (diabetes, stroke, or heart failure). They were followed from the previously mentioned index date or date of diagnosis, whichever came last. The proportional hazard assumption was verified by assessment of graphical evaluation using log-minus-log plots. All statistical analyses were conducted using STATA software (14th edition, StataCorp LP, College Station, TX).

Results

We identified 10,632 CHD adults alive at 30 years of age, 46% of whom were male (Table 1). The birth period stretched from 1890 to 1982, with the majority born between 1960 and 1982. The most common types of CHD diagnoses were atrial septal defects (n=2,737, 26%) and ventricular septal defects (n=2,361, 22%). Additionally, 44% (n=4,705) had a mild severity of CHD not requiring surgery. Diagnosed ECDs were more frequent among CHD adults (14%) than in the comparison cohort (4%).

During the follow-up period, 1,072 adults were diagnosed with dementia across both cohorts (Table 2). The cumulative incidence of dementia was 4% at 80 years of age in both cohorts. However, all-cause mortality at 80 years of age differed between the cohorts (60% for CHD adults and 35% for the comparison cohort). The incidence rate per 1,000 person-years at risk was 0.78 in the CHD cohort and 0.75 in the general population cohort. The overall HR of dementia was 1.61 (95% CI: 1.29-2.02) among adults with CHD compared to the general population cohort.

When considering the risk of dementia among CHD adults without extra cardiac defects, the increased HR persisted (1.38; 95% CI: 1.08-1.76). The HRs did not vary according to gender (male 1.55; 95% CI: 1.06-2.26, and female 1.65; 95% CI: 1.25-2.19). The risk of dementia in the CHD cohort relative to the comparison cohort was elevated for both early onset (HR 2.59; 95% CI: 1.76-3.81) and late onset dementia (HR 1.32; 95% CI: 1.00-1.75). Adults with se-

vere and univentricular CHD had a HR of 1.96 (95% CI: 1.14-3.34), while the HRs were 1.23 (95% CI: 0.71-2.11) and 1.62 (95% CI: 1.18-2.21) for moderate and mild CHD, respectively. The HR for CHD lesions with cyanotic potential was 1.83 (95% CI: 0.69-4.87), and for acyanotic lesions the HR was 1.42 (95% CI: 1.08-1.89).

The HRs according to completed education by 30 years of age comparing CHD adults to the general population cohort were as follows: Basic 1.82 (95% CI: 1.32-2.51), moderate 2.65 (95% CI: 1.30-5.38), and advanced 0.52 (95% CI: 0.16-1.69). CHD adults with as well as without additional acquired cardiovascular disease or diabetes were at increased risk of dementia (HR 1.48; 95% CI: 1.11-1.97 and HR 1.82; 95% CI 1.26-2.64, respectively). The incidence rate for CHD adults with acquired disease and for their matched members of the comparison cohort was 2.16 and 2.01 per 1,000 person-years at risk, respectively, while for individuals without acquired disease and for their matched members the incidence rate was 0.37 and 0.30 per 1,000 person-years at risk, respectively. The increased risk of dementia among CHD adults did not vary by ICD-versions. The HR comparing CHD adults to the restricted general population cohort (n=8,699) was 0.74 (95% CI: 0.57-0.96).

Discussion

We found an increased risk of dementia among adults with CHD relative to the age- and gender-matched general population cohort. The elevated risk persisted across the spectrum of CHD complexity, in individuals without associated ECD, and was notable for an earlier age of onset. The risk was lower than among adults with diabetes, stroke, or heart failure, previously recognized risk factors for dementia[13,14,20,21].

Our findings extend the existing knowledge of mental health and long-term functional morbidities in the CHD population. Previous studies have reported an elevated risk of adverse neurodevelopmental outcomes among CHD individuals, as well as increased occurrence of depression, autism, and epilepsy compared to the general population[6-8,18,30-33]. While the underlying pathophysiologic mechanisms are not completely understood, the potential etiologic factors appear multifactorial.

The concept of cerebral reserve provides an explanatory framework for considering the variation between individuals in susceptibility and tolerance of age-related brain changes and pathology, including dementia[34]. Cerebral reserve has been divided into two types of reserve:

brain reserve and cognitive reserve[34]. Brain reserve refers to the structural differences of the brain, whereas cognitive reserve is the ability to cope through compensatory mechanisms, which continues to evolve across a lifespan[34].

The potential etiologic factors for reducing brain reserve in the CHD population differ over a lifetime and may involve neurologic malformations, the effects of the abnormal physiology, complex medical and surgical management strategies, chromosomal abnormalities, and acquired morbidities. Previous studies have suggested that impaired fetal oxygen delivery and altered brain metabolism contribute to dysmaturation in patients with more complex CHD[18,35-38]. The higher incidence of brain injuries and hypoxemia affects the very same cellular pathways and may enhance this effect[6,18,37,39]. In this study, the risk of dementia was observed to be increased among adults with severe and univentricular CHD, as well as among lesions with a cyanotic potential. However, the risk remained for individuals with acyanotic disease and those with mild CHD, which suggests that there are risk factors that extend beyond hypoxia and complex cardio-pulmonary interactions.

