Circulation

ORIGINAL RESEARCH ARTICLE

Risk of Dementia in Adults With Congenital Heart Disease

Population-Based Cohort Study

Editorial, see p XXX

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BACKGROUND: More children with congenital heart disease (CHD) are surviving to adulthood, and CHD is associated with risk factors for dementia. We compared the risk of dementia in CHD adults to that of the general population.

METHODS: In this cohort study, we used medical registries and a medical record review covering all Danish hospitals to identify adults with CHD diagnosed between 1963 and 2012. These individuals with CHD were followed from January 1, 1981, 30 years of age, 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 31, 2012). For each individual with CHD, we identified 10 members of 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.

RESULTS: The cumulative incidence of dementia was 4% by 80 years of age in 10 632 adults with CHD (46% male). The overall HR comparing adults with CHD with the general population cohort was 1.6 (95% confidence interval [CI], 1.3–2.0). The HR among individuals with CHD without extracardiac defects was 1.4 (95% CI, 1.1–1.8). Adults with mild-to-moderate CHD had an HR of 1.5 (95% CI, 1.1–2.0), whereas the HR was 2.0 (95% CI, 1.2–3.3) for severe CHD, including univentricular hearts. The HR for early onset dementia (<65 years of age) was 2.6 (95% CI, 1.8–3.8), whereas the late-onset HR was 1.3 (95% CI, 1.0–1.8).

CONCLUSIONS: CHD was associated with an increased risk of dementia compared with the general population, in particular for early onset dementia. Further understanding of dementia risk in the population with CHD is a potential target for future investigation.

Key Words: cohort study ■ congenital heart disease ■ dementia ■ epidemiology ■ long-term outcome

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Clinical Perspective

What Is New?

- Congenital heart disease is associated with adverse neurodevelopmental outcomes during childhood and early adulthood; however, data on long-term neurological outcomes are sparse.
- In a nationwide population-based cohort study including 10 632 adults with congenital heart disease, the risk of all-cause dementia was increased by ≈60% compared with a matched general population cohort.
- The risk was higher for early onset dementia (<65 years of age; more than double) than late-onset dementia (≈30% elevated risk) and was elevated for all levels of congenital heart disease complexity, including those with cyanotic potential.
- The relative risk remained increased for those without extracardiac defects or acquired cardiovascular diseases.

What Are the Clinical Implications?

- Adults with congenital heart disease are at increased risk for dementia, particularly early onset dementia, and these results support the importance of understanding the risk of adverse long-term neurological outcomes in the growing and aging population with congenital heart disease.
- Although it remains unknown whether the results are directly generalizable to children diagnosed today, they appear relevant for the large population of adults with congenital heart disease alive today.
- In the absence of disease-modifying treatments for most dementias, the specific influence of etiologic factors on congenital heart disease is a potential target for future investigations to delay dementia onset in this vulnerable population.

Congenital heart disease (CHD) occurs in 6 to 10 per 1000 live births and represents the most common group of congenital malformations.[1–3] Because of recent advances in CHD management and an overall reduction in mortality, increased attention is being paid to acquired morbidities in the aging population with CHD.[4,5]

Neurodevelopmental deficits among infants and children with CHD are well described.[6–8] However, research on long-term neurological outcomes in adults with CHD is more limited. Dementia is among the most important late-life neurological diseases in the general population. The prevalence of dementia is growing dramatically as a result of increased life expectancy. In the Danish population, ≈7% of those above 65 years of age are diagnosed with dementia,[9] and prevalence estimates are similar in other countries.[10] Dementia is the 5th most common cause of death in Denmark[11] and the 6th most common in the United States.[12]

Risk factors for dementia are increased in the population with CHD.[13–15] These factors include genetic disorders such as Down syndrome and cardiovascular diseases such as ischemic and hemorrhagic stroke, hypertension, heart failure, atrial fibrillation, and diabetes mellitus.[16–22] In addition, some adults with CHD have poor exercise tolerance,[23] which is a dementia risk factor.[24]

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 associated risk factors for dementia in CHD, we hypothesized that the risk of dementia is higher in adults with CHD than in the general population.

METHODS

Study Design and Setting

This nationwide population-based cohort study was conducted in Denmark using linked medical registries. 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). The data will not be made available to other researchers for purposes of reproducing the results. Analytic methods are described below.

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 10-digit identifier, and the Danish Civil Registration System, which contains data on all Danish residents since 1968.[25] The Civil Registration System is updated daily and has electronic records on dates of birth, emigration, and death.[25]

Congenital Heart Disease Cohort

The International Classification of Diseases (ICD) codes used in the study are provided in Table I in the online-only Data Supplement. We used 2 nationwide registries to identify all adults who received a diagnosis of CHD between 1963 and 1974 (before 15 years of age) and between 1977 and 2012 (at any age). The identification of survivors of CHD diagnosed between 1963 and 1974 was based on a medical record review and has been described elsewhere.[26] The identification of those diagnosed between 1977 and 2012 was performed using the Danish National Patient Registry (DNPR), which 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.[27] Diagnoses were coded according to the 8th revision of the ICD from 1966 until the end of 1993 and the 10th revision thereafter. The individuals diagnosed with CHD during the 2-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 adults with CHD were grouped according to a hierarchy of physiological complexity: univentricular represents a history of single-ventricle diagnoses or palliative surgery such as Norwood, Glenn, and Fontan; severe represents more complex biventricular physiology, including tetralogy of Fallot, transposition of the great arteries, and atrioventricular canal defect; mild to moderate included simple biventricular physiology with and without a history of surgery or catheter-based intervention for atrial septal defect, ventricular septal defect, isolated coarctation of the aorta, and patent ductus arteriosus; or unclassified.

