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Early-onset dementia among privately-insured adults with and without congenital heart defects in the United States, 2015–2017

Karrie F. Downing[a,*,1], **Matthew E. Oster**[a,b,1], **Benjamin S. Olivari**[c,1], **Sherry L. Farr**[a,1]

[a]National Center on Birth Defects and Developmental Disabilities, CDC, Atlanta, GA, USA

[b]Department of Pediatrics, Emory University School of Medicine and Children's Healthcare of Atlanta, Atlanta, GA, USA

[c]National Center for Chronic Disease Prevention and Health Promotion, CDC, Atlanta, GA, USA

Keywords

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1. Introduction

Congenital heart defects (CHD) are the most common birth defect worldwide, affecting between 2 and 10 per thousand births globally [1]. CHD range in severity from minor defects that may resolve spontaneously over time to severe defects that require surgical or catheter intervention in the first year of life [2]. Due to advances in diagnostics and treatment, an estimated 1.4 million adults are living with CHD in the United States (U.S.) [3].

While studies have shown that neurocognitive issues are common among this growing population of adults with CHD [4–7], risk of dementia, or the impaired ability to remember, think, or make decisions that interferes with doing everyday activities, has been less studied [8]. Though dementia is a leading cause of death globally [9], only one study to our knowledge, a Danish population-based cohort, investigated dementia among adults with CHD compared to adults in the general population [10]. The authors found CHD to be associated with a 2.6 times increased risk of early-onset dementia (before age 65 years)

*Corresponding author at: 4770 Buford Hwy, Mailstop S106-3, Atlanta, GA 30341, USA. yyx9@cdc.gov (K.F. Downing).

[1]This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

Conflicts of interest

The authors report no relationships that could be construed as a conflict of interest.

Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

CRediT authorship contribution statement

Karrie F. Downing: Conceptualization, Methodology, Formal analysis, Writing – original draft. **Matthew E. Oster:** Conceptualization, Methodology, Writing – review & editing. **Benjamin S. Olivari:** Conceptualization, Methodology, Writing – review & editing. **Sherry L. Farr:** Conceptualization, Methodology, Supervision, Writing – review & editing.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2022.04.019.

compared to the general population of adults ages 30 years and older. However, differences between Denmark and the U.S. may limit the study's generalizability to the population of adults with CHD living in the U.S.; several modifiable risk factors for dementia can be clinically managed or prevented [11,12], and Denmark provides free and universal healthcare access unlike the U.S. [10]. Furthermore, they did not stratify early-onset dementia estimates by age group, sex, or CHD severity.

Dementia is more common in women, which may be attributable to differential survival after 80 years of age [13], but fewer differences in rates of early-onset dementia by sex have been observed in the general population [13,14]. Among those with CHD, a few studies have suggested that neurocognitive impairments are more common for males than females in childhood and adolescence [15–17]. However, less is known about sex differences in the prevalence of early-onset dementia among those with CHD.

Dementia among adults with CHD in the U.S., and specifically prevalence of early-onset dementia by age and sex, has yet to be investigated. Therefore, using 2015–2017 IBM® MarketScan® Commercial data, our objectives were to assess the association between CHD and prevalence of diagnosed early-onset dementia, including Alzheimer's disease, among U.S. adults ages 45–64 years, whether this association persists for only non-severe CHD, and if the association is modified by age group (45–54, 55–64 years) and sex.

2. Materials and methods

2.1. Data source

We performed a cross-sectional study using the IBM® MarketScan® Commercial Database. The IBM® MarketScan® Commercial Database provides individual-level healthcare claims data including enrollment, inpatient and outpatient medical, pharmaceutical, and limited socio-demographic (i.e., age, sex, U.S. Census region of residence) data on a large, convenience sample of individuals < 65 years of age with employer-sponsored insurance and their dependents per year. Healthcare encounter claims from 2007 to 2017 in the IBM® MarketScan® Commercial Database were used to identify privately insured adults with and without CHD. Among them, claims from 2015 to 2017 were used to identify those who were diagnosed with early-onset dementia.