Risk factors for brain injuries that impact brain reserve include medical and surgical management of CHD, which has been especially well-studied, and includes embolic events inducing cerebral ischemia, the impact of hemodilution, and postoperative low cardiac output physiology[7,30,31]. Genetic disorders and chromosomal abnormalities, an important element in the etiology of a larger proportion of CHD subjects, are known to influence neurodevelopment[19]. In particular, Down Syndrome (trisomy 21), which is associated with accumulation of beta-amyloid in the brain, is classically associated with neuropathological features of Alzheimer's disease[19]. After excluding individuals diagnosed with ECD, the observed elevated risk of dementia persisted, indicating that additional pathways should be considered.

Adults with CHD acquire cardiovascular disease earlier than the general population and have an increased occurrence of diseases associated with enhanced risk of cognitive decline and dementia such as diabetes mellitus, atrial fibrillation, stroke, coronary artery disease, and heart failure[14-17,40-42]. We observed an increased risk of dementia among CHD adults with and without acquired cardiovascular diseases or diabetes relative to their matched members from the general population. Noteworthy, CHD adults without acquired diseases and their matched comparison cohort members were younger than those with acquired diseases (data not shown). This likely explains the variation of the incidence rates, as dementia is strongly associated with age[10,12].

Our observations indicate a reduced risk of dementia among those with advanced education (university training), suggesting a higher cognitive reserve among these individuals. Cognitive reserve is the more dynamic form of cerebral reserve. Higher cognitive reserve, measured by premorbid intelligence and long-term exposures to education, occupation, and mentally stimulating leisure activities, is associated with lower risk of dementia[43]. However, educational attainment might be considered a surrogate for CHD severity or acquired medical complexity, as well as learning difficulties due to neurodevelopmental disorders. This limits our capacity to separate completely the division between brain reserve and cognitive reserve.

When considering age of dementia onset, we observed an increased risk of both early and late onset dementia comparing the CHD cohort to the general population cohort. The slight variation in the estimates likely reflects the lower incidence rate of dementia in the general population cohort below 65 years of age, when the burden of age-related dementia pathologies and other comorbidities is lower. Since CHD is considered a lifelong condition, and the pathological substrates of Alzheimer's disease and other dementias unfolds decades before clinical symptoms emerge[42], the potential benefits of early intervention may be of importance in the CHD population.

The following strengths and limitations should be considered when interpreting our results. Our large population-based cohort study with long-term virtually complete follow-up for migration, death and hospital-diagnosed dementia minimized the risk of selection bias.

The quality of our data is dependent on the validity of diagnosis coding for CHD, dementia and the covariates. The positive predictive value of the overall CHD diagnosis in the DNPR has previously been reported to be high, approximately 90%[44]. Several criteria were applied to increase the validity of the CHD diagnosis (Supplemental table 2). Misclassification of CHD is limited and believed to be independent of future dementia diagnosis; thus, misclassification would have biased our estimates towards no association. Prevalence estimates and distribution of CHD types in our data are similar to those of contemporary studies[25]. The positive predictive value of all-cause dementia in the DNPR is approximately 86%[45], and the risk of dementia among CHD adults relative to the general comparison cohort did not differ between ICD-versions (Table 2). For both cardiovascular diseases and cardiac surgery, the positive predictive values have also been reported high[46-48].

The possibility of surveillance bias, and consequently overestimation of the risk of dementia among CHD adults compared with the general population cohort, should be considered, since the CHD population may be more frequently in contact with the medical establishments. The CHD adult's risk of dementia was lower than that of adults with diabetes, stroke, or heart failure (Table 2), which may indicate a role of surveillance bias. On the other hand, these diseases have previously been associated with cognitive decline and increased dementia risk[13,14,20,21].

No adjustments for the potential effect of e.g. atrial fibrillation, depression, or educational level, were made, as they could represent intermediate factors. By adjusting for these mediators, the observed effect of CHD on dementia risk may be underestimated. We did not have sufficient data on potential confounders or risk factors of dementia such as prematurity, smoking, physical activity or other lifestyle factors.

In conclusion, congenital heart disease was associated with an increased risk of dementia compared to the general population, in particular for early onset dementia. Subgroup analyses suggested a lower overall dementia risk among CHD adults relative to a cohort of individuals with recognized risk factors for dementia (diabetes, stroke, and heart failure). We believe that continued investigation is warranted in the growing and aging CHD population.

SUPPLEMENTARY

The following supplementary section serves as an extension to the manuscript and includes presentation of relevant aspects of congenital heart disease (CHD), additional methodological and statistical considerations, a discussion of strengths and limitations as well as clinical perspectives.

Congenital heart disease

The development of the heart is a heavily regulated sequence of events, including a complex folding of the cardiac tube to accommodate the pericardial cavity, growth of the endocardial cushions and apoptosis[49,50]. CHD is "*a gross structural abnormality of the heart or intrathoracic great vessels that is actually or potentially of functional significance*"[51] with different recognized subtypes and a vast number of anatomic variations[50]. Classification of CHD is based on the location of the involved structures as well as presence of obstruction, hypoplasia, shunts and cyanosis. The most frequent types in Denmark are ventricular septal defects, atrial septal defects, pulmonary stenosis and persistent ductus artriosus[50]. The spectrum of disease spans from asymptomatic or milder symptoms such as shortness of breath and easier fatigability to more severe and life-threatening defects with central cyanosis, heart failure and shock[50].