The CHD cohort was subdivided according to cyanotic potential to examine potential variation in dementia risk. Because of the inability to identify duration and severity of cyanosis exposure based on the ICD coding, the analysis was performed after restriction to those lesions with the highest certainty of being cyanotic for some period of time. Specifically, the defects selected to have cyanotic potential were 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, coarctation of the aorta, and patent ductus arteriosus. All other individuals were defined as unclassified for cyanosis-related analysis. Those with Eisenmenger's physiology were excluded from this analysis.

General Population Comparison Cohort

For each CHD adult, 10 individuals from the general population were randomly sampled through the Civil Registration System matched on sex and birth year.[25]

Dementia

The primary outcome was a first-time hospital diagnosis of all-cause dementia in the inpatient or outpatient clinic setting obtained from the DNPR. We also categorized dementia diagnoses into Alzheimer disease, vascular dementia, and other dementias (including unspecified dementias). Because the age of dementia onset is rarely <30 years of age,[28] we restricted the analysis to those ≥30 years of age. Dementia onset was divided into early and late onset by use of the conventional threshold of 65 years of age.[29]

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- to 4-year vocational programs after primary education), or advanced (completion of university education). By means of the DNPR, extracardiac defects (ECDs) and chromosomal abnormalities diagnosed 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.[30] Information on hospital-diagnosed cardiovascular diseases (atrial fibrillation or flutter, heart failure, stroke, and hypertension) and diabetes mellitus at any time during follow-up was also obtained using 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. Individuals who received a dementia diagnosis before the index date were excluded.

We computed the cumulative incidence of dementia in both cohorts considering death as a competing risk. All-cause mortality was estimated using the Kaplan-Meier estimator. The incidence rates of dementia were estimated as the count of individual diagnosed with dementia divided by the total person-time at risk. In addition, the incidence rates were calculated for 3 different age groups. Cox proportional hazard regression was used to compute the hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) of time to all-cause dementia diagnosis as well as subtypes of dementia diagnoses. We compared adults with CHD to the general population cohort using age as a time scale and adjusted for sex and birth year. 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 CHD complexity, cyanosis potential, age at first CHD diagnosis, CHD diagnosis type, presence of ECDs, and educational attainment. Separate analyses were performed for follow-up periods < and >65 years of age to differentiate early and late onset dementia, respectively. To investigate the role of cardiovascular diseases (atrial fibrillation or flutter, heart failure, stroke, and hypertension) and diabetes mellitus, we evaluated the HRs during time at risk before and after such diagnoses in the CHD cohort (index date for matched comparison cohort members). The proportional hazard assumption was verified using log-minus-log plots.

Sensitivity Analyses

We performed 4 sensitivity analyses. First, we excluded all adults with CHD and members of the matched general population cohort with diagnosis of mild cognitive impairments or amnestic syndromes at the start of follow-up to ensure capture of only incident events of dementia (ICD codes are presented in Table I in the online-only Data Supplement). Second, we redefined Alzheimer disease to also include the ICD code for dementia without specification because a previous study has reported many Alzheimer disease cases to be misclassified as unspecified dementia.[31] Third, we adjusted separately for extracardiac defects, acquired cardiovascular diseases, including diabetes mellitus and stroke, and education. Forth,

separate analyses were performed before and after the year 1994, when ICD-10 superseded ICD-8.

All statistical analyses of data were conducted using STATA software (14th edition, StataCorp LP).

RESULTS

We identified 10 632 adults with CHD 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 (n=2737, 26%) and ventricular (n=2361, 22%) septal defects. In this cohort of adults with CHD, 65% (n=6900) had a mild-to-moderate CHD complexity. Diagnoses of ECDs were more frequent among adults with CHD (14%) than in the comparison cohort (4%).

During the follow-up period, 1072 adults were diagnosed with dementia across both cohorts. The cumulative incidence of dementia was 4% at 80 years of age in both cohorts. However, the all-cause mortality at 80 years of age differed between cohorts (60% for CHD adults and 35% for the comparison cohort). The overall incidence rate per 1000 person-years at risk was 0.78 in the cohort with CHD and 0.75 in the general population cohort. Although the incidence rates increased with age in both cohorts, the incidence rise rate of the population with CHD was relatively greater compared with the general population cohort in all age groups (30–64 years, 65–79 years, and 80+ years) (Table 2).

The overall HR of dementia was 1.61 (95% CI, 1.29–2.02) among adults with CHD compared with the general population cohort (Table 3). The elevation was similar for diagnoses of Alzheimer disease, vascular dementia, and other dementias. The HRs did not vary according to sex (male, 1.55; 95% CI, 1.06–2.26; female, 1.65; 95% CI, 1.25–2.19) (Table 4). Adults with severe and univentricular CHD had an HR of 1.96 (95% CI, 1.15–3.34), whereas the HR was 1.50 (95% CI, 1.14–1.97) for the mild-to-moderate CHD complexity. The HR for CHD types with cyanotic potential was 1.83 (95% CI, 0.69–4.87) compared with 1.42 (95% CI, 1.08–1.89) for acyanotic defects. When considering the risk of dementia among adults with CHD without ECD, the increased HR persisted (1.38; 95% CI, 1.08–1.76). The risk of dementia in the cohort with CHD relative to the general population cohort was more elevated more for early onset dementia (HR, 2.59; 95% CI, 1.76–3.81) than late-onset dementia (HR, 1.32; 95% CI, 1.00–1.75).

