Comparison of Economic Self-Sufficiency and Educational Attainment in Adults With Congenital Heart Disease Versus Siblings Without Heart Disease and to General Population

Nicolas L. Madsen, MD, MPH[a,b,*], Bradley S. Marino, MD, MPP, MSCE[c,d], Jessica G. Woo, PhD[e], and Morten Olsen, MD, PhD[f]

Among children with congenital heart disease (CHD), there is often neurodevelopmental and behavioral impairment with unclear implications regarding adult socioeconomic achievements. We aimed to compare economic self-sufficiency and educational attainment in CHD adults with sibling and general population controls. Using Danish population-based nationwide registries, this cohort study aimed to include all CHD subjects greater than 13 years born between 1963 and 1993. Comparison cohorts included: (1) sibling cohort and (2) general population cohort matched 10:1 on birth year and gender. We computed cumulative incidences of time to first full year of economic self-sufficiency, as well as educational attainment. We assessed the relative probability of self-sufficiency in all cohorts before 30 years of age, defined by Statistics Denmark federal standard. In total, we identified 7,019 CHD subjects, 6,257 full siblings, and 68,805 general population controls. The cumulative incidence of self-sufficiency by age 20 and 35 years for CHD subjects (49% and 84%, respectively) was lower than sibling (68% and 96%) and general population cohorts (67% and 95%). The relative probability of self-sufficiency for CHD subjects compared with siblings was 0.44 (95% confidence interval 0.39 to 0.49). By age 30, adults with CHD were less likely than their siblings to attain all levels of education. Among those achieving higher educational milestones, differences in self-sufficiency between cohorts were absent by age 35. In conclusion, CHD is associated with reduced adult economic self-sufficiency, and the relation between educational level attained and self-sufficiency may suggest that targeted interventions have the potential to improve adult self-sufficiency.
 (Am J Cardiol 2020;135:135−142)

As more and more children with congenital heart disease (CHD) successfully reach adulthood, research has increasingly transitioned to include a greater assessment of long term morbidities.[1−4] Within the CHD population, there is a distinctive pattern of neurodevelopmental and psychosocial challenges characterized by impairment of cognition, social interaction, core communication skills, as well as increased prevalence of inattention, impulsive behavior, and impaired executive function.[4−13] Previous speculation suggests that these risk factors are potentially modifiable, both positively and negatively, by environmental factors in the home, at school, and in places of employment.[4] Although limited literature exists on the educational attainment of the CHD population,[14] it is presently unknown to what degree these neurodevelopmental and psychosocial challenges restrict those with CHDs' ultimate capacity to achieve economic self-sufficiency consistent with the transition to adulthood. As a result, we aim to compare achievement of self-sufficiency in adults with CHD with that of sibling and general population cohorts. We hypothesize that CHD is associated with a lower probability of self-sufficiency, and that increasing CHD complexity further lowers or delays this probability. In addition, we aim to determine whether variation in educational level attained is associated with, and potentially contributes to, adult self-sufficiency.

Methods

We conducted a cohort study based on prospectively collected data from the Danish nationwide population-based medical registries. The study was approved by the Danish Data Protection Agency (record number: 2013-41-1754), whose role is to protect the privacy of individuals whose data are recorded in Danish registries. No informed consent was required for this study.

Our study was conducted in Denmark, with a current population of approximately 5.8 million individuals. The Danish National Health Service provides tax-supported

[a]Heart Institute, Cincinnati Children's Hospital Medical Center, University of Cincinnati School of Medicine, Cincinnati, OH; [b]Department of Clinical Epidemiology, University of Aarhus, Aarhus, Denmark; [c]Heart Center at the Ann and Robert H. Lurie Children's Hospital of Chicago, Chicago, IL; [d]Department of Pediatrics and Medical Social Sciences, Northwestern University Feinberg School of Medicine, Chicago, IL; [e]Division of Biostatistics and Epidemiology, Cincinnati Children's Hospital Medical Center, University of Cincinnati School of Medicine, Cincinnati, OH; and [f]Department of Radiology, Horsens Regional Hospital, Aarhus, Denmark. Manuscript received September 27, 2018; revised manuscript received and accepted August 11, 2020.

See page 141 for disclosure information.

*Corresponding author: Tel: (513) 636-5476; fax: (513) 636-3952
E-mail address: nicolas.madsen@cchmc.org (N.L. Madsen).

0002-9149/
https://doi.org/10.1016/j.amjcard.2020.08.035

healthcare, with universal and free access to hospital-based and primary medical care, including care for CHD. A unique 10-digit civil personal registration number has been assigned to all residents of Denmark since 1968 by the Central Office of Civil Registration. The civil personal registration numbers are used in all Danish registries, permitting unambiguous individual-level linkage of data from all sources used in this study.[15] This provided us with virtually complete follow-up for death, emigration, and the outcomes under study. The Civil Registration System also made it possible to identify the sibling and the general population comparison cohorts.