2.2. CHD definition

An individual with CHD was defined as having at least 1 inpatient encounter with a CHD code (ICD-9-CM codes between 745 and 747 or ICD-10-CM codes between Q20-Q26 with some exceptions; Appendix A) and/or at least 2 outpatient encounters with a CHD code > 30 days apart. The CHD could be documented as early as 2007, to ensure adequate opportunity for a CHD-related encounter and to identify those likely diagnosed before dementia onset, up through 2017. CHD severity was assigned using a previously published algorithm based on ICD-9-CM codes, because CHD functional status was unavailable, and further modified for use with ICD-10-CM [18]. All CHD severity categories other than severe were collapsed into a non-severe CHD group to generate sufficient sample size for analysis.

An individual without CHD had no ICD-9-CM or ICD-10-CM codes for CHD. Individuals with only 1 outpatient CHD code were excluded from analysis. Additionally, individuals with no other CHD diagnoses except ostium secundum type atrial septal defect (ICD-9-CM 745.5; ICD-10-CM Q21.1) and/or CHD of "other" severity per the algorithm were excluded, due to low positive predictive values (PPV).

2.3. Outcomes

Early-onset dementia is a diagnosis of dementia, or any of its types (e. g. Alzheimer's), before age 65 years [19]. Within the IBM® MarketScan® sample of individuals <65 years old, early-onset dementia was defined as ≥ 1 inpatient ICD-9-CM or ICD-10-CM dementia diagnosis codes or ≥ 2 outpatient dementia codes diagnosed on different days. We used the diagnosis code list for dementia provided by the Center for Medicare & Medicaid Services Chronic Conditions Data Warehouse [20] with the addition of codes for dementia with Lewy bodies (ICD-9-CM 331.82 and ICD-10-CM G31.83) and exclusion of codes that indicate symptoms of dementia but may have causes other than cognitive decline or secondary codes intended to accompany a different primary diagnosis (Appendix B). As a sensitivity analysis, we then expanded the definition of early-onset dementia to include codes for alcohol-induced dementia and other diagnoses related to cognitive decline that may be used to indicate early-onset dementia (Appendix B). For all analyses, we excluded individuals with only 1 outpatient dementia code or ≥ 2 outpatient dementia codes all documented on the same date to improve the PPV of dementia.

2.4. Analysis

Individuals included in the analytic sample were ≥ 45 years old on January 1, 2015 and continuously enrolled from 2015 to 2017 (i.e., not missing > 30 days of enrollment per year). Age was then collapsed into two groups (45–54 years and 55–64 years). Due to its association with both dementia and CHD [21,22], individuals were excluded from the sample if they had any diagnosis of Down Syndrome (ICD-9-CM 758.0; ICD-10-CM Q90.9) from 2007 to 2017. Individuals were also excluded if they had no healthcare encounters from 2015 to 2017. We further conducted a sensitivity analysis limited to those who had at least 44 days of healthcare (inpatient or outpatient) from 2015 to 2017, the median for those with CHD, to ensure similar opportunity for dementia diagnosis among adults with and without CHD.

We describe the distribution of age group (as of January 2015) and sex among the analytic sample, by presence of CHD. We report the prevalence of early-onset dementia during 2015–2017 by presence of any CHD and of only non-severe CHD. Prevalence estimates per 1000 are provided overall and further stratified by age group and sex. We were unable to examine prevalence of early-onset dementia specific to the group with severe CHD (i.e. heart defects typically requiring intervention in the first year of life) due to low sample size. We used log-binomial regression to estimate adjusted prevalence ratios (aPRs) and 95% confidence intervals (CIs) for the overall associations between CHD and early-onset dementia. We performed additional regression analyses including interaction terms between CHD and age group and, separately, sex. All models included age group and sex.

All analyses were conducted using SAS version 9.4 (SAS Institute Inc., Gary, NC, USA). Data are deidentified, administrative data and not considered human subjects research by the Centers for Disease Control and Prevention.

3. Results

There were 12,250 adults with CHD diagnoses, of whom 89% had non-severe CHD, and 3,942,077 adults with no CHD diagnosis (Table 1). About 51% of those with CHD and 57% of those without CHD were between 45 and 54 years old. Approximately 57% of those with CHD and 46% of those without CHD were male.

Overall, 2.9/1000 adults ages 45–64 years with CHD were diagnosed with early-onset dementia whereas 1.2/1000 without CHD had early-onset dementia (Fig. 1). While prevalence of early-onset dementia was consistently higher among those with CHD than those without CHD across all age and sex strata, individuals in the 55- to 64-year age group with CHD had the highest point prevalence overall (5.0/1000), followed by males with CHD (3.7/1000). Using the expanded definition of dementia (Appendix B), prevalence increased to 4.7/1000 for those with CHD and 2.0/1000 for those without CHD.