The HRs computed according to completed education by 30 years of age comparing adults with CHD to the matched general population cohort members 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). Adults with CHD with and without

Table 1. Characteristics of 10 632 Adults Born Between 1890 and 1982 and Diagnosed With Congenital Heart Disease From 1963 to 2012 in Denmark and the Matched General Population Cohort

Characteristic	Cohort With Congenital Heart Disease n (%)	General Population Cohort n (%)
All	10 632 (100)	103 403 (100)
Male	4936 (46)	47 869 (46)
Birth year		
1890–1939	1391 (13)	13 723 (13)
1940–1959	2636 (25)	26 080 (25)
1960–1982	6605 (62)	63 600 (62)
Severity*		
Mild to moderate	6900 (65)	—
Severe	2063 (19)	—
Univentricular	62 (1)	—
Not classified	1607 (15)	—
Cyanosis†		
Acyanotic	6714 (64)	—
Cyanotic	667 (6)	—
Unclassified	3183 (30)	
Age at first congenital heart disease diagnosis, y		
0–35	7086 (67)	—
>35	3546 (33)	—
Major congenital heart disease diagnoses		
Atrial septal defect	2737 (26)	—
Ventricular septal defect	2361 (22)	—
Patent ductus arteriosus	884 (8)	—
Coarctation of the aorta	732 (7)	—
Tetralogy of Fallot	409 (4)	—
Transposition of the great arteries	157 (1)	—
Truncus arteriosus	39 (0)	—
Other	3313 (32)	—
Education‡		
Basic	5379 (51)	48 202 (47)
Moderate	1367 (13)	14 480 (14)
Advanced	2127 (20)	24 505 (24)
Missing	1759 (17)	16 216 (16)
Extracardiac defects§	1504 (14)	3624 (4)
Acquired cardiovascular disease or diabetes mellitus‖		
Yes	3888 (37)	—
No	6744 (63)	—

*Mild to moderate: simple biventricular with and without history of surgical intervention; severe: complex biventricular physiology, including tetralogy of Fallot, transposition of the great arteries, and atrioventricular canal defect; univentricular: history of single-ventricle diagnoses or palliative surgery such as Norwood, Glenn, and Fontan.

†Cyanotic potential: tetralogy of Fallot, transposition of the great arteries, truncus arteriosus/common arterial trunk, and univentricular physiology; acyanotic: atrial septal defects, ventricular septal defects, coarctation of the aorta, and patent ductus arteriosus.

‡Highest completed education at 30 years of age: basic (completion of primary education), moderate (completion of 3 years of secondary education known as gymnasium or completion of 3- to 4-year vocational programs after primary education), or advanced (completion of university education).

§Including syndromes and chromosomal abnormalities.

‖At least 1 of the following at any time: atrial fibrillation or flutter, diabetes mellitus, heart failure, stroke, and hypertension.

Table 2. Incidence Rates Among Adults With Congenital Heart Disease and the General Population, by Age Group

Age Group	Number of Dementia Events		Incidence Rate per 1,000 Person-Years	
	Cohort With Congenital Heart Disease	General Population Cohort	Cohort With Congenital Heart Disease (122 397 Person-Years at Risk)	General Population Cohort (1 302 010 Person-Years at Risk)
Overall	95	977	0.78	0.75
30–64 y	33	145	0.03	0.01
65–79 y	36	384	0.39	0.31
80+ y	26	448	1.93	1.59

additional acquired cardiovascular disease or diabetes mellitus were at increased risk of dementia (HR, 1.48; 95% CI, 1.11–1.97; HR, 1.82; 95% CI, 1.26–2.64, respectively). The incidence rates for adults with CHD with these acquired diseases and for matched members of the comparison cohort were 2.16 and 2.01 per 1000 person-years at risk, respectively. For individuals without these acquired diseases and for their matched members, the incidence rates were 0.37 and 0.30 per 1000 person-years at risk, respectively.

Sensitivity Analyses

The results did not change substantially when excluding all individuals with diagnosed mild cognitive impairments and amnestic syndromes (Table II in the online-only Data Supplement). The reclassification of unspecified dementias as Alzheimer disease did not change the result substantially. After adjusting for potential mediating factors—extracardiac defects, acquired cardiovascular diseases including diabetes mel-

Table 3. Hazard Ratios of All-Cause Dementia Diagnosis and Dementia Subtype Diagnosis Among Adults With Congenital Heart Disease Compared With the General Population Cohort

	Number of Dementia Events		Hazard Ratio (95% CI)*
	Cohort With Congenital Heart Disease	General Population Cohort	
All-cause dementia	95	977	1.61 (1.29–2.02)
Alzheimer disease	22	246	1.35 (0.86–2.15)
Vascular dementia	11	107	1.62 (0.84–3.11)
Other dementias	62	624	1.73 (1.30–2.30)

CI indicates confidence interval.
*Adjusted for sex and birth year.