We identified Danish persons with CHD 13 years of age or older born between January 1, 1963, and December 31, 1993, who had received a diagnosis of a CHD before 13 years of age. CHD subjects diagnosed between 1963 and 1974 were identified based on review of medical records in all Danish pediatric and medical departments by an experienced medical doctor, Henning Bækgaard Laursen (Danish Registry of CHD, DRCHD).[16] The review was done in the years 1970 to 1974 and the diagnoses were later translated from the International Society of Cardiology (1970) classification to the International Classification of Diseases 10th revision (ICD-10).[17] CHD survivors diagnosed after 1977 were identified by use of the Danish National Registry of Patients (DNRP). The DNRP contains information on all hospital admissions in Denmark and includes subject's civil registration numbers, dates of admission and discharge, surgical procedures, and up to 20 discharge diagnoses coded by physicians according to the ICD.[15] Since 1995, the DNRP also contains information on hospital outpatient clinic contacts. We were not able to capture those subjects diagnosed exclusively between January 1, 1974 and December 31, 1976 who were never again hospitalized, as this particular 3-year period is not captured in either data source. ICD-8 codes obtained by way of the DNRP were used to identify all CHD patients between 1977 and 1993 (ICD-8: 746 to 747 except for 746.7 and 747.5 to 747.9, which are not specific to CHD).

We used a previously described algorithm to exclude patients with invalid CHD or inaccurate coding in the DNRP.[18] Severity of CHD were defined as mild (simple biventricular anatomy/physiology without any history of surgery or catheter-based intervention including atrial septal defects, ventricular septal defects, patent ductus arteriosus greater than 37 weeks gestation, and isolated coarctation of the aorta), moderate (identical biventricular anatomy/physiology subtypes categorized as "mild" but with a history of at least 1 surgery or catheter-based intervention), severe (complex biventricular physiology such as tetralogy of Fallot, atrioventricular canal defect, or transposition of the great arteries), univentricular (history of single ventricle diagnoses or palliative surgery such as Norwood, Glenn, and/or Fontan), and unclassified.

In addition to CHDs, we used the DNRP and the DRCHD to identify diagnoses of extra-cardiac defects (ECDs) and chromosomal abnormalities. In accordance with a guideline from the European Surveillance of Congenital Anomalies, we disregarded isolated minor defects such as subluxation or unstable hip, cryptorchidism, torticollis, or protuberant ears.[19] We obtained data on gestational age from the Danish Medical Birth Registry and defined preterm birth as gestational age <37 weeks.

Relative to each CHD subject, we created 2 comparison cohorts utilizing the Danish Civil Registration System: (1) general population cohort (10:1) matched by gender and birth year and (2) sibling cohort—all full siblings of the CHD cohort members alive at 13 years of age born before December 31, 1993. The sibling cohort was included in an effort to account for unmeasured potential confounders secondary to family-related factors, such as general socioeconomic status, parental educational status or IQ, and similar factors.[20]

From the Employment Classification Module, Statistics Denmark, we extracted the BESKST (data prior to 2002) and BESKST02 (data from 2002 until present) variables to determine economic self-sufficiency based on personal yearly income. Self-sufficiency is defined according to the federal standard by Statistics Denmark as total income from all available sources greater than 50% of a student's annual subsidy. We measured the time interval from age 13 years to the first date the subject was determined to be economically self-sufficient. These variables are adjusted yearly for inflation.

From Statistics Denmark, we extracted data on the highest educational attainment obtained by the study population in each calendar year during the study period. The educational attainment was separated into 4 categories: basic (completion of primary education), vocational (3- to 4-year programs completed after primary education), high school (3-year secondary education known as gymnasium), and higher (university education). In Denmark, completing gymnasium is required for university education, but not for vocational training. In addition, higher education is typically completed before the age of 30 years.

Observation time was computed from age 13 years to outcome of interest, death, emigration, age 35 years, or December 31, 2011, whichever came first. For all subjects, we calculated cumulative incidence of self-sufficiency and educational levels. We computed the relative probability of achieving economic self-sufficiency before the age of 30 years, using a pseudo-observation approach and generalized linear models while adjusting for birth year and gender.[21] Two subanalyses were performed: (1) excluding all individuals in the study population diagnosed with premature birth or ECD and (2) stratifying by birth era to account for improved mortality and morbidity results of the CHD population: 1963 to 1972, 1973 to 1982, 1983 to 1993. Analyses were performed using the STATA 14 package (StataCorp LP, College Station, TX).