After adjusting for age group and sex (Fig. 1), prevalence of early-onset dementia remained more than twice as high for adults with CHD (aPR = 2.2, 95% CI: 1.6–3.0, $p < 0.0001$); results were similar when limiting to only non-severe CHD (2.8/1000; aPR = 2.1, 95% CI: 1.5–3.1, $p < 0.0001$; data not shown). When comparing 6219 with CHD and 971,525 without CHD who had 44 or more healthcare encounter days from 2015 to 2017 (the median for those with CHD), the prevalence estimates of early-onset dementia were 5.1/1000 and 3.5/1000, respectively (aPR = 1.4, 95% CI: 1.0–1.9, $p = 0.07$; data not shown).

Among 45- to 54-year-olds, the aPR for early-onset dementia was elevated among those with CHD compared to those without (aPR = 1.8, 95% CI: 1.0–3.6, $p = 0.07$; Fig. 1), though prevalence estimates were less than 1/1000 for both groups. Among 55- to 64-year-olds, prevalence was also elevated (5.0/1000 among those with CHD and 2.1/1000 among those without; aPR = 2.3, 95% CI: 1.6–3.4, $p < 0.0001$). The age group-specific aPRs comparing non-severe CHD to no CHD (data not shown) were similar to the overall associations (*45–54 years* aPR = 1.9, 95% CI: 0.9–3.8, $p = 0.07$; *55–64-years* aPR = 2.3, 95% CI: 1.5–3.4, $p < 0.0001$).

Stratifying by sex, comparing individuals with CHD to those without, the aPR was elevated among males (aPR = 2.8, 95% CI:1.9–4.1, $p < 0.0001$; Fig. 1). We did not find a similar association when comparing females with CHD to females without CHD (aPR = 1.3, 95% CI: 0.7–2.6, $p = 0.37$), though the confidence interval was wide and overlapped with that of males. The sex-specific aPRs comparing non-severe CHD to no CHD (data not shown) were similar to the overall associations (*male* aPR = 2.7, 95% CI: 1.8–4.0, $p < 0.0001$; *female* aPR = 1.4, 95% CI: 0.7–2.7, $p = 0.38$).

4. Discussion

Among privately insured adults ages 45 to 64 years, the prevalence of diagnosed early-onset dementia was more than twice as high for adults with CHD compared to adults without CHD. The prevalence of early-onset dementia was greatest for adults ages 55 to 64 years with CHD (5.0/1000), followed by males with CHD (3.7/1000). In both age groups, prevalence of early-onset dementia was 1.8 to 2.3 times higher for adults with CHD compared to adults without CHD. Among males, having CHD was associated with a 2.8-times increase in prevalence of early-onset dementia whereas, among females, this association was attenuated. Associations between CHD and early-onset dementia were also elevated when limiting to adults with non-severe CHD.

In the one prior study on CHD and dementia, from Denmark, adults with CHD born between 1890 and 1982, identified from two nationwide registries, were followed from 30 years of age to either the date of dementia diagnosis, death, emigration, or to the end of 2012 and matched by sex and birth year to a random sample from the general population [10]. Prevalence was not reported for direct comparison with our study but, similar to our study, onset of dementia before age 65 years was rare; their reported incidence rate of early-onset dementia (between 30 and 64 years of age) was 0.03 per 1000 person-years for those with CHD and 0.01 per 1000 person-years among the general population. Furthermore, the risk of early-onset dementia was increased among adults with CHD compared to adults without (hazard ratio [HR] = 2.6, 95% CI: 1.8–3.8). Estimates among 30- to 64-year-olds were not further stratified by age, sex, or severity.

Our findings extend our understanding about the role that age plays in the relationship between early-onset dementia and CHD. Our estimates suggest that disparities in the onset of dementia for adults with and without CHD might start before the age of 55, such that those 45- to 54-years-old with CHD are almost twice as likely to experience dementia compared to those of the same age without CHD. Though research on dementia among individuals with CHD is limited, reduced cognitive functioning or impairment has been documented from early life through young adulthood [4–7,23–28]. In the fetal stage and infancy, evidence of negative impacts on the brain and early neurodevelopment have been documented among those with CHD [23–26]. In childhood, children with CHD have lower average scores on intelligence and achievements tests, are more likely to have a learning disability, and are more likely to require special education services [24,27]. Cognitive research on adults with CHD have identified deficits in attention and memory, executive function, mood, language, and social cognition that affect socioeconomic outcomes and quality of life, most of which are first detected in childhood and continue to manifest in adolescence and adulthood [24,28]. Though severity of CHD is correlated with severity of neurological deficits [15,29], even adults with mild-to-moderate CHD had poorer performance on neurocognitive tests compared to those without CHD [4]. The present analysis builds on this documented evolution of impaired cognitive function with age.