The etiology of CHD is often unknown, but considered multifactorial and an interplay of genetics and environmental exposures[52]. Chromosomal abnormalities have been found in at least 10% of all newborns with CHD, including genetic syndromes also involving craniofacial malformations such as DiGeorge and Downs syndrome[49,50]. Environmental factors associated with CHD include maternal rubella infection, intrauterine alcohol and thalidomide exposure, advanced maternal age, and maternal illnesses including pre-gestational diabetes mellitus, hypertension, and anti-SSA/RO antibodies[49,50,52].

The diagnostic techniques and management of CHD have changed over time and continue to improve. Diagnosis using catheterization and selective angiocardiography was introduced at major Danish hospitals in the 1950's and 60's, while non-invasive fetal echocardiography was performed from the mid 1980's[53]. The universal fetal malformation screening using ultrasound was not introduced before 2004. Today, the major part of CHD is diagnosed prenatally by fetal echocardiography or during the first year of life, most often because of symp-

toms or murmurs[50]. Treatment has improved survival substantially, especially through the availability of high quality cardiac surgery and catheter-based intervention[4,5]. The surgical interventions became in earnest successful in infants in 1980's, decades after the introduction of extracorporal circulation. Prostaglandins were put into practice to stabilize ductus-dependent lesions in 1978[53]. Furthermore, the use of interventional catheterization increased marked throughout the 1980's. Today, management vary greatly depending on the type and severity of the CHD as well as patient factors including age and general health[50]. Additionally, medication for intercurrent illnesses such as pulmonary hypertension, heart failure and arrhythmias may be initiated to better the heart function.

Over 90% of CHD patients survive into adulthood[4,5,50]. The aging CHD population represent a challenge for the healthcare system, since these patients are at increased risk of a range of late complications including congestive heart failure, stroke, and sudden death, but also experience adverse events during pregnancy and show impaired mental health[6-8,15-19,22,54]. CHD is a lifelong condition; however the research on outcomes in late adulthood and the geriatric CHD population is limited.

Methodological considerations

Study design

As described in the introduction, the study hypothesis was that the CHD population had a higher dementia risk relative to the general population. To investigate of our hypothesis, we wanted to choose the most suitable study design.

The randomized controlled trial, where the exposure is allocated randomly as an experiment, is high in the hierarchy of research design strength[55]. The aim of the randomization is to create intervention groups only differing on the exposure, thereby minimizing the influence of known and unknown confounders, as they are endeavored to be equally distributed[56]. However, to apply our exposure, CHD, to a group of individuals is technical impossible and completely unethical. Another study design, which in fact is feasible, is the case-control study. The selection of cases is based on the outcome status and this design is often used for rare diseases[56]. However, the case-control study does not provide the opportunity of readily establishing cumulative incidences and other absolute risk measurements. One other possible choice of design is the cross-sectional study. The primary limitation is that data on exposures

and outcomes is collected simultaneously with no indication of the sequence of events, which makes it impossible to infer causality.

We chose an observational study design utilizing prospectively collected data from nationwide hospital registries. In cohort studies, groups of individuals defined by exposure status are followed over a time period and subsequent evaluations with respect to event(s) of interest are conducted[55]. By use of the matched cohort design, we created two balanced cohorts with regard to sex and birth year to minimize the potential confounding.

To summarize the advantages of our matched cohort design, they included; the longitudinal design, the possibility to directly observe risk and rates as well as being ethically acceptable. Furthermore, this study design has lower expenses, is less time demanding and cumbersome. However, the patient characteristics are limited to the available data from secondary data sources, and the study is susceptible to bias and confounding.

Statistical considerations

Survival analysis

Our cohorts were dynamic with delayed entry and administrative censoring. Owing to the incomplete follow-up caused by censoring, we used time-to-event analyses or survival analyses[57]. To the best of our ability, we pre-specified our statistical model, but we also performed secondary analyses.

To avoid conditioning on the future, our subjects entered at initiation of Statistic Denmark's database on completed education in 1981, at 30 years of age, or the date of the admission where the CHD diagnosis was made (index date for matched members of the comparison cohort), whichever came last. There were two main reasons for choosing entry age at 30 years. First, dementia onset is rarely below this age, and we wanted to examine the risk in adults[27]. Second, we performed a subgroup analysis on the highest completed education, which has shown to be achieved at 30-35 years of age. All subjects were followed until first-time hospital-diagnosis of dementia, emigration, death, or end of study (December 2012). Dementia is an incurable chronic syndrome, wherefore subjects were censored after receiving the first dementia diagnosis, not considering dementia as a recurrent event. All persons diagnosed with dementia before entry were excluded to avoid prevalent outcomes at study entry.

Cumulative incidence and Kaplan-Meier

We computed an absolute outcome measure, the cumulative incidence of dementia, at a fixed time point with death as a competing risk using the Aalen-Johansen estimator. Total mortality was estimated using the Kaplan-Meier estimator. While the cumulative incidence is useful for planning purposes and allocating funds, the hazard ratio (HR) is of greater importance from a biological point of view.