Table 4. Hazard Ratios of Dementia Diagnosis Among Adults With Congenital Heart Disease Compared With the General Population Cohort

Variable	Number of Dementia Events		Hazard Ratio (95% CI)*
	Cohort With Congenital Heart Disease	General Population Cohort	
Overall	95	977	1.61 (1.29–2.02)
Sex			
Male	33	354	1.55 (1.06–2.26)
Female	62	623	1.65 (1.25–2.19)
Birth period			
1890–1939	58	815	1.26 (0.95–1.69)
1940–1959	21	131	1.93 (1.21–3.10)
1960–1982	16	31	5.25 (2.84–9.72)
Severity†			
Mild to moderate	64	672	1.50 (1.14–1.97)
Severe and univentricular	17	173	1.96 (1.15–3.34)
Not classified	14	133	1.85 (1.01–3.40)
Cyanosis‡			
Acyanotic	60	663	1.42 (1.08–1.89)
Cyanotic	5	66	1.83 (0.69–4.87)
Not classified	29	244	2.09 (1.38–3.18)
Age at congenital heart disease diagnosis, y			
0–35	17	72	2.71 (1.57–4.66)
>35	78	905	1.47 (1.15–1.89)
Congenital heart disease diagnosis			
Atrial septal defect	30	386	1.20 (0.81–1.77)
Ventricular septal defect	17	146	1.85 (1.08–3.17)
Patent ductus arteriosus	6	63	1.74 (0.71–4.28)
Coarctation of the aorta	7	68	1.58 (0.67–3.74)
Tetralogy of Fallot	3	44	2.25 (0.63–8.11)
Other	31	249	1.89 (1.30–2.76)
Education§			
Basic	47	414	1.82 (1.32–2.51)
Moderate	11	44	2.65 (1.30–5.38)
Advanced	3	85	0.52 (0.16–1.69)
Missing	34	434	1.47 (1.01–2.15)
Extracardiac defects‖			
Yes	16	50	7.88 (3.96–15.71)
No	79	927	1.38 (1.08–1.76)
Age during follow-up, y			
<65	33	145	2.59 (1.76–3.81)
≥65	62	832	1.32 (1.00–1.75)

(*Continued*)

Table 4. Continued

Variable	Number of Dementia Events		Hazard Ratio (95% CI)*
	Cohort With Congenital Heart Disease	General Population Cohort	
Acquired cardiovascular disease or diabetes mellitus#			
Yes	60	691	1.48 (1.11–1.97)
No	35	286	1.82 (1.26–2.64)

CI indicates confidence interval.

*Adjusted for sex and birth year.

†Mild to moderate: simple biventricular with and without history of surgical intervention; severe and univentricular: complex biventricular physiology, history of single-ventricle diagnoses, or palliative surgery such as Norwood, Glenn, and Fontan.

‡Cyanotic potential: tetralogy of Fallot, transposition of the great arteries, truncus arteriosus/common arterial trunk, and univentricular physiology; acyanotic: atrial septal defects, ventricular septal defects, coarctation of the aorta, and patent ductus arteriosus.

§Highest completed education at 30 years of age: basic (completion of primary education), moderate (completion of 3 years of secondary education known as gymnasium or completion of 3- to 4-year vocational programs after primary education), or advanced (completion of university education).

‖Including syndromes and chromosomal abnormalities.

#At least one of the following diagnoses at any time: atrial fibrillation or flutter, diabetes mellitus, heart failure, stroke, and hypertension.

litus and stroke, and education—the HR remained approximately the same. Last, the increased relative risk of dementia among adults with CHD did not vary by ICD version in use at time of dementia diagnosis.

DISCUSSION

Among adults with CHD, we found that the risk of dementia was increased relative to a sex- and birth year-matched general population cohort. Elevated relative risk of dementia was present across the entire spectrum of adults with CHD, including individuals with both mild and complex CHD, with or without potential cyanotic lesions, with and without ECDs or chromosomal abnormalities, and with or without acquired conditions such as diabetes mellitus or cardiovascular disease. The relative risk of dementia was particularly increased for middle-age adults who demonstrated evidence of early onset dementia.

Our findings extend the knowledge of long-term neurological impairment and mental health functional morbidities in the population with CHD. Although previous studies have reported elevated risks of adverse neurodevelopmental outcomes among individuals with CHD, including increased occurrence of depression, autism, and epilepsy compared with the general population,[6–8,19,32–35] our study examined an older adult population to determine the later-life consequences of this neurological outcome. Although the underlying pathophysiological mechanisms are not completely understood, the potential etiologic factors appear multifactorial and consistent with previous findings within the neurodevelopmental scientific literature.

The concept of cerebral reserve provides an explanatory framework for considering the interindividual variation in susceptibility and tolerance of age-related brain changes and pathology, including dementia. The reserve can be considered within categories of brain reserve and cognitive reserve.[36] CHD is associated with a number of factors that may impact adversely both brain and cognitive reserve, and thus increase the risk of dementia.

