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ORIGINAL RESEARCH

Incidence and Predictors of Stroke in Australian Adults With Congenital Heart Disease (2000–2017)

Nita Sodhi-Berry, PhD; Luke J. Burchill, MBBS, PhD; Timothy J. Kleinig, MBBS, PhD; Lee Nedkoff, BSc, MPH, PhD*; Judith M. Katzenellenbogen, BSc, MSc, PhD*

BACKGROUND: Adults with congenital heart disease (CHD) are at increased risk of stroke but high-quality population level data on stroke incidence in these patients are scant.

METHODS AND RESULTS: A retrospective whole-population Western Australian cohort of adult patients with CHD aged 18 to 64 years was created and followed from January 2000 to December 2017 using linked hospital data. Stroke incidence rates within the adult cohort with CHD were calculated and compared with the general population via direct standardization. A nested case–control design assessed predictors of ischemic and hemorrhagic stroke within the cohort. Among 7916 adults with CHD, 249 (3.1%) incident strokes occurred at a median age of 47 years; 186 (2.3%) ischemic, 33 (0.4%) hemorrhagic and 30 (0.4%) unspecified strokes. Ischemic and hemorrhagic stroke incidence was, respectively, 9 and 3 times higher in adults with CHD than the general population. Absolute risk was low with annual rates of 0.26% (ischemic) and 0.05% (hemorrhagic). Highest rates were observed in adults with shunt and left-sided lesions. Predictors of ischemic stroke in adults with CHD included recent cardiac surgery, left-sided valve repair/replacements, shunt lesions, and traditional risk factors (hypertension, infective endocarditis, peripheral vascular disease, and tobacco use). Mental health disorders and increasing Charlson's comorbidity scores were strongly associated with higher risk of ischemic and hemorrhagic stroke. The CHA_2DS_2VASc score was associated with ischemic stroke incidence.

CONCLUSIONS: This study provides the first population-based stroke incidence estimates for adults with CHD in Australia, showing elevated stroke risk across different CHD lesions. It highlights the potential clinical importance of managing comorbidities, especially mental health.

Key Words: congenital heart disease ■ epidemiology ■ incidence ■ risk factors ■ stroke

See Editorial by Alsaeed and Field.

The worldwide prevalence of congenital heart disease (CHD) in adults is approximately 0.3%.[1,2] Improved survival has led to an exponential growth in the number of CHD patients surviving to adulthood, with about 100 000 adults with CHD estimated to be currently living in Australia.[1] However, increased longevity is associated with a high burden of residual heart defects and atherosclerotic and systemic comorbidities such as hypertension, hyperlipidemia, diabetes, chronic kidney disease, ischemic heart disease, arrhythmias,

Correspondence to: Nita Sodhi-Berry, PhD, Cardiovascular Epidemiology Research Centre, School of Population and Global Health, The University of Western Australia, M431, 35 Stirling Hwy, Crawley, WA 6009, Australia. Email: nita.sodhi@uwa.edu.au

*L. Nedkoff and J. M. Katzenellenbogen are co-last authors.

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CLINICAL PERSPECTIVE

What Is New?

- By 65 years of age, 2.3% adults with CHD had developed ischemic stroke and 0.42% had developed hemorrhagic stroke; absolute risk was low with annual rates of 0.26% and 0.05%, respectively.
- Compared with the general population, incidence of ischemic and hemorrhagic stroke in adults with CHD was on average 9 and 3 times higher, respectively, with differentials being up to 40 times higher than the general population for shunt, left-sided, and "other" lesions, especially for patients aged 18 to 44 years.
- Mental health disorders, Charlson's comorbidity index, and CHA_2DS_2VASc scores were independent predictors of ischemic and hemorrhagic stroke in this cohort, apart from other traditional risk factors.

What Are the Clinical Implications?

- Clinicians caring for adult patients with CHD should be aware that despite their young age, this population is at increased risk for stroke.
- Independent associations with mental health disorders, Charlson's comorbidity index and CHA_2DS_2VASc scores suggest both a component of preventability and the importance of closely managing comorbidities in adult patients with CHD.
- The presence of left-sided lesion, residual shunt, recent cardiac surgery, mental health disorders, multimorbidity, or higher CHA_2DS_2VASc scores identifies adult patients with CHD most likely to benefit from stroke risk surveillance and stroke prevention strategies.