Risk factors and contributing causes of dementia may differ for each individual and by the type of dementia [8]. Modifiable risk factors for dementia in the general population include cardiovascular disease risk factors, such as arrhythmia, high blood pressure,

high cholesterol, atherosclerosis, and obesity; diabetes; depression; and sedentary lifestyle [8,12,30]. Therefore, some proposed strategies to address these risk factors and potentially reduce the risk for cognitive decline in the general population include managing blood pressure; managing diabetes; eating healthy foods; limiting alcohol intake; and increasing physical and social activity [12,31,32]. The relative influence of these risk factors and prevention strategies among the aging population of adults with CHD has yet to be investigated; however, adults with CHD may be at increased risk for cardiovascular comorbidities relative to the general population [33–35], which may contribute to potential causal pathways between CHD and dementia. Men are also more likely to have cardiovascular and other risk factors for dementia [36–38], which may partially explain the effect modification we observed by sex; however, small sample size limited our ability to investigate the role of comorbidities or other potential pathways between CHD and early-onset dementia. Nevertheless, among all individuals with CHD, improvements in early detection of dementia might allow more opportunity to prepare for disease progression and/or improve dementia-related outcomes, given about 40% of probable dementia cases ≥ 65 years of age are undiagnosed [39].

4.1. Strengths and limitations

This is the first study, to our knowledge, to investigate the relationship between early-onset dementia and CHD among a large sample of individuals in the U.S. However, findings from this study should be interpreted within the context of its limitations. The IBM® MarketScan® Commercial Database is a convenience sample of individuals with employer-sponsored private insurance and their dependents who must have been continuously enrolled for three years to be included in the analytic sample. Therefore, the findings of this analysis may not be generalizable to all individuals in the U.S. or those without private employer-sponsored health insurance. Individuals with early-onset dementia are more likely to leave employment than those without early-onset dementia, [40] which may mean prevalence estimates reported here are underestimates, although comparisons should be valid. However, those with early-onset dementia may also be insured dependents of employed caregivers (e.g. spouse), whose rates of job loss were comparable to families not impacted by early-onset dementia. [40].

Results from this large IBM® MarketScan® Commercial Database show that early-onset dementia is rare among both individuals with and without CHD. Given its rarity, we could not investigate relationships with severe CHD, CHD types, or narrower age groups. Furthermore, because the database does not include data on adults after the age of 64, we were limited in our ability to examine dementia in general.

Because we are using administrative claims data, there may be misclassification of CHD status and dementia, as reported estimates on the sensitivity and PPV of diagnosis codes in administrative data vary for both depending on population and reference standards [41–47]. Furthermore, PPV of dementia codes may be lower in adults younger than 65 years compared to older adults; some studies reporting this observation included non-specific diagnosis codes for dementia with lower PPV, such as codes for “other psychotic conditions” or alcohol-induced dementia, codes to describe symptoms of dementia that may have causes

other than cognitive decline, and codes that only identify cognitive decline "due to a known physiological condition" [46,47]. To improve PPV, we implemented an established algorithm [48–50] for CHD status as well as an algorithm requiring at least 1 inpatient or 2 outpatient codes to identify dementia. Non-specific diagnosis codes for dementia were not included in our primary dementia case definition, and these codes did not substantially change findings when included as a sensitivity analysis.

Healthcare encounters due to CHD may lead to better identification of dementia, but we used data from 2007 to identify those who were likely aware of CHD status prior to experiencing dementia, we restricted the analysis to only those who had a healthcare encounter between 2015 and 2017, and we repeated the analysis among those with similarly high opportunities for diagnosis (≥44 days of healthcare). Future studies on the relationship between CHD and dementia among older adults could inform whether risk remains elevated among those with CHD beyond early onset.