The potential etiologic factors for reducing brain reserve in the population with CHD differ over a lifetime and may involve neurological malformations, the effects of the abnormal physiology, complex medical and surgical management strategies, chromosomal abnormalities, and acquired morbidities. Studies have suggested that impaired fetal oxygen delivery and altered brain metabolism contribute to dysmaturation in individuals with more complex CHD.[19,37–40] Medical and surgical management of CHD, which may result in embolic events and brain injuries inducing cerebral ischemia, hemodilution, and postoperative low-cardiac output physiology, all may negatively contribute to decreased brain reserve.[7,32,33] For example, vascular brain injuries, including clinically silent strokes, have been observed both pre- and postoperatively in infants with CHD.[6] Hypoxemia affects the same cellular pathways and may enhance this effect.[6,19,39,41] In our study, the relative risk of dementia was increased among adults with severe CHD, as well as among lesions with a cyanotic potential. However, the risk remained for individuals with acyanotic disease and those with mild-to-moderate CHD, which suggests that hypoxia hemodynamics alone cannot explain the risk of dementia.

Genetic disorders and chromosomal abnormalities are known to influence neurodevelopment.[20] One of these, Down syndrome (trisomy 21), is associated with excess production of the amyloid precursor protein and neuropathological features of Alzheimer disease.[20] However, we observed a persisted elevated risk even among individuals without ECDs and chromosomal abnormalities, indicating that other etiologic pathways should be considered.

Adults with CHD acquire cardiovascular morbidities earlier than members of the general population, which may impact the brain reserve. These morbidities, which include atrial fibrillation, stroke, diabetes mellitus, coronary artery disease, and heart failure, are associated with an enhanced risk of cognitive decline and dementia.[14,16–18,42–44] We observed an increased relative risk among adults with CHD with and without acquired cardiovascular diseases or diabetes mellitus relative to their matched members from the general population. Furthermore, the HRs did not vary sub-

stantially for vascular dementia, Alzheimer disease, and other dementias.

Higher cognitive reserve, reflected in higher premorbid intelligence and longer exposures to education, mentally demanding occupation, and mentally stimulating leisure activities, is associated with lower risk of dementia.[45] The absence of increased risk in the advanced education group might suggest a protective effect of education in the setting of CHD, but the number of observations is small for conclusions. Furthermore, lower educational attainment might be considered a surrogate for CHD complexity or acquired medical complexity, as well as baseline learning difficulties related to neurodevelopmental disorders.

When considering the age of dementia onset, we observed an increased risk for both early and late-onset dementia when comparing the cohort with CHD to the general population cohort. However, the degree of risk in adults with CHD was significantly higher for early onset dementia. This variation may reflect the lower incidence rate of dementia in the general population cohort <65 years of age (Table 2), when the burden of age-related dementia pathologies and other comorbidities is expected to be low and the relative impact of CHD-related risk may be greater.

The following strengths and limitations should be considered when interpreting the results. Our large population-based cohort study with 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: ≈90%.[46] As previously described, an algorithm developed by experienced cardiac surgeons, cardiologists, and epidemiologists and based on extensive medical record review allowed inclusion of all adults with valid CHD diagnoses.[24] However, misclassification of specific CHD diagnosis, and therefore also CHD complexity, may be present. Furthermore, where the ICD diagnostic code was insufficiently specific to infer CHD complexity, we were not able to categorize adults with CHD according to complexity. The positive predictive value of all-cause dementia in the DNPR is ≈86% and that of Alzheimer's disease is 81%, but the validity of other dementia subtypes is lower,[31] and misclassification of dementia subtypes may be present. It is notable that the risk of dementia in the cohort with CHD relative to the general comparison cohort did not differ between ICD versions (Table II in the online-only Data Supplement). For cardiovascular diseases and cardiac surgery, the positive predictive values in the DNPR have also been reported to be high.[47–49] However, conditions such as hypertension and uncomplicated diabetes mellitus may often be treated in the primary care units and thus not be completely registered in the DNPR.

The possibility of surveillance bias, and consequently overestimation of the risk of dementia among adults with CHD compared with the general population cohort, should be considered because the CHD population may be more frequently in contact with the medical providers, and the sensitivity of the dementia diagnosis is unknown. However, the risk was similar in the mild-to-moderate adults with CHD, who by nature of their less complex condition are less likely to experience frequent medical contact. In addition, medical care in Denmark is free and universal, helping to ensure that access to health care is not limited in the general population.

The population with CHD in our study represented adults who survived to ≥30 years of age. These survivors, with an increased risk of dementia, reflect a healthier cohort with CHD, and our analyses may underestimate the true association between CHD and dementia.

We did not adjust our analyses for such factors as cardiovascular disease or educational level because these factors may be intermediates in the pathway between CHD and dementia. We did not have sufficient data on some potentially confounding factors such as smoking or other lifestyle factors.

New CHD diagnostic tools and the development of novel management strategies for CHD are ongoing. Therapeutic outcomes have improved greatly, as reflected in the declining mortality and shifted age distribution of the CHD population. Therefore, it is important to recognize that the birth period of this cohort (1890–1982) represents an era of more limited opportunities for surgical and medical interventions. Consequently, these results cannot be directly applied to young adults diagnosed with CHD in the present eras. However, it is important to recognize healthcare needs and risk factors affecting the larger number of middle-age and older adults currently living with CHD.

CONCLUSIONS

Congenital heart disease was associated with an increased risk of dementia compared with the general population, particularly for early onset dementia. Increased understanding of dementia risk in the population with CHD is a potential target for future investigation.