Nonstandard Abbreviations and Acronyms

ASR	age-standardized rate
ICH	intracerebral hemorrhage
IRR	incidence rate ratio
WA	Western Australia

pulmonary hypertension, heart failure and endocarditis.[3–7] Interplay of such comorbidities with underlying or residual structural heart defects and corrective cardiac operations increases stroke risk over and above the risk of CHD itself.[8–10] Antithrombotic treatments widely used in CHD further increase the risk of hemorrhagic stroke (ie, intracerebral hemorrhage [ICH] and subarachnoid hemorrhage [SAH]).[4,11]

Very few multicenter or population-based longitudinal data sets on adult patients with CHD exist from which stroke incidence can be accurately estimated or their unique risk factors ascertained.[12–17] Based on these studies, the risk of ischemic stroke in adults with CHD is between 2.5 and 10 times higher than the general population or other adults without CHD.[3,13,14,16] Studies on hemorrhagic stroke are rare, but reports suggest a 5- to 8-times greater risk in adults with CHD.[14,17]

Western Australia (WA) provides a unique setting for accurate population-based estimates of stroke incidence due to the presence of long-standing whole-population linked administrative health data sets inclusive of people living in urban, rural, and remote areas and people from diverse races and ethnicities, including Australia's First Nations Peoples. Further, contemporary stroke rates in Australian population-based studies are low (compared internationally),[18] probably due to effective primary prevention, which we hypothesized would allow a purer assessment of the effects of CHD on stroke incidence. Our study leveraged these data to create a whole-population longitudinal cohort of adults with CHD to (1) measure incidence rates of ischemic stroke, ICH, and SAH among adults with CHD, (2) compare incidence rates for these stroke types in adults with CHD with the general population, and (3) investigate the predictors of ischemic stroke and hemorrhagic stroke in adults with CHD.

METHODS

This study is set in WA comprising 10.3% (2.6 million people) of the Australian population, 49.8% female, 3.9% Indigenous, and 21.0% living in rural/remote regions.[19] This retrospective whole-population cohort study comprised adults (18–64 years) living in WA who were identified as having CHD using linked administrative hospital data.

Data and Materials Transparency Statement

Data for this study were linked and provided by the WA Department of Health. Ethics approval was provided under waiver of consent by the human research ethics committees at the WA Department of Health (#2014/55) and the University of Western Australia (#RA/4/1/5227). Individual-level data cannot be shared due to ethics and governance restrictions. All supporting data have been made available within the article and its supplements to allow replication.

Data Sources

Routinely collected, probabilistically linked and deidentified administrative hospital and death records for all

WA residents with a cardiovascular disease hospitalization or death for the period 1985 to 2017 were available. This data set has been used before to study the epidemiology of stroke.[20,21] Hospital data included the admission and separation dates, principal diagnosis and 21 secondary diagnosis fields, inpatient procedures, and core sociodemographic variables (age, sex, Indigenous status, residential remoteness, and socioeconomic disadvantage). Ethnicity data apart from Indigenous status are not recorded in Australian hospital administrative data sets. Death data included the date of death and the underlying and 48 associated cause of death fields. Absence of a death record in WA was presumed as being alive. All diagnosis, procedure and cause of death codes were identified from the *International Classification of Diseases, Ninth Revision* (*ICD-9*) or *Tenth Revision* (*ICD-10*) (pre/post July-1999, respectively); *ICD-9* and *ICD-9-Clinical Modification* (*ICD-9-CM*) codes were harmonized to the *ICD-10-Australian Modification* (*ICD-10-AM*).

Congenital Heart Disease Definition

WA residents with an *ICD* code of at least 1 CHD admission (*ICD-9/ICD-9-CM*: 745.0–747.4 and *ICD-10-AM*: Q20–Q26) in any diagnosis field of a hospital record between 1985 and 2017 were eligible for inclusion (Figure 1). Diagnostic exclusions included isolated patent foramen ovale (745.5 code assigned within 1 year after stroke or transient ischemic attack,[14] or Q21.11), acquired ventricular septal defects (745.5 or Q21.0) assigned within 30 days after myocardial infarction; congenital heart block (746.86 or Q24.6), and non-cardiac congenital circulatory conditions including other congenital malformations of peripheral vascular system (747.6 or Q27) and other congenital malformations of circulatory system (747.8 or Q28).[22]