Results

We identified 7,019 CHD subjects (50% male) who met our inclusion criteria. Divided into categories of CHD complexity, we identified: 2,426 (35%) mild, 1,858 (26%) moderate, 1,719 (24%) severe, 108 (1.5%) univentricular, and 895 (13%) unclassified (Table 1). We identified 6,257 CHD siblings and 68,805 general population subjects for comparison.

By 30 years of age, 93% of CHD adults had completed basic education compared with 97% in both sibling and general population cohorts. The cumulative incidence of attaining higher educational levels, including vocational

Table 1
Characteristics of 3 comparison cohorts (congenital heart disease, sibling, and general population)

Variable	CHD cohort n (%)	CHD sibling cohort n (%)	General population cohort n (%)
All	7,019 (100%)	6,257 (100%)	68,805 (100%)
Men	3,529 (50%)	3,181 (51%)	34,554 (50%)
Birth year			
1963 to 1972	2,332 (33%)	2,164 (35%)	23,035 (33%)
1973 to 1982	1,868 (27%)	2,089 (33%)	18,158 (26%)
1983 to 1992	2,819 (40%)	2,004 (32%)	27,612 (40%)
Extra cardiac defects	1,632 (23%)	98 (2%)	3,241 (5%)
Preterm birth	910 (13%)	202 (3%)	1,671 (5%)
Missing gestational age data	1,588 (23%)	3,653 (58%)	35,218 (51%)
CHD complexity			
Mild	2,426 (35%)	-	-
Moderate	1,858 (27%)	-	-
Severe	1,719 (25%)	-	-
Univentricular	108 (2%)	-	-
Not classified	895 (13%)	-	-
Age at first CHD diagnosis			
0 to 29 days	1,033 (15%)	-	-
30 days to 1 year	2,066 (29%)	-	-
>1 year to <5 years	2,002 (29%)	-	-
>5 years to <13 years	1,918 (27%)	-	-
Major CHD diagnoses			
Atrial septal defect	902 (13%)	-	-
Coarctation	386 (5%)	-	-
Patent ductus arteriosus	857 (12%)	-	-
Transposition great arteries	203 (3%)	-	-
Tetralogy of Fallot	342 (5%)	-	-
Ventricular septal defect	2,048 (29%)	-	-
Other	2,281 (32%)	-	-

education, was reduced in the CHD cohort compared with the sibling and general population cohorts (Table 2).

The cumulative incidence of self-sufficiency by age 20 years for all CHD subjects was 49%. Both the sibling cohort (68%) and the population cohort (67%) demonstrated higher rates of self-sufficiency achievement by the equivalent age. Although the rate of self-sufficiency was improved by age 35 years, CHD subjects remained less self-sufficient (84%) than both comparison cohorts (sibling 96% and general population 95%, Figure 1). This difference between cohorts, although less pronounced, remained after exclusion of those subjects with ECDs or prematurity (Figure 1). Further analysis by categories of CHD complexity demonstrated that reduced adult self-sufficiency was not limited to severe biventricular and univentricular CHD categories. Although relatively less impacted, mild and moderate forms of CHD were also impaired compared to sibling and general population cohorts (Figure 2).

We calculated relative probabilities of self-sufficiency as achieved by CHD adults relative to their siblings, which demonstrated reduced self-sufficiency across all strata investigated (Table 3). The risk of reduced self-sufficiency was present regardless of gender, birth era, age at diagnosis, and CHD subtype.

We examined self-sufficiency of the cohorts according to the highest level of education attained (Figure 3). If no basic education was attained, the degree of self-sufficiency was impaired in all cohorts; however, the CHD cohort was more reduced relative to the others throughout the study period (Figure 3). If basic education was attained, self-sufficiency was improved for all groups, but again the relatively reduced rate of the CHD cohort persisted (Figure 3). In the

Table 2
Educational attainment by age 30 years for congenital heart disease (CHD) subjects, their sibling(s), and the birth year and gender-matched general population cohort

	Cumulative incidence of attaining educational level by 30 years of age		
	CHD cohort	CHD sibling cohort	General population cohort
Basic education	93%	97%	97%
Vocational education	9.6%	11%	10%
High school education	23%	30%	32%
Higher education	19%	25%	26%
Long-term higher education	3.7%	5.3%	5.4%