ARTICLE INFORMATION

Received June 5, 2017; accepted December 12, 2017.

The online-only Data Supplement is available with this article at http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIRCULATIONAHA.117.029686/-/DC1.

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Sources of Funding

This work was supported by the Department of Clinical Epidemiology at Aarhus University Hospital and the Heart Institute at Cincinnati Children's Hospital as well as by grants from the National Institutes of Health (P50-AG047366), the Foundation of the Family Kjaersgaard Sunds, the Foundation of 1870, the Foundation of Raimond and Dagmar Ringgaard-Bohn, the Foundation of Torben and Alice Frimodt, the Foundation of the Family Hede-Nielsen, and the Oticon Foundation.

Disclosures

None.

REFERENCES

1. Sun R, Liu M, Lu L, Zheng Y, Zhang P. Congenital heart disease: causes, diagnosis, symptoms, and treatments. *Cell Biochem Biophys*. 2015;72:857–860. doi: 10.1007/s12013-015-0551-6.
2. Hoffman JI, Kaplan S, Liberthson RR. Prevalence of congenital heart disease. *Am Heart J*. 2004;147:425–439. doi: 10.1016/j.ahj.2003.05.003.
3. Garne E. Congenital heart defects: occurrence, surgery and prognosis in a Danish County. *Scand Cardiovasc J*. 2004;38:357–362. doi: 10.1080/14017430410024379.
4. Stuart AG. Changing lesion demographics of the adult with congenital heart disease: an emerging population with complex needs. *Future Cardiol*. 2012;8:305–313. doi: 10.2217/fca.12.8.
5. Afilalo J, Therrien J, Pilote L, Ionescu-Ittu R, Martucci G, Marelli AJ. Geriatric congenital heart disease: burden of disease and predictors of mortality. *J Am Coll Cardiol*. 2011;58:1509–1515. doi: 10.1016/j.jacc.2011.06.041.
6. Martinez-Biarge M, Jowett VC, Cowan FM, Wusthoff CJ. Neurodevelopmental outcome in children with congenital heart disease. *Semin Fetal Neonatal Med*. 2013;18:279–285. doi: 10.1016/j.siny.2013.04.006.
7. Ballweg JA, Wernovsky G, Gaynor JW. Neurodevelopmental outcomes following congenital heart surgery. *Pediatr Cardiol*. 2007;28:126–133. doi: 10.1007/s00246-006-1450-9.
8. Olsen M, Sørensen HT, Hjortdal VE, Christensen TD, Pedersen L. Congenital heart defects and developmental and other psychiatric disorders: a Danish nationwide cohort study. *Circulation*. 2011;124:1706–1712. doi: 10.1161/CIRCULATIONAHA.110.002832.
9. Sundhedsstyrelsen MMT. Udredning og behandling af demens: en medicinsk teknologivurdering (The National Board of Health: Investigation and management of dementia: a medical technological assessment). *Medicinsk Teknologivurdering*. 2008;1:5–65.
10. Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, Ferri CP. The global prevalence of dementia: a systematic review and metaanalysis. *Alzheimers Dement*. 2013;9:63.e2–75.e2. doi: 10.1016/j.jalz.2012.11.007.
11. Sundhedsdatastyrelsen. Dødsårsagsregisteret 2014: Tal og analyse (The cause of death register 2014: numbers and analysis). *Sundhedsdatastyrelsen*. 2015:1–58.
12. 2015 Alzheimer's disease facts and figures. *Alzheimers Dement*. 2015;11:332–384.
13. Baumgart M, Snyder HM, Carrillo MC, Fazio S, Kim H, Johns H. Summary of the evidence on modifiable risk factors for cognitive decline and dementia: a population-based perspective. *Alzheimers Dement*. 2015;11:718–726. doi: 10.1016/j.jalz.2015.05.016.
14. de la Torre JC. Cardiovascular risk factors promote brain hypoperfusion leading to cognitive decline and dementia. *Cardiovasc Psychiatry and Neurol*. 2012;2012:367516.
15. Wolters FJ, Zonneveld HI, Hofman A, van der Lugt A, Koudstaal PJ, Vernooij MW, Ikram MA; Heart-Brain Connection Collaborative Research Group. Cerebral perfusion and the risk of dementia: a population-based study. *Circulation*. 2017;136:719–728. doi: 10.1161/CIRCULATIONAHA.117.027448.
16. Bouchardy J, Therrien J, Pilote L, Ionescu-Ittu R, Martucci G, Bottega N, Marelli AJ. Atrial arrhythmias in adults with congenital heart disease. *Circulation*. 2009;120:1679–1686. doi: 10.1161/CIRCULATIONAHA.109.866319.
17. Rodriguez FH III, Marelli AJ. The epidemiology of heart failure in adults with congenital heart disease. *Heart Fail Clin*. 2014;10:1–7. doi: 10.1016/j.hfc.2013.09.008.
18. Lanz J, Brophy JM, Therrien J, Kaouache M, Guo L, Marelli AJ. Stroke in adults with congenital heart disease: incidence, cumulative risk, and predictors. *Circulation*. 2015;132:2385–2394. doi: 10.1161/CIRCULATIONAHA.115.011241.
19. Miller SP, McQuillen PS, Hamrick S, Xu D, Glidden DV, Charlton N, Karl T, Azakie A, Ferriero DM, Barkovich AJ, Vigneron DB. Abnormal brain development in newborns with congenital heart disease. *N Engl J Med*. 2007;357:1928–1938. doi: 10.1056/NEJMoa067393.
20. Lott IT, Dierssen M. Cognitive deficits and associated neurological complications in individuals with Down's syndrome. *Lancet Neurol*. 2010;9:623–633. doi: 10.1016/S1474-4422(10)70112-5.
21. Adelborg K, Horváth-Puhó E, Ording A, Pedersen L, Toft Sørensen H, Henderson VW. Heart failure and risk of dementia: a Danish nationwide population-based cohort study. *Eur J Heart Fail*. 2017;19:253–260. doi: 10.1002/ejhf.631.
22. Corraini P, Henderson VW, Ording AG, Pedersen L, Horváth-Puhó E, Sørensen HT. Long-term risk of dementia among survivors of ischemic or hemorrhagic stroke. *Stroke*. 2017;48:180–186. doi: 10.1161/STROKEAHA.116.015242.
23. Buys R, Cornelissen V, Van De Bruaene A, Stevens A, Coeckelberghs E, Onkelinx S, Thomaes T, Delecluse C, Budts W, Vanhees L. Measures of exercise capacity in adults with congenital heart disease. *Int J Cardiol*. 2011;153:26–30. doi: 10.1016/j.ijcard.2010.08.030.
24. Nyberg J, Åberg MA, Schiöler L, Nilsson M, Wallin A, Torén K, Kuhn HG. Cardiovascular and cognitive fitness at age 18 and risk of early-onset dementia. *Brain*. 2014;137(Pt 5):1514–1523. doi: 10.1093/brain/awu041.
25. Schmidt M, Pedersen L, Sørensen HT. The Danish Civil Registration System as a tool in epidemiology. *Eur J Epidemiol*. 2014;29:541–549. doi: 10.1007/s10654-014-9930-3.
26. Olsen M, Videbæk J, Johnsen SP; Danish Register of Congenital Heart Disease. The Danish Register of Congenital Heart Disease. *Scand J Public Health*. 2011;39(7 Suppl):50–53. doi: 10.1177/1403494811399169.
27. Schmidt M, Schmidt SA, Sandegaard JL, Ehrenstein V, Pedersen L, Sørensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin Epidemiol*. 2015;7:449–490. doi: 10.2147/CLEP.S91125.
28. Sampson EL, Warren JD, Rossor MN. Young onset dementia. *Postgrad Med J*. 2004;80:125–139.
29. Rossor MN, Fox NC, Mummery CJ, Schott JM, Warren JD. The diagnosis of young-onset dementia. *Lancet Neurol*. 2010;9:793–806. doi: 10.1016/S1474-4422(10)70159-9.
30. European Surveillance of Congenital Anomalies. Guide 1.3: Instructions for the Registration and Surveillance of Congenital Anomalies. 2005.http://www.eurocat-network.eu/content/EUROCAT-Guide-1.3.pdf.
31. Phung TK, Andersen BB, Høgh P, Kessing LV, Mortensen PB, Waldemar G. Validity of dementia diagnoses in the Danish hospital registers. *Dement Geriatr Cogn Disord*. 2007;24:220–228. doi: 10.1159/000107084.
32. Wernovsky G. Current insights regarding neurological and developmental abnormalities in children and young adults with complex congenital cardiac disease. *Cardiol Young*. 2006;16(Suppl 1):92–104. doi: 10.1017/S1047951105002398.
33. Chock VY, Reddy VM, Bernstein D, Madan A. Neurologic events in neonates treated surgically for congenital heart disease. *J Perinatol*. 2006;26:237–242. doi: 10.1038/sj.jp.7211459.
34. Pauliks LB. Depression in adults with congenital heart disease-public health challenge in a rapidly expanding new patient population. *World J Cardiol*. 2013;5:186–195. doi: 10.4330/wjc.v5.i6.186.
35. Leisner MZ, Madsen NL, Ostergaard JR, Woo JG, Marino BS, Olsen MS. Congenital heart defects and risk of epilepsy: a population-based co-