CHD lesion classification: Mutually exclusive hierarchical groups that integrated both anatomic complexity and hemodynamic severity of all CHD lesions were created based on published classifications.[22,23] These comprised severe> shunt-and-valve> shunt> left-sided> right-sided> "other" CHDs (Table S1). However, due to the small number of stroke cases (≤5) in people with shunt-and-valve lesions, this group was combined with shunt lesions to allow meaningful analyses and interpretations. Certain "minor" lesions that are usually associated with another CHD (eg, anomalies of pulmonary artery), are nonspecific (eg, unspecified defect of heart), or are noncongenital or incidental findings (eg, valve insufficiency) were not used for classification in people with multiple CHDs (Table S1).[22]

Severe lesions were life-threatening conditions necessitating surgical intervention within the first year of life, including univentricular/hypoplastic heart lesions, endocardial cushion defects, transposition complex, and tetralogy of Fallot. Shunt lesions included atrial and ventricular septal defects and persistent ductus arteriosus. Due to pathophysiological differences in the risk of stroke by side of lesion,[14] valvular defects were classified as left-sided (mitral and aortic valve defects) and right-sided (tricuspid and pulmonary valve defects). In addition, coarctation of aorta was classified as a left-sided lesion, and anomalies of the pulmonary artery and Ebstein's anomaly were classified as right-sided lesions.[14] All remaining lesions were classified as "other."[22]

Incident Stroke Definition

The first stroke hospital admission or stroke-related death between 2000 and 2017 was the primary outcome of interest. Incident strokes were identified from the principal or secondary diagnosis fields and from underlying or associated cause of death fields.[21] Secondary diagnoses allowed inclusion of stroke events that occurred during an admission for another presenting condition (for example, infective endocarditis) or where stroke was not the primary reason for treatment in hospital.[24,25] Date of stroke hospitalization was the date when an episode of care began unless this record was a nonstroke hospitalization and lasted more than 2 days, wherein the date of the subsequent stroke record was assigned.[21]

Stroke types included ischemic (I63), hemorrhagic (comprising ICH [I61 or I62.9] and SAH [I60]) or unspecified (I64) stroke. Nontraumatic subdural and extradural hemorrhage (I62.0, I62.1) were excluded.[21] Stroke episodes with a combination of ischemic or ICH or SAH (n=16, 6.5%) were assigned the principal or first listed diagnosis. Fatal stroke was defined as death from any cause within 28 days of stroke admission; death from stroke within 28 days of a nonstroke admission; or death from stroke with no hospital record in the preceding 28 days.[20]

Stroke Incidence

A retrospective cohort study design was used to estimate rates of incident (first-ever) ischemic and hemorrhagic stroke in a whole-population cohort of CHD patients and compare these with the general population of WA. Adults with CHD aged 18 to 64 years during 2000 to 2017 constituted the study cohort (Figure 1). For people aged ≥18 years on January 1, 2000, the follow-up period for incident stroke began on this date. For people aged <18 years on January 1, 2000, follow-up began on their 18th birthday during the study period (2000–2017). Follow-up continued until either the date of incident stroke, 65th birthday, death, or the end of follow-up (December 31, 2017), whichever was the earliest for each participant. Children (<18 years) were excluded as stroke in childhood is relatively uncommon