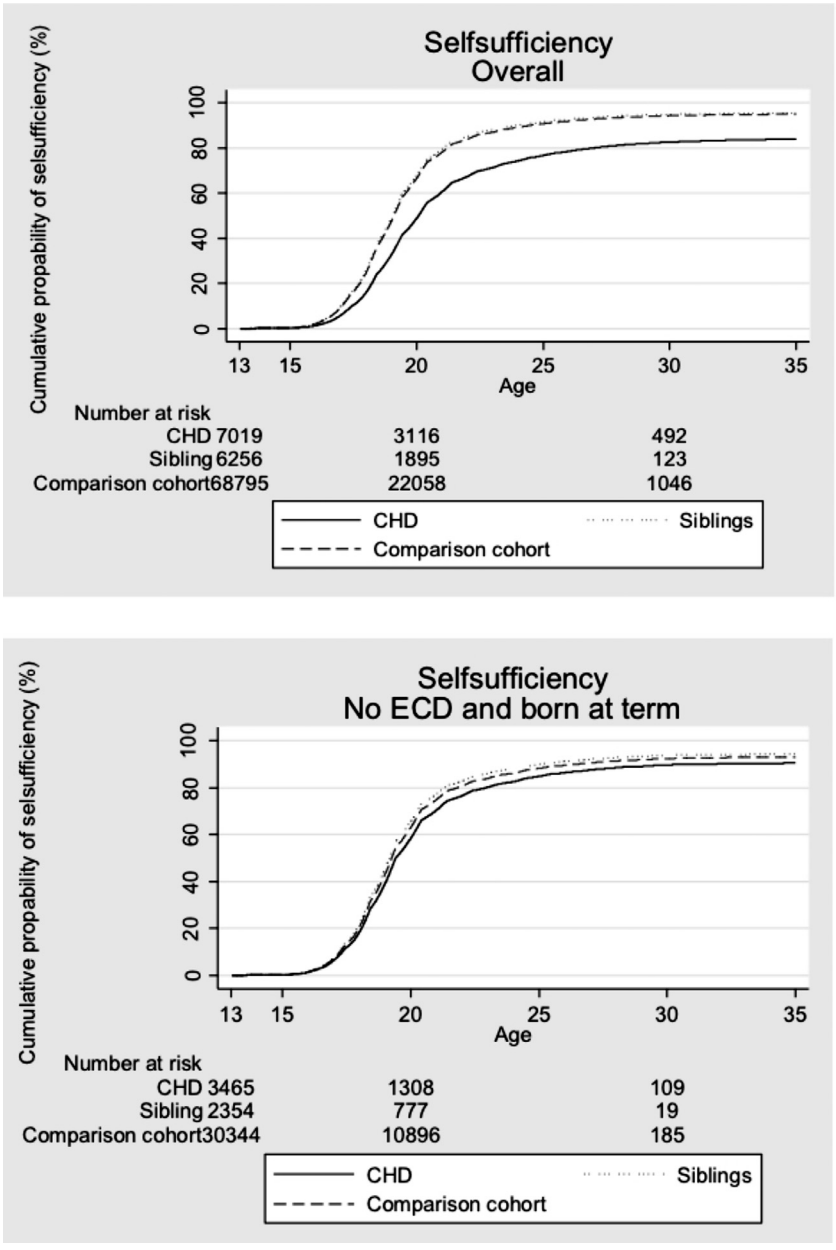

Figure 1. Overall cumulative probability of self-sufficiency between ages 13 and 35 years demonstrated in 3 separate cohorts (congenital heart disease, sibling, and general population comparison) (*A*), and after exclusion of those with extra-cardiac defects and born at less than 37 weeks gestation (*B*).

CHD populations who attained a high school level of education, although there was a delayed time to self-sufficiency relative to the comparison cohorts, there was ultimately no difference in achievement of self-sufficiency between cohorts by age 35 (Figure 3). This was also reflected by the birth year and gender adjusted relative probability of 0.98 (95% confidence interval 0.96 to 1.00) of achieving self-sufficiency among high school graduates. A similar analysis could not be performed for those with vocational and higher education attainment, as all individuals in these educational tracks in Denmark receive either a salary (for vocational trainees) or state funding (for ongoing higher education enrollment) that exceeds the self-sufficiency threshold.

Discussion

To our knowledge, this is the first study to describe on a national scale the achievement of self-sufficiency in adults born with CHD. Our results, in over 7,000 individuals with CHD demonstrate that adult self-sufficiency is impaired relative to not only the general population, but also compared with CHD subjects' own siblings. The consistency of these results across CHD severity classification, birth year and presence or absence of ECDs calls attention to how CHD, potentially even in its mildest forms, presents lifelong challenges.