Incidence rate and Cox proportional hazard regression

The incidence density of dementia was defined as the number of new dementia events per total person-time at risk[57]. Since the birth period stretched from 1890 to 1982, the study subjects could potentially survive to a great age. Contrary to the Kaplan-Meier method, Cox proportional hazard regression is a multivariate model applicable when competing risks are presented. It estimates the ratio of hazard rates at all given time points[55]. The assumption of independent censoring given the covariates is believed to be fulfilled, while the assumption of proportional rates was graphically evaluated using log-minus-log-plots. We investigated the time trend over calendar time by stratifying on entry periods, and found no difference in dementia risk. A feature of the stratified Cox regression is the ability to include covariates which change over time, time-dependent or time-varying covariates. We split on age 65 years during follow-up, cardiovascular diseases or diabetes, and 1994, the year were the 8th edition of the International Classification of Diseases (ICD-8) was superseded by ICD-10. This allowed us to compare the risk e.g. between those with and without a cardiovascular event.

Strengths and limitations

Considerations of limitations in observational studies are crucial, when interpreting the results. The true value of an estimate can never be known, and a potential causal relationship between CHD and dementia can never be proven or rejected. The internal validity, the degree to which the results are credible for the sample being studied, is threatened by bias, confounding and random variation (Supplemental Figure 1)[55]. By considering to what extent, the observed association can be explained by bias and chance, we can get closer to conclude a causal association to be likely or unlikely.

Random error

Random error is a statistical chance resulting in imprecision. Chance cannot be eliminated, but it can be minimized by increasing the sample size[56]. As a result of this larger sized study, including more than 10,000 adults with CHD and their matched comparison cohort, the effect of random error was sought to be minimized. The precision of the effect measurements was illustrated using 95% confidence intervals (CIs). Nevertheless, when we investigated subgroups of covariates, the groups were smaller resulting in greater random error.

Selection bias

Selection bias occurs when the association between exposure and outcome among participants diverge from non-participants[56]. This systematic error causing inaccuracy can be related to factors influencing study participation and loss to follow-up. The lack of information on individuals with undiagnosed CHD could cause selection bias, if their dementia risk differed from those with diagnosed CHD. Participation in the present register-based study was not influenced by self-selection. Furthermore, the study had a virtually complete follow-up for migration, death, and diagnosis of dementia, thereby minimizing selection bias due to loss to follow-up.

Information bias

A limitation of concern was the possibility of misclassification, as our findings were reliant on accuracy of the diagnosis coding. Information bias is another systematic error and a consequence of measurement error or misclassification with respect to either exposure or outcome[56].

The positive predictive value (PPV), the probability that a subject diagnosed with a CHD indeed has a CHD, has previously been reported high in the Danish National Patient Registry (DNPR), approximately 90%[44]. Moreover, the following criteria were applied to increase the validity of the CHD diagnosis (Supplemental Table 2): Individuals were excluded if diagnosed with isolated atrial septal defect, ventricular septal defect, and patent ductus arteriosus before two months of age without subsequently repeated diagnosis, and no therapeutic cardiac procedures recorded within the first two months of age. Furthermore, everyone diagnosed

with congenital malformation of the aortic and mitral valves as well as aorta stenosis above 40 years of age were not included. Subjects diagnosed with unspecific CHD, bicuspid aortic valve, and congenital heart block were disregarded.

Misclassification of the exposure, CHD, was viewed as independent of future dementia diagnosis. Any misclassification is expected to be non-differential with the measurement error uniformly distributed between the two cohorts, thus creating bias towards no association. Misclassification of defect types and CHD severity could have biased our estimates. Especially in the medical record review, the contemporary diagnostic possibilities and potential shortcomings might have resulted in misdiagnosed patients and a larger degree of underdiagnosed CHD. The misclassification could bias the HR of dementia upwards in the mild severity category, as some CHD subjects in this category might have had severe or multiple defects.

The PPV of all-cause dementia in the DNPR has been reported high, approximately 86%, though the PPVs for major subtypes are much lower[45]. Therefore, we used all-cause dementia as our outcome in preference to subtypes. The Danish Psychiatric Central Register and the Danish National Prescription Database were not used in this study, as the data was not available. Additionally, patients diagnosed with dementia and followed by general practitioners were not captured. It was not possible to determine the severity of dementia at diagnosis. Usually, the severe and more complex cases of dementia are referred to either psychiatric or somatic clinics for further investigation, hereof appearing in the utilized hospital registries. Therefore, the milder dementia cases might be underrepresented in this study.

Surveillance bias was an issue causing concern, because the CHD population may be more frequently in contact with medical establishments than the general population. If CHD subjects were more likely than the general population to be referred to specialized hospital wards and outpatient clinics with the purpose of dementia evaluation, this information bias would result in a differential misclassification, and consequently an overestimation of the HR.

In a subgroup analysis, we aimed to investigate the dementia risk in adults with CHD relative to members from the general population with contacts to the healthcare system, but defined by diseases not associated with increased dementia risk. We restricted the comparison cohort to those who received diagnoses of different congenital malformations or hernia. However, the subjects showed to have other comorbidities, and a larger number received their congenital diagnosis later in life. Therefore, we restricted the comparison cohort to those who re-

ceived a hospital-diagnosis of diseases associated with cognitive decline and increased risk of dementia (diabetes, stroke, and heart failure[13,14,20,21]) in order to provide a perspective on our results. The restriction was made after the matching process. The dementia risk was lower among CHD adult relative to the restricted comparison cohort (HR 0.74; 95% CI: 0.57-0.96), which suggests that CHD is not as strong a risk factor for dementia as diabetes, stroke, and heart failure in this population. It was not possible to completely determine the role of surveillance bias in this observational study.