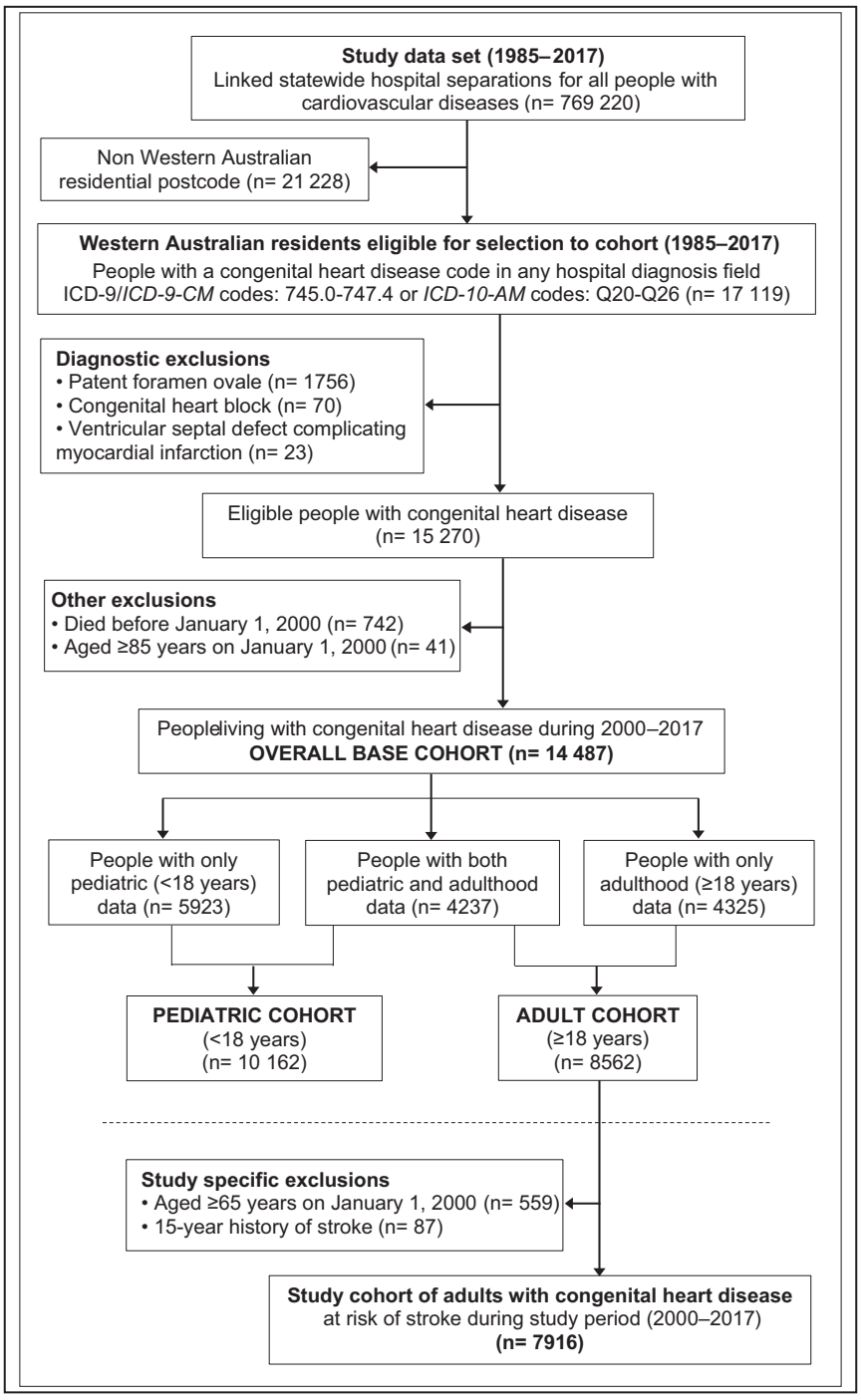

Figure 1. Flow diagram of the creation of cohort of people with congenital heart disease and the study-specific subset cohort of adults at risk of stroke.
ICD-9-CM indicates International Classification of Diseases, Ninth Revision, Clinical Modification; and ICD-10-AM, International Classification of Diseases, Tenth Revision, Australian Modification.

and causally distinct from stroke in adults with CHD.[13] Conversely, people aged 65 years and above were excluded due to the increasing prevalence of traditional risk factors for stroke with aging.[26] In addition, people with a prior admission for stroke (430, 431, 432.9 or 436 [1985–1999]; or 434.x [1985–1987]; or 433.x1 or 434.x1 [1988–1999]; or I60–I64 [1999–2017]) or late effects or sequelae of cerebrovascular disease (438 or I69) in the 15-year period before follow-up commencement were excluded.[21]

For external comparisons of stroke incidence against the general population, all incident strokes in the WA general population were identified from the study data set using methods used to identify incident strokes in the cohort with CHD. However, person-years for the general population were derived from the annual age- and sex-stratified population estimates for WA for 2000 to 2017.[19]

Predictors of Stroke

A nested case–control design was used to assess potential predictors of ischemic and hemorrhagic stroke within adults with CHD. For each stroke case, controls were selected from all adults with CHD at risk of stroke (ie, a fixed case-to-controls ratio was not assigned) to increase power and precision. Controls were selected without replacement via incidence density sampling[27] if they were the same age (±6 months) as the case at the time of stroke. An individual could serve as a control for multiple cases; a case could serve as a control while still at risk of stroke before becoming a case.[27] The date of selection as a case or control served as the baseline (time-zero) for capturing information on covariates.