hort study. *Circulation*. 2016;134:1689–1691. doi: 10.1161/CIRCULATIONAHA.116.024538.
36. Stern Y. Cognitive reserve in ageing and Alzheimer's disease. *Lancet Neurol*. 2012;11:1006–1012. doi: 10.1016/S1474-4422(12)70191-6.
37. Limperopoulos C, Tworetzky W, McElhinney DB, Newburger JW, Brown DW, Robertson RL Jr, Guizard N, McGrath E, Geva J, Annese D, Dunbar-Masterson C, Trainor B, Laussen PC, du Plessis AJ. Brain volume and metabolism in fetuses with congenital heart disease: evaluation with quantitative magnetic resonance imaging and spectroscopy. *Circulation*. 2010;121:26–33. doi: 10.1161/CIRCULATIONAHA.109.865568.
38. Miller SP, Ferriero DM. From selective vulnerability to connectivity: insights from newborn brain imaging. *Trends Neurosci*. 2009;32:496–505. doi: 10.1016/j.tins.2009.05.010.
39. Sun L, Macgowan CK, Sled JG, Yoo SJ, Manlhiot C, Porayette P, Grosse-Wortmann L, Jaeggi E, McCrindle BW, Kingdom J, Hickey E, Miller S, Seed M. Reduced fetal cerebral oxygen consumption is associated with smaller brain size in fetuses with congenital heart disease. *Circulation*. 2015;131:1313–1323. doi: 10.1161/CIRCULATIONAHA.114.013051.
40. Miller G, Vogel H. Structural evidence of injury or malformation in the brains of children with congenital heart disease. *Semin Pediatr Neurol*. 1999;6:20–26.
41. Back SA, Miller SP. Brain injury in premature neonates: a primary cerebral dysmaturation disorder? *Ann Neurol*. 2014;75:469–486. doi: 10.1002/ana.24132.
42. Cermakova P, Eriksdotter M, Lund LH, Winblad B, Religa P, Religa D. Heart failure and Alzheimer's disease. *J Intern Med*. 2015;277:406–425. doi: 10.1111/joim.12287.
43. Rusanen M, Kivipelto M, Levälahti E, Laatikainen T, Tuomilehto J, Soininen H, Ngandu T. Heart diseases and long-term risk of dementia and Alzheimer's disease: a population-based CAIDE study. *J Alzheimers Dis*. 2014;42:183–191. doi: 10.3233/JAD-132363.
44. Jefferson AL. Vascular risk factors and midlife cognition: rethinking the exposure window. *Circulation*. 2014;129:1548–1550. doi: 10.1161/CIRCULATIONAHA.114.008906.
45. Valenzuela MJ, Sachdev P. Brain reserve and dementia: a systematic review. *Psychol Med*. 2006;36:441–454. doi: 10.1017/S0033291705006264.
46. Jepsen B JP, Johnsen SP, Espersen GT and Sørensen HT. Validity of diagnoses of cardiac malformations in a Danish population-based hospital-discharge registry. *Int J Risk Saf Med*. 2006;18:77–81.
47. Sundbøll J, Adelborg K, Munch T, Frøslev T, Sørensen HT, Bøtker HE, Schmidt M. Positive predictive value of cardiovascular diagnoses in the Danish National Patient Registry: a validation study. *BMJ Open*. 2016;6:e012832. doi: 10.1136/bmjopen-2016-012832.
48. Johnsen SP, Overvad K, Sørensen HT, Tjønneland A, Husted SE. Predictive value of stroke and transient ischemic attack discharge diagnoses in The Danish National Registry of Patients. *J Clin Epidemiol*. 2002;55:602–607.
49. Adelborg K, Sundbøll J, Munch T, Frøslev T, Sørensen HT, Bøtker HE, Schmidt M. Positive predictive value of cardiac examination, procedure and surgery codes in the Danish National Patient Registry: a population-based validation study. *BMJ Open*. 2016;6:e012817. doi: 10.1136/bmjopen-2016-012817.