4.2. Conclusions

With improvements in survival of individuals with CHD, scientific and public health research on long-term neurodevelopmental outcomes, including that of cognitive decline and dementia, is now both important and feasible. In a large sample of privately insured U.S.-based adults with and without CHD, we found that individuals with CHD, and males in particular, are more likely to experience early-onset dementia than individuals without CHD. Even those with non-severe CHD had greater risk of early-onset dementia compared to those without CHD. These findings may provide more information for scientists studying how cardiac health affects cognitive decline. In addition, improved awareness of dementia risk by age may help individuals with CHD and their providers prioritize risk factor management and better identify, prevent, or manage signs and symptoms of early dementia onset.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

aPR	adjusted Prevalence Ratio
CHD	Congenital Heart Defect
CI	Confidence Interval

ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
ICD-10-CM	International Classification of Diseases, Tenth Revision, Clinical Modification
PPV	Positive Predictive Value

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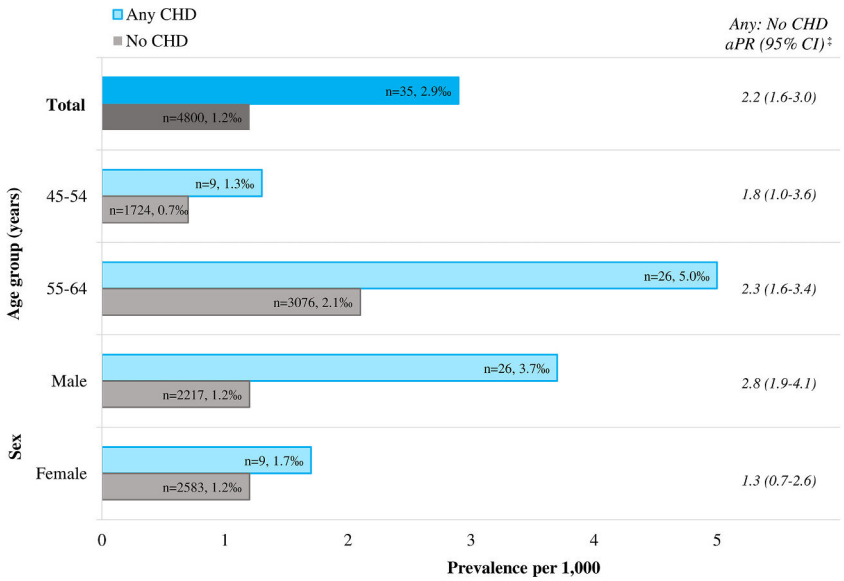

Fig. 1.

Early-onset dementia* among privately insured adults with and without congenital heart defects †in the United States.

Overall, 2.9/1000 adults (ages 45–64 years) with CHD and 1.2/1000 adults without CHD had early-onset dementia (aPR = 2.2, 95% CI: 1.6–3.0). While prevalence of early-onset dementia was consistently higher among those with CHD than those without CHD across all age group and sex strata, individuals in the 55- to 64-year age group with CHD had the highest point prevalence overall (5.0/1000), followed by males with CHD (3.7/1000).

aPR: prevalence ratio adjusted for age group as of January 2015 and sex; CHD: congenital heart defects.

*Defined as ≥ 2 outpatient dementia diagnosis codes ≥ 1 day apart or ≥ 1 inpatient code identified between 2015 and 2017.

†Defined as ≥ 2 outpatient CHD diagnosis codes > 30 days apart or ≥ 1 inpatient code identified between 2007 and 2017.

‡Model for age group and sex strata include interaction terms for CHD and age group or sex, respectively.

Table 1

Characteristics of privately insured adults, ages 45–64 years, with and without congenital heart defects in the United States.

		CHD* (*n* = 12,250)		No CHD (*n* = 3,942,077)	
Characteristic	**Levels**	**N**	**%**	**N**	**%**
CHD severity	Severe	1352	11.0	N/A	
	Non-severe	10,898	89.0		
Age Group (years)†	45–54	6250	51.0	2,259,208	57.3
	55–64	6000	49.0	1,682,869	42.7
Sex	Male	6972	56.9	1,805,363	45.8
	Female	5278	43.1	2,136,714	54.2

CHD: congenital heart defects; N/A: Not applicable.

*Defined as ≥ 2 outpatient congenital heart defect diagnosis codes > 30 days apart or ≥ 1 inpatient code identified between 2007 and 2017. Congenital heart defect diagnosis codes include ICD-9-CM codes between 745 and 747 and ICD-10-CM codes between Q20-Q26, excluding non-specific codes and ostium secundum type atrial septal defect.

†As of January 2015.