Effect measure modification and confounding

Effect measure modification is present when a covariate modifies the observed effect of the exposure on the disease status. In the present study, age was seemingly an effect measure modifier of the HR and, hereby, modifying the observed effect of CHD on dementia status. The effect of CHD appeared higher among younger (Table 2, Age during follow-up) than older individuals, while the burden of age-related dementia pathologies and other comorbidities is lower. Since it was not decided before study initiation, we did not include interaction terms in the regression models.

Confounding is a confusion of effects leading to bias and an over- or underestimation of an association[56]. The confounding covariate must be associated to the outcome of interest or be a proxy for a variable associated to the outcome. Furthermore, the covariate must be associated to the exposure and not be an intermediate step in the chain of cause and effect[56]. Confounding can be minimized both by optimizing the study design (randomization, restriction, matching) and in the statistical analyses (matching, standardizing, stratification, adjustments and best/worst case scenarios)[56] (Supplemental Figure 1).

Gender and birth year were potential confounders as illustrated in the direct acyclic graph (Supplemental Figure 2). By conditioning on the two covariates, the open backdoor paths would be closed, and the observed association would not be confounded by sex and birth year, if the confounders were handled appropriately. Initially, we expected an equal distribution of the two matched factors across the cohorts created by an individual matching. However, due to the long follow-up, the matching was not expected to be maintained, wherefore we adjusted for sex and birth year using Cox regression. We also adjusted for age using the variable as the underlying time scale.

Several covariates, including atrial fibrillation, hypertension, and educational level, could be regarded as having a confounding effect based on existing literature and clinical knowledge. However, they violate one of the criteria of being a confounder, forasmuch as they are part of indirect paths between CHD and dementia, and could be regarded as intermediate factors (Supplemental Figure 2). By conditioning on potential mediators of the observed association, the paths are blocked. For that reason, we did not adjust for these covariates in the primary analyses. In a sensitivity analysis, we compared the CHD cohort to the general comparison cohort adjusting for educational attainment at 30 years of age as a categorical variable. The CHD cohort was still at higher risk of dementia (HR 1.60; 95% CI: 1.28-2.01). Unfortunately, we did not have available data on other potential confounders or risk factors for dementia such as prematurity, smoking and other lifestyle factors. Additionally, unknown confounders may still bias the results of this study.

External validity

External validity is the transferability or generalizability to other populations than the study population. The present study was a large, nationwide cohort study, which to some degree is generalizable to similar populations e.g. other Scandinavian countries. However, we restricted our cohorts to those who survived until 30 years of age; hence we cannot transfer the results to younger individuals. The transferability to milder dementias might also be an issue, as we expected milder illnesses to be treated outside of hospitals and, therefore, not appearing in the utilized registries. Lastly, the development in CHD management is ongoing, wherefore the results of this study cannot necessarily be extrapolated to CHD subjects diagnosed and treated today.

Clinical perspectives and future studies

Previous studies have focused on a wide range of neurodevelopmental impairments and psychosocial functioning in the CHD population during childhood and early adult life. The adult CHD population is growing and aging creating an increase in complexity of disease. In this study, we observed an overall increased risk of first-time hospital-diagnosis of dementia among CHD adults relative to a general population cohort, especially regarding early onset

dementia. The risk among CHD adults was lower than in the restricted comparison cohort with established dementia risk factors (diabetes, stroke, and heart failure).

To our knowledge, no previous study has investigated the risk of dementia in the CHD population. Therefore, studies examining the same potential cause-effect-relationship in different ways and in other populations are necessary to accumulate evidence, before any clinical recommendations and the like are drafted. More knowledge of long-term neurologic outcomes in the CHD population is important to further understand the underlying biological mechanisms, to detect and potentially postpone disease onset as well as potentially prevent late complications, preserve cognitive function and sustain quality of life.

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TABLES

Table 1 Characteristics of 10,632 patients with congenital heart disease (CHD) diagnosed from 1963 to 1982 in Denmark and the matched comparison cohort.

	CHD cohort n (%)	General population cohort n (%)
All	10,632 (100)	103,403 (100)
Male	4,936 (46)	47,869 (46)
Birth year		
1890 - 1939	1,391 (13)	13,723 (13)
1940 - 1959	2,636 (25)	26,080 (25)
1960 - 1982	6,605 (62)	63,600 (62)
Severity		
Mild (biventricular, no surgery)	4,705 (44)	-
Moderate (biventricular, surgery)	2,195 (21)	-
Severe	2,063 (19)	-
Univentricular	62 (1)	-
Not classified	1,607 (15)	-
Cyanosis		
Acyanotic	6,714 (64)	-
Cyanotic	667 (6)	-
Unclassified	3,183 (30)	
Age at first CHD diagnosis (years)		
0 - 35	7,086 (67)	-
> 35	3,546 (33)	-
Major CHD diagnoses		
Atrial septal defect	2,737 (26)	-
Coarctation of the aorta	732 (7)	-
Patent ductus arteriosus	884 (8)	-
Transposition of the great arteries	157 (1)	-
Tetralogy of Fallot	409 (4)	-
Ventricular septal defect	2,361 (22)	-
Truncus arteriosus	39 (0)	-
Other	3,313 (32)	-
Education		
Basic	5,379 (51)	48,202 (47)
Moderate	1,367 (13)	14,480 (14)
Advanced	2,127 (20)	24,505 (24)
Missing	1,759 (17)	16,216 (16)
Acquired cardiovascular disease or diabetes*		
Yes	3,888 (37)	-
No	6,744 (63)	-
Extracardiac defects	1,504 (14)	3,624 (4)

*At least one of the following: atrial fibrillation or flutter, diabetes, heart failure, stroke, and hypertension.