Although extensive literature has examined the neurodevelopmental and psychosocial impairments associated with

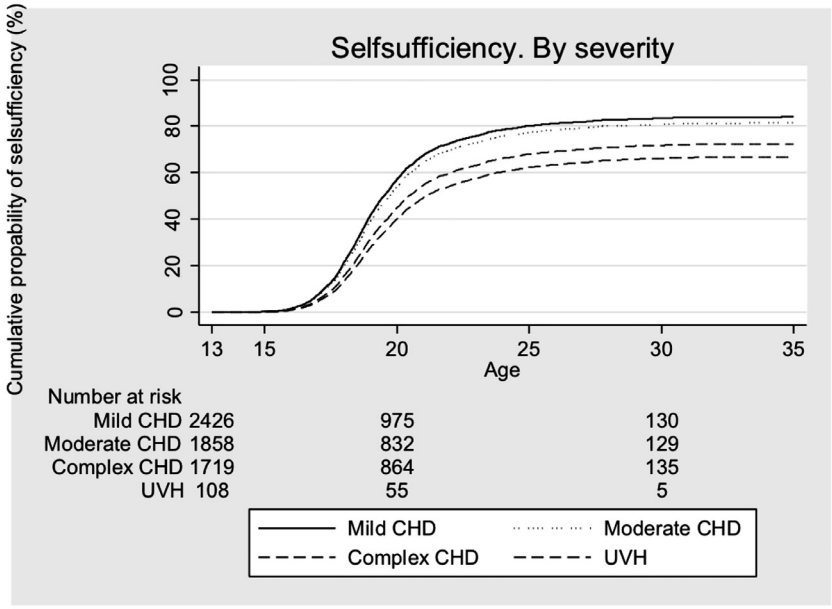

Figure 2. Cumulative probability of self-sufficiency between ages 13 and 35 years in congenital heart disease individuals as divided by defect complexity (mild, moderate, complex, and univentricular).

CHD,[4] this is the first examination to ask if CHD may hinder the opportunity to become self-sufficient as an adult. Learning, memory and behavioral difficulties are well described among individuals with CHD, and have previously been shown to affect educational attainment in adolescents.[14] Studies have highlighted that children with complex CHD have significantly increased risk for impairments in the areas of intelligence, academic achievement, language (development, expressive, and receptive), visual construction and perception, attention, executive functioning, fine motor skills, gross motor skills, and psychosocial maladjustment (internalizing problems).[4] Our study raises the likelihood that these risks have long-term consequences.

It is not a provocative statement to suggest that educational attainment is associated with the capacity to become

Table 3
Relative probability of self-sufficiency by age 30 of adults with congenital heart disease (CHD) compared with their sibling(s)

	Individuals attaining self-sufficiency during follow-up		Relative probability of self-sufficiency by age 30(95% CI)*
	CHD cohort	Sibling cohort	
Overall	5,060	5,582	0.85 (0.84 - 0.87)
No ECD and full term	2,745	2,036	0.92 (0.90 - 0.94)
Men	2,609	2,895	0.85 (0.83 - 0.87)
Women	2,451	2,687	0.85 (0.83 - 0.87)
Birth period			
1963 to 1972	1,921	2,034	0.87 (0.85 - 0.89)
1973 to 1982	1,478	1,942	0.84 (0.82 - 0.87)
1983 to 1992	1,661	1,606	0.84 (0.82 - 0.86)
Age at diagnosis			
0 to 29 days	583	680	0.80 (0.76 - 0.84)
30 days to 1 year	1,422	1,683	0.78 (0.76 - 0.81)
>1 year to <5 years	1,510	1,535	0.87 (0.85 - 0.90)
>5 years to <13 years	1,545	1,684	0.93 (0.91 - 0.95)
Severity			
Mild (biventricular, no surgery)	1,830	1,824	0.89 (0.87 - 0.92)
Moderate (biventricular, surgery)	1,400	1,577	0.88 (0.85 - 0.91)
Severe	1,121	1,350	0.79 (0.76 - 0.82)
Univentricular	63	89	0.78 (0.69 - 0.89)
Not classified	638	732	0.81 (0.77 - 0.85)
Educational level			
Basic	4,905	5,417	0.86 (0.85 - 0.87)
High school	1,394	1,750	0.98 (0.96 - 1.00)

* Adjusted for birth year and gender.