Potential predictors included (1) sociodemographics: age, sex, Indigenous status, geographical remoteness, and socioeconomic disadvantage; (2) variables specific to or highly associated with CHD: lesion type, cardiac/high-risk surgery, and valve repair/replacement procedures; (3) common CHD-associated complications: heart failure, endocarditis, atrial fibrillation, pulmonary hypertension, and secondary erythrocytosis[5]; (4) traditional cardiovascular risk factors: hypertension, diabetes, coronary heart disease, peripheral vascular disease and pulmonary embolism/deep vein thrombosis, chronic kidney disease, chronic obstructive pulmonary disorder, and malignancy; (5) other disorders/lifestyle factors: any mental disorders, tobacco use disorders, and alcohol/drug use disorders; and (6) other procedures: pacemaker, life-support and catheter-based procedures. Specifically, the full spectrum of mental disorders was considered, including organic disorders, substance use disorders, schizophrenia, schizotypal and delusional disorders, affective/neurotic disorders, personality disorders, and other disorders (including mental retardation, disorders of psychological development, and other/unspecified behavioral and emotional disorders). Furthermore, the CHA_2DS_2VASc score[28] and Charlson's comorbidity index[29] were created and evaluated separately as potential predictors of stroke after replacing variables listed in aforementioned groups (3) to (4) from the regression models. For CHA_2DS_2VASc score, no points were assigned for age >65 years and history of stroke or transient ischemic attack as these were our exclusion criteria. The Charlson's comorbidity index/score is based on 17 comorbidities strongly associated with mortality,[29] of which cerebrovascular diseases were excluded because incident stroke is the study outcome. Both scores were examined as continuous and class variable (with scores 0, 1, and ≥2) for clinical context. All comorbidities (Table S2) and surgical procedures (Table S3) were identified in the 15-year period before baseline through the 22 diagnosis or 11 procedure fields on hospital data, respectively. For cardiac/high-risk surgery (including procedures on the heart, aorta, coronary and carotid arteries), both 15-year and 90-day history were determined.

An individual was considered Indigenous if recorded as such at least twice for people with >2 records, or once if ≤2 records.[30] Socioeconomic disadvantage and geographical remoteness to health services were derived from the area of residence at the hospital separation closest to the baseline, according to the Index of Relative Socio-Economic Disadvantage,[31] and the census-based Accessibility/Remoteness Index of Australia,[32] respectively. Residential accessibility/remoteness was dichotomized into metro/inner regional, and other (outer regional/remote/very remote) areas.

Statistical Analysis

Stroke Incidence

Age-specific incidence rates of stroke between 2000 and 2017 were calculated by dividing the number of incident strokes in the cohort by the accrued person-years within each 10-year age-group (18–24, 25–34, 35–44, 45–54, and 55–64 years), and within broad categories of younger (18–44 years) and older (45–64 years) adults (Table S4). Cases were allocated to age groups based on their age at the time of the incident stroke. Rates were stratified by sex, type of CHD lesion and stroke type. Age-standardized rates (ASRs) were calculated by directly standardizing to the age distribution of the Australian population on June 30, 2016.[19] Direct standardization was used to compare crude incidence rates across equivalent age- and sex-strata in adults with CHD and the general population to obtain incidence rate ratios (IRRs) and corresponding 95% CI via Proc STDRATE in SAS (SAS Institute, Cary, NC, USA).[33]

Predictors of Stroke

Within the nested case–control study, the distribution of sociodemographics, comorbidities, and interventions are presented as proportions and compared via univariable unconditional logistic regression models. Multivariable unconditional logistic regression

models[34] were used to determine independent risk factors for ischemic, ischemic/unspecified and hemorrhagic stroke. Firth's Penalized Likelihood method[35] was used to address small sample bias and improve model convergence for hemorrhagic stroke. Covariates with a *P* value <0.1 in univariable models were included in multivariable models, where a *P* value <0.05 was considered significant.