Table 2 Incidence rates and hazard ratios of dementia diagnosis among congenital heart disease (CHD) patients compared with the general population comparison cohort.

	Number of dementia events		Incidence rate per 1,000 person-years		HR (95% CI)*
	CHD cohort	General population cohort	CHD cohort (122,397 person-years at risk)	General population cohort (1,302,010 person-years at risk)	
Overall	95	977	0.78	0.75	1.61 (1.29-2.02)
Male	33	354	0.60	0.61	1.55 (1.06-2.26)
Female	62	623	0.92	0.87	1.65 (1.25-2.19)
Birth period					
1890 – 1939	58	815	4.24	4.30	1.26 (0.95-1.69)
1940 – 1959	21	131	0.51	0.29	1.93 (1.21-3.10)
1960 – 1982	16	31	0.24	0.05	5.25 (2.84-9.72)
Severity					
Mild (biventricular, no surgery)	48	494	0.94	0.89	1.62 (1.18-2.21)
Moderate (biventricular, surgery)	16	177	0.59	0.65	1.23 (0.71-2.11)
Severe and univentricular	17	173	0.67	0.63	1.96 (1.14-3.34)
Not classified	14	133	0.74	0.67	1.85 (1.01-3.40)
Cyanosis					
Acyanotic	60	663	0.79	0.83	1.42 (1.08-1.89)
Cyanotic	5	66	0.63	0.72	1.83 (0.69-4.87)
Not classified	29	244	0.77	0.61	2.09 (1.38-3.18)
CHD diagnosis					
Atrial septal defect	30	386	1.09	1.30	1.20 (0.81-1.77)
Ventricular septal defect	17	146	0.62	0.50	1.85 (1.08-3.17)
Patent ductus arteriosus	6	63	0.55	0.56	1.74 (0.71-4.28)
Coarctation of the aorta	7	68	0.73	0.67	1.58 (0.67-3.74)
Tetralogy of Fallot	3	44	0.55	0.70	2.25 (0.63-8.11)
Other	31	249	0.79	0.60	1.89 (1.30-2.76)

	Number of dementia events		Incidence rate per 1,000 person-years		HR (95% CI)*
	CHD cohort	General population cohort	CHD cohort (122,397 person-years at risk)	General population cohort (1,302,010 person-years at risk)	
Age at CHD diagnosis (years)					
0 - 35	17	72	0.19	0.08	2.71 (1.57-4.66)
> 35	78	905	2.47	2.34	1.47 (1.15-1.89)
Education					
Basic	47	414	0.78	0.64	1.82 (1.32-2.51)
Moderate	11	44	0.56	0.23	2.65 (1.30-5.38)
Advanced	3	85	0.15	0.42	0.52 (0.16-1.69)
Missing	34	434	1.55	1.71	1.47 (1.01-2.15)
Extracardiac defects					
Yes	16	50	0.96	0.28	7.88 (3.96-15.71)
No	79	927	0.75	0.82	1.38 (1.08-1.76)
Age during follow-up					
<65 years	33	145	0.29	0.13	2.59 (1.76-3.81)
65 or older	62	832	5.92	5.45	1.32 (1.00-1.75)
Acquired cardiovascular disease or diabetes[†]					
Yes	60	691	2.16	2.01	1.48 (1.11-1.97)
No	35	286	0.37	0.30	1.82 (1.26-2.64)
Time of dementia diagnosis					
Before 1994	5	70	0.31	0.39	1.25 (0.48-3.24)
Since 1994	90	907	0.85	0.81	1.64 (1.03-2.08)
Subgroup analysis[‡]	95	262	0.78	5.53	0.74 (0.57-0.96)

CHD; Congenital heart disease, CI; Confidence interval, HR; Hazard ratio.

*Adjusted for sex and birth year

[†]At least one of the following: atrial fibrillation or flutter, diabetes, heart failure, stroke, and hypertension.

[‡]Restricted the general population cohort to those who had at least one of the following: diabetes, stroke, or heart failure.