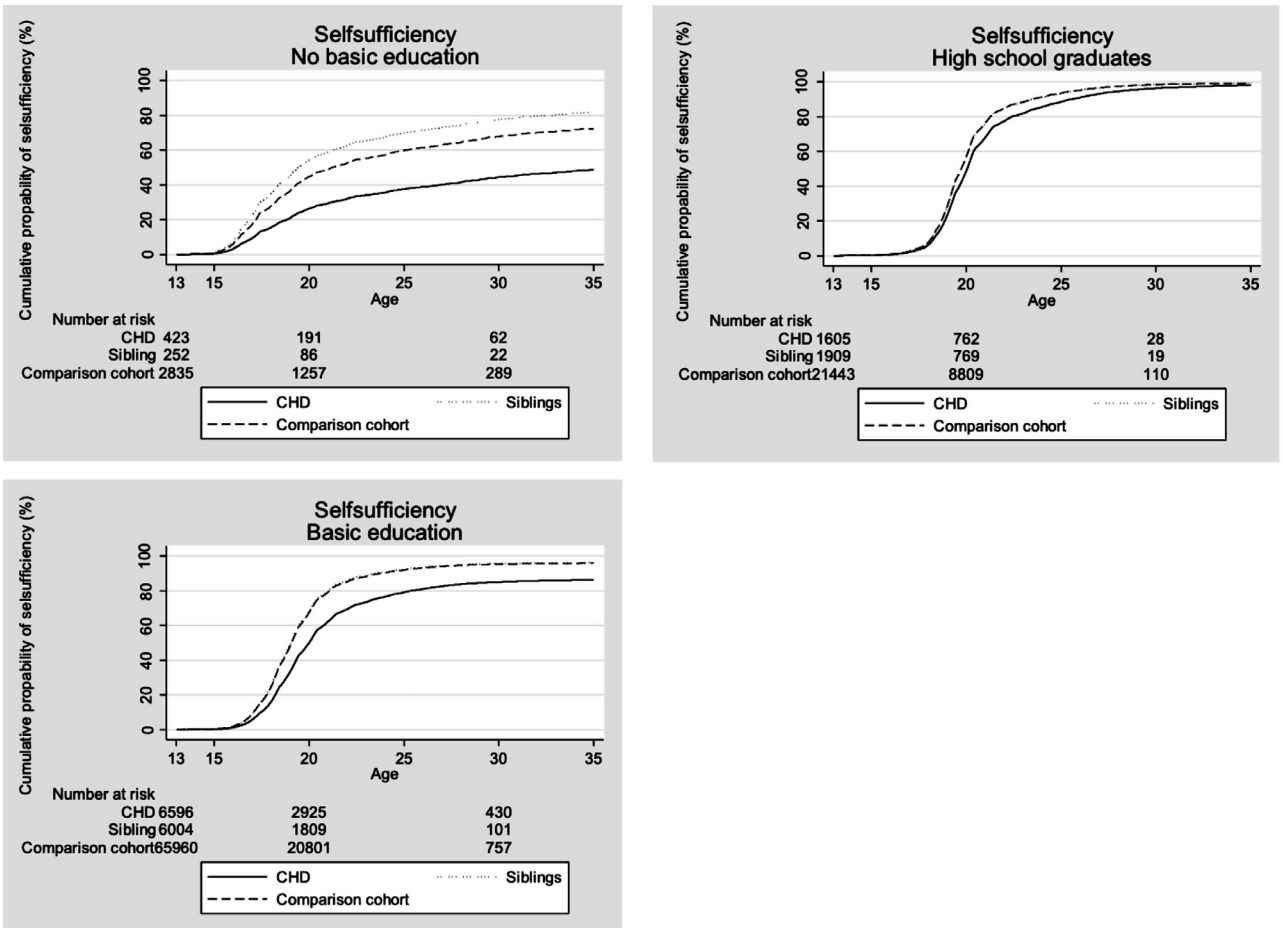

Figure 3. Cumulative probability of self-sufficiency between ages 13 and 35 years demonstrated in 3 separate cohorts (congenital heart disease, sibling, and general population comparison) according to those without basic education (*A*), those who completed only basic education (*B*), and those who completed high school education (*C*).

self-sufficient as an adult.[22,23] In fact, the results of this study's comparison cohorts (sibling and general population) underscore this point as demonstrated by the differences in achievement of self-sufficiency between those without basic education compared with those with completion of a higher level of education. Given this accepted premise, it is important to note that adults with CHD are less likely to attain these educational milestones as demonstrated by our results. However, importantly, those who do attain these milestones demonstrate self-sufficiency rates that approximate their siblings and peers. Although our study is not able to separate these factors, which align along a causal pathway, it is worth considering how modifiable educational attainment may be in the CHD population. We speculate that targeted education-based interventions and directed therapies augment educational attainment, and thereby may improve adult self-sufficiency.

Failing to achieve economic self-sufficiency is unusual in Denmark with a less than 5% unemployment rate. This is substantiated by this study's demonstration of a high percentage of self-sufficiency in the general population and sibling cohorts. However, those who fail to achieve self-sufficiency are uniquely well cared for within the Danish welfare system. As a result, given that many of the complications and complexities of unsuccessfully achieving self-sufficiency are not fully appreciated by these Danish cohorts, there is reason to pursue additional research in other geopolitical climates.