Risk of Dementia in Adults With Congenital Heart Disease: Population-Based Cohort Study

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Circulation. published online February 12, 2018;
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539

SUPPLEMENTAL MATERIAL

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

	ICD-8	ICD-10
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
Other diseases		
Atrial fibrillation or flutter	427.93-427.94	I48
Diabetes mellitus	249-250	E10-E14, G63.2, H36.0, N08.3
Extracardiac defects	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
Outcomes		
Alzhemier's disease	290.09, 290.10	F00 series (includes F00.0x, F00.1x, F00.2x, F00.9x), G30 (includes G30, G30.0, G30.1, G30.8, G30.9)
Vascular dementia	293.09, 293.19	F01 series (includes F01.0x, F01.1x, F01.2x, F01.3x, F01.8x, F01.9x)
Other dementias	094.19, 290.11, 290.18, 290.19, 292.09	F02 series, F03 series, F1x.73 series (includes F10.73 through F19.73), G23.1, G31.0, G31.1, G31.8B, G31.8E, G31.85
Diagnoses related to dementia (mild cognitive impairment and amnestic syndromes)	291.19	F04, F04.9, F05.1, F06.7, F06.7x, F1x.6 (F10.6, F18.6, F19.6)

Abbreviations: CHD, Congenital Heart Disease; ICD, International Classification of Diseases

Supplemental table 2 Sensitivity analyses of the association between congenital heart disease (CHD) and risk of dementia.

	Number of dementia events		HR (95% CI)
	CHD cohort	General population cohort	
Excluding all individuals with previously diagnosed mild cognitive impairments or amnestic syndromes	-	-	1.62 (1.29-2.04)
Alzheimer's disease, including unspecified dementias*	81	832	1.61 (1.26-2.06)
Additional adjustment for			
Extracardiac defects†	95	977	1.56 (1.23-1.95)
Education‡	95	977	1.60 (1.28-2.01)
Acquired cardiovascular diseases or diabetes§	95	977	1.68 (1.33-2.11)
Time of dementia diagnosis			
Before 1994	5	70	1.25 (0.48−3.24)
Since 1994	90	907	1.64 (1.03−2.08)

Abbreviations: CHD, Congenital Heart Disease; CI, Confidence Interval; HR, Hazard Ratio

* Including *International Classification of Diseases* code F03 (unspecified dementia) in the definition of Alzheimer's disease.

† Including syndromes and chromosomal abnormalities.

‡ Highest completed education at 30 years of age: 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).

§ At least one of the following diagnoses at any time: Atrial fibrillation or flutter, diabetes mellitus, heart failure, stroke, and hypertension.