SUPPLEMENTAL TABLES AND FIGURES

Supplemental table 1 International Classification of Diseases (ICD) diagnostic codes, 8th and 10th edition

	ICD-8	ICD-10
Atrial fibrillation or flutter	427.93-427.94	I48
CHD	746-747, except 746.99, 747.59, 747.69, 747.89, 747.99	Q20-Q26, except Q20.9, Q21.9, Q23.1A, Q24.6, Q24.9, Q25.9, Q26.1, Q26.5, Q26.6, Q26.9, Q27
Dementia	094.19, 290.09, 290.10, 290.11, 290.18, 290.19, 292.09, 293.09, 293.19	F00, F01, F02, F03, F1x.73 (F10.73 through F19.73), G23.1, G30, G31.0, G31.1, G31.8B, G31.8E, G31.85
Diabetes mellitus	249-250	E10-E14, G63.2, H36.0, N08.3
ECD	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	Q00.0–Q99.9, except Q20-Q26
Heart failure	427.09, 427.10, 427.11. 427.19, 428.99, 782.49	I50, I11.0, I13.0, I13.2
Hypertension	400-404	I10-I15, I16.7
Stroke	431, 433-434	I61, I63-I64

CHD; Congenital heart disease, ECD; Extra cardiac defects, ICD; International Classification of Diseases.

Supplemental table 2 The following International Classification of Diseases (ICD) diagnostic codes were ignored when defining congenital heart disease (CHD).

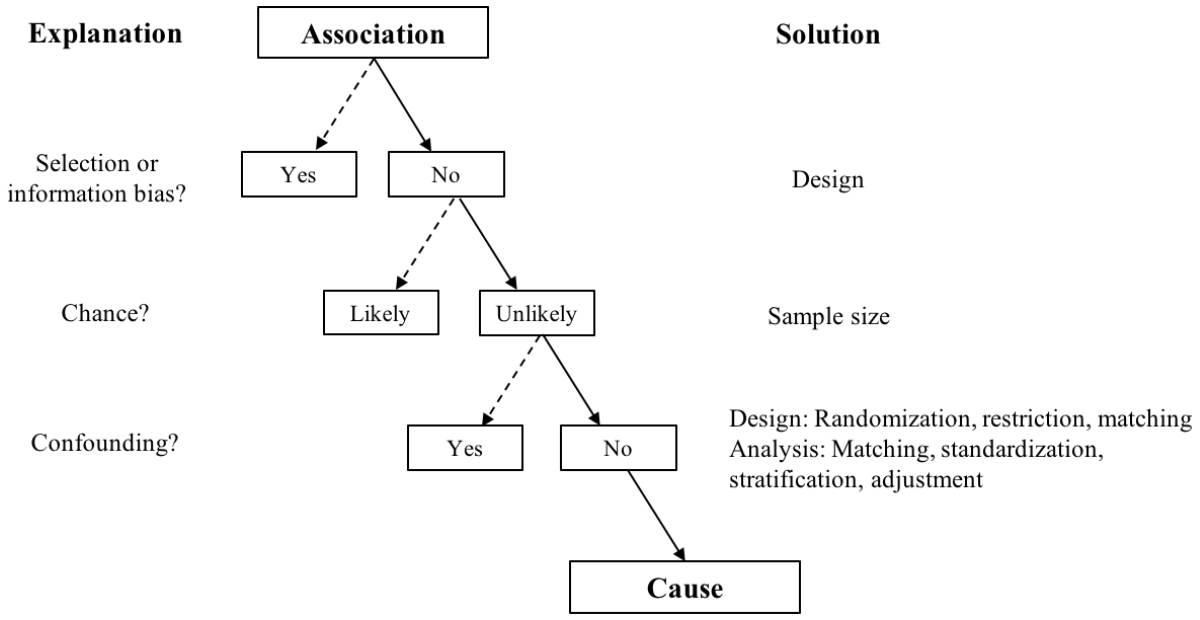
ICD-8		**Ignored/ignored if**
746.3	VSD	Age at diagnosis is less than 2 months, diagnosis is not repeated later in life, and no therapeutic cardiac procedure is recorded within the first 2 month of age.
746.3	VSD	Age at diagnosis is above 40 years and simultaneous diagnosis of acute myocardial infarction.
746.4	ASD	Age at diagnosis is less than 2 months, diagnosis is not repeated later in life, and no therapeutic cardiac procedure is recorded within the first 2 month of age.
746.62	Congenital malformation of the aortic valve	Age at first diagnosis is above 40 years.
746.99	Unspecific	Ignored
747.0	PDA	Age at diagnosis is less than 2 months, diagnosis is not repeated later in life, and no therapeutic cardiac procedure is recorded within the first 2 month of age.
747.59,747.69, 747.89,747.99	Not considered to be CHD	Ignored

ICD-10		**Ignored/ignored if**
Q20.9	Unspecific	Ignored
Q21.0	VSD	Age at diagnosis is less than 2 months, diagnosis is not repeated later in life, and no therapeutic cardiac procedure is recorded within the first 2 month of age.
Q21.0	VSD	Age at diagnosis is above 40 years and simultaneous diagnosis of acute myocardial infarction.
Q21.1	ASD	Age at diagnosis is less than 2 months, diagnosis is not repeated later in life, and no therapeutic cardiac procedure is recorded within the first 2 month of age.
Q21.1	ASD	Simultaneous percutaneous closure of an ostium secundum atrial septal defect AND prior diagnosis of apoplexy, migraine, transient cerebral ischemic attack, or vascular syndromes of the brain. To exclude patent foramen ovale.
Q21.9	Unspecific	Ignored

ICD-10		Ignored/ignored if
Q23.0, Q23.1, Q23.2, Q23.3, Q23.9	Congenital malformation of aortic and mitral valves	Age at first diagnosis is above 40 years.
Q23.1A	Bicuspid aortic valve	Ignored
Q24.6	Congenital heart block	Ignored
Q24.9	Unspecific	Ignored
Q25.0	PDA	Age at diagnosis is less than 2 months, diagnosis is not repeated later in life, and no therapeutic cardiac procedure is recorded within the first 2 month of age.
Q25.3	Stenosis of aorta	Age at first diagnosis is above 40 years.
Q25.9	Unspecific	Ignored
Q26.1, Q26.5, Q26.6, Q26.9, Q27	Not considered to be CHD	Ignored

ASD; Atrial septal defect, CHD; Congenital heart disease, ICD; International Classification of Diseases, PDA; Patent ductus arteriosus, VSD; Ventricular septal defect.