It is accepted that complex subtypes of CHD have an association with negative long-term outcomes such as increased mortality and morbidity, as well as more pronounced neurodevelopmental and psychosocial issues.[4] However, more recently, studies have demonstrated that less complex CHD conditions are not spared important lifelong outcomes such as "re-intervention" or acquired disease.[24] The CHD category labeled as "mild" in our study is comprised exclusively of biventricular physiology that has never required a cardiac intervention, and yet, these individuals have impaired self-sufficiency compared with their siblings and the general population.

The major strengths of our study are its large size, its population-based design, and the complete and long-term follow-up for economic self-sufficiency and educational attainment provided by the Danish Civil Registration system, which substantially reduces the impact of selection bias. We also took the important step to account for residual confounding from difficult to measure (or presently unknown) factors by establishing the CHD sibling cohort. Comparison to this cohort enabled analyses and interpretation while minimizing the impact of family-related factors.

Finally, we benefitted from the ability to utilize a federally supported measure of economic self-sufficiency to accurately determine economic conditions throughout adult life.

Our study should also be considered in terms of the possible limitations. Our data were obtained from registry-based discharge diagnoses and outcome measurements, which are vulnerable to being inaccurate or incomplete. However, in regard to CHD, the positive predictive value in the DNRP, as well as the older CHD registry (1963 to 1974), has been shown to be highly sensitive and specific and any misclassification is small and independent of future development of self-sufficiency.[16,25] In order to avoid any misclassification among subtypes of CHD complexity, we took the additional steps to develop a hierarchical approach to define the CHD subtype for each participant drawing on the opportunity to identify the qualifications of the medical center determining each diagnosis. It should also be noted that the univentricular group is small in sample size as a result of the era of birth under study. As a consequence, when data from this group are presented, it is advisable to not draw any firm conclusions based on the wide statistical variation inherent when analyzing a small sample size. In addition, there is not, at present, the opportunity to study the adult outcomes of those children born with CHD in the recent 2 decades, and as a result, it remains unknown if they will mirror this early generation relative to self-sufficiency. Lastly, the validity of the educational attainment in the Danish Educational Attainment Registry, Statistics Denmark, as well as the variable for economic self-sufficiency has been previously described.[20]

In conclusion, CHD is associated with impaired or delayed adult self-sufficiency, as well as lower educational attainment. This is not explained by differences in socioeconomic status, or other family-related factors, as demonstrated by comparisons with the sibling cohort. The relation between educational level attained and self-sufficiency achieved may reflect underlying CHD related factors; however, it may also suggest that educationally targeted interventions have the potential to augment adult self-sufficiency.

Author Contributions

Nicolas Madsen: Conceptualization, Methodology, Investigation, Writing - Original Draft Preparation, Funding Acquisition. Bradley Marino: Validation, Writing - Reviewing and Editing. Jessica Woo: Formal Analysis, Writing - Reviewing and Editing. Morten Olsen: Supervision, Methodology, Validation, Writing - Reviewing and Editing.

Disclosures

The authors have no conflicts of interest to disclose.

Acknowledgment

Cincinnati Children's Hospital Heart Institute and the Department of Clinical Epidemiology at the University of Aarhus, Denmark.