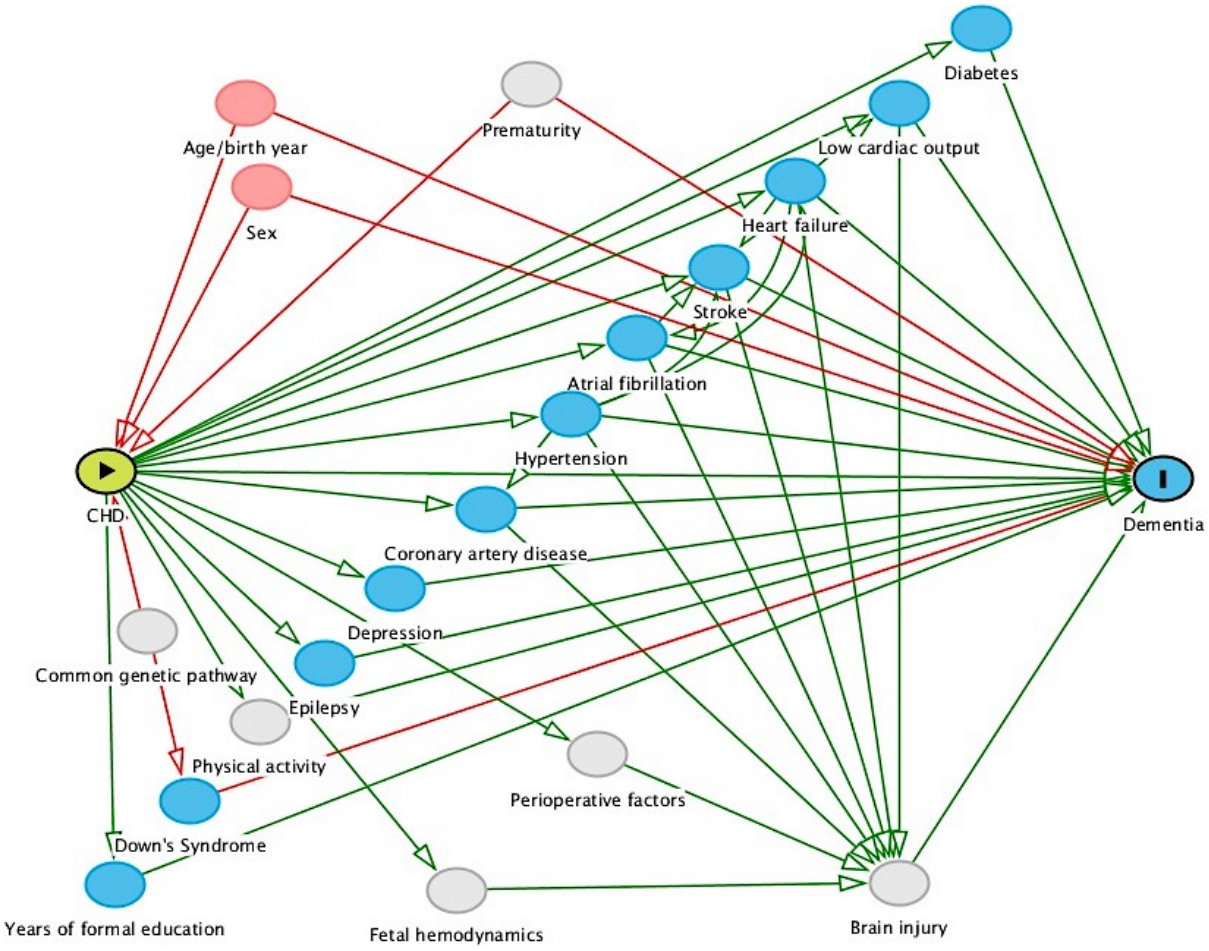
Supplemental figure 1 Association and cause



Modified from Fletcher and Fletcher: Clinical Epidemiology – The Essentials[55]

Bias, chance, and confounding should be evaluated to allow the conclusion of a likely causal association.

Supplemental figure 2 Directed acyclic graph (DAG)



Abbreviation: CHD; Congenital heart disease

Causal diagrams based on DAGs translate background information and assumptions into a graph, which is useful for planning a study, identifying which data to be collected and deciding on the statistical analyses[58]. The blue nodes are ancestors of dementia, the red are ancestors of CHD and dementia, while the grey are unobserved variables. The green arcs are causal paths, and the red are biasing paths. For instance, CHD has been associated to an increased risk of stroke[17], which further is associated with increased risk of dementia[59]. This translates into an indirectly causal path with an intermediate variable, stroke.

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