1. Boneva RS, Botto LD, Moore CA, Yang Q, Correa A, Erickson JD. Mortality associated with congenital heart defects in the United States: trends and racial disparities, 1979-1997. *Circulation* 2001;103:2376–2381.
2. Oster ME, Lee KA, Honein MA, Riehle-Colarusso T, Shin M, Correa A. Temporal trends in survival among infants with critical congenital heart defects. *Pediatrics* 2013;131:e1502–e1508.
3. Marelli AJ, Mackie AS, Ionescu-Ittu R, Rahme E, Pilote L. Congenital heart disease in the general population: changing prevalence and age distribution. *Circulation* 2007;115:163–172.
4. Marino BS, Lipkin PH, Newburger JW, Peacock G, Gerdes M, Gaynor JW, Mussatto KA, Uzark K, Goldberg CS, Johnson WH Jr, Li J, Smith SE, Bellinger DC, Mahle WT, American Heart Association Congenital Heart Defects Committee, Council on Cardiovascular Disease in the Young, Council on Cardiovascular Nursing, and Stroke Council. Neurodevelopmental outcomes in children with congenital heart disease: evaluation and management: a scientific statement from the American Heart Association. *Circulation* 2012;126:1143–1172.
5. Gaynor JW, Nord AS, Wernovsky G, Bernbaum J, Solot CB, Burnham N, Zackai E, Heagerty PJ, Clancy RR, Nicholson SC, Jarvik GP, Gerdes M. Apolipoprotein E genotype modifies the risk of behavior problems after infant cardiac surgery. *Pediatrics* 2009;124:241–250.
6. Bellinger DC, Newburger JW, Wypij D, Kuban KC, duPlessis AJ, Rappaport LS. Behavior at eight years in children with surgically corrected transposition: the Boston Circulatory Arrest Trial. *Cardiol Young* 2009;19:86–97.
7. Bellinger DC, Wypij D, duPlessis AJ, Rappaport LS, Jonas RA, Wernovsky G, Newburger JW. Neurodevelopmental status at eight years in children with dextro-transposition of the great arteries: the Boston Circulatory Arrest Trial. *J Thorac Cardiovasc Surg* 2003;136:1385–1396.
8. Shillingford AJ, Glanzman MM, Ittenbach RF, Clancy RR, Gaynor JW, Wernovsky G. Inattention, hyperactivity, and school performance in a population of school age children with complex congenital heart disease. *Pediatrics* 2008;121:e759–e767.
9. Van Rijen EH, Utens EM, Roos-Hesselink JW, Meijboom FJ, van Domburg RT, Roelandt JR, Bogers AJ, Verhulst FC. Psychosocial functioning of the adult with congenital heart disease: a 20-33 years follow-up. *Eur Heart J* 2003;24:673–683.
10. Kaltman JR, Di H, Tian Z, Rychik J. Impact of congenital heart disease on cerebrovascular blood flow dynamics in the fetus. *Ultrasound Obstet Gynecol* 2005;25:32–36.
11. 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.
12. Licht DJ, Shera DM, Clancy RR, Wernovsky G, Montenegro LM, Nicolson SC, Zimmerman RA, Spray TL, Gaynor JW, Vossough A. Brain maturation is delayed in infants with complex congenital heart defects. *J Thorac Cardiovasc Surg* 2009;137:529–536.
13. D. Andropoulos DB, Hunter JV, Nelson DP, Stayer SA, Stark AR, McKenzie ED, Heinle JS, Graves DE, Fraser CD Jr.. Brain immaturity is associated with brain injury before and after neonatal cardiac surgery with high-flow bypass and cerebral oxygenation monitoring. *J Thorac Cardiovasc Surg* 2010;139:543–556.
14. Olsen M, Hjortdal VE, Mortensen LH, Christensen TD, Sørensen HT, Pedersen L. Educational achievement among long-term survivors of congenital heart defects: a Danish population-based follow-up study. *Cardiol Young* 2011;21(2):197–203.
15. Schmidt M, Pedersen L, Sørensen HT. The Danish civil registration system as a tool in epidemiology. *Eur J Epidemiol* 2014;29:541–549.
16. Laursen HB. Some epidemiological aspects of congenital heart disease in Denmark. *Acta Paediatr Scand* 1980;69:619–624.
17. Olsen M, Videbæk J, Johnsen SP. Danish register of congenital heart disease. The Danish register of congenital heart disease. *Scand J Public Health* 2011;39:50–53.
18. Olsen M, Garne E, Svaerke C, Sondergaard L, Nissen H, Andersen HO, Hjortdal VE, Johnsen SP, Videbaek J. Cancer risk among patients with congenital heart defects: a nationwide follow-up study. *Cardiol Young* 2014;24:40–46.
19. European Surveillance of Congenital Anomalies. *Guide 1.3: Instructions for the Registration and Surveillance of Congenital Anomalies*. Available at: https://eu-rd-platform.jrc.ec.europa.eu/eurocat_en Accessed Aug 6, 2020.

20. Roed C, Omland LH, Skinhoj P, Rothman K, Sorensen HT, Obel N. Educational achievement and economic self-sufficiency in adults after childhood bacterial meningitis. *JAMA* 2013;309:1714–1721.
21. Parner ET, Andersen PK. Regression analysis of censored data using pseudo-observations. *Stata J* 2010;10:408–422.
22. Hardy JB, Shapiro S, Mellits D, Skinner EA, Astone NM, Ensminger M, LaVeist T, Baumgardner RA, Starfield BH. Self-sufficiency at ages 27 to 33 years: factors present between birth and 18 years that predict educational attainment among children born to inner-city families. *Pediatrics* 1997;99:80–87.
23. London RA. The role of postsecondary education in welfare recipients' paths to self-sufficiency. *J Higher Educ* 2006;77:472–496.
24. Videbæk J, Laursen HB, Olsen M, Høfsten DE, Johnsen SP. A long-term nationwide follow-up study of simple congenital heart disease diagnosed in otherwise healthy children. *Circulation* 2015;133:474–483.
25. Jepsen P, Johnsen SP, Espersen GT, Sorensen HT. Validity of diagnoses of cardiac malformations in a Danish population-based hospital-discharge registry. *Int J Risk Safe* 2006;18:77–81.