Sensitivity Analyses

Prior validation work shows a high proportion of ischemic strokes to be miscoded as unspecified stroke on hospital data.[36] As such, sensitivity analyses where unspecified strokes were combined with ischemic strokes were undertaken for all analyses. Furthermore, a sensitivity analysis for incidence rates was also undertaken by including strokes identified only via the principal diagnosis fields (Table S5).

All analyses were undertaken in SAS version 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

Among 7916 CHD patients aged 18 to 64 years with mean follow-up time of 11 ± 6 years, 249 (3.15%) people had an incident stroke between 2000 and 2017, including 186 (2.35%) ischemic, 33 (0.42%) hemorrhagic (20 ICH, 13 SAH), and 30 (0.37%) unspecified strokes. Of all strokes, 14 (5.6%) were fatal.

Incidence Rates in Adults With CHD

Age-specific incidence rates for ischemic stroke ranged between 45/100 000 person-years (95% CI, 25–82) during 18 to 24 years of age to 437 (95% CI, 338–565) in 55 to 64 years (Table S4). Rates for ICH (16–70/100 000) and SAH (21–38/100 000) were substantially lower than ischemic stroke across all age groups. ASRs for ischemic and hemorrhagic stroke were, respectively, about 2-fold and 4-fold higher in older (45–64 years) than younger (18–44 years) adults with CHD, although differences were not statistically significant for ICH and SAH (Table 1). There were no significant differences between ASRs for male and female patients for all stroke types among younger (IRR, 1.33 [95% CI, 0.90–1.97]) or older (IRR, 1.08 [95% CI, 0.78–1.51]) adults with CHD (Table S6). The overall ASRs (18–64 years) for ischemic stroke were highest for adults with shunt, left-sided, and "other" lesions (ASRs 397, 202 and 138/100 000, respectively) (Table 1). Likewise, ASRs for hemorrhagic stroke were highest among adults with "other," shunt, and left-sided lesions (59, 54, and 39/100 000, respectively).

Comparing Incidence Rates in Adults With CHD With the General Population

Stroke cases in the CHD cohort were younger and had lower prevalence of most comorbidities as compared with stroke cases in the general population (Table S7). Stroke incidence in CHD patients aged 18 to 64 years was 6.5-times (95% CI, 6.4–6.6) higher than the general population, with greater differentials among younger (IRR, 13.4 [95% CI, 13.2–13.6]) than older (IRR, 4.8 [95% CI, 4.6–5.0]) adults (Table S8, Figure 2). The differential between female patients and the general population was greater than that in male patients for ischemic stroke (IRR 12.5 versus 7.4), but similar for ICH (3.3 versus 3.1) and SAH (1.8 versus 2.5). Within lesion types, shunt and left-sided lesions had the highest incidence for both younger and older adults with CHD relative to the general population.

Predictors of Ischemic Stroke

CHD-specific variables were the strongest predictors of ischemic stroke in adults with CHD (Table 2), that is, having a shunt lesion (odds ratio [OR], 3.22, 95% CI, 1.83–5.68]), or history of left-sided valve repair/replacement (OR, 4.35 [95% CI, 1.31–14.4]), endocarditis (OR, 4.89 [95% CI, 1.88–12.7) or recent cardiac/high-risk surgery (OR, 41.1 [95% CI, 15.4–110]). Hypertension, peripheral vascular disease, mental disorders, and tobacco abuse were associated with a doubling of odds. Heart failure (OR, 1.51 [95% CI, 0.54–4.21]), atrial fibrillation (OR, 0.62 [95% CI, 0.24–1.57]), diabetes (OR, 1.87 [95% CI, 0.84–4.13]), and malignancy (OR, 1.92 [95% CI, 0.75–4.96]) were not significantly associated despite their higher prevalence among adult CHD patients with stroke than those without. Moreover, higher composite scores had higher odds of ischemic stroke; CHA_2DS_2VASc (OR, 1.66 [95% CI, 1.20–2.30]) and Charlson's (OR, 1.74 [95% CI, 1.52–1.98]). Furthermore, predictors of ischemic/unspecified stroke (Table S9) were consistent with those of ischemic stroke with similar effect sizes apart from mental disorders, which was not significant.

Predictors of Hemorrhagic Stroke

The strongest independent predictors of hemorrhagic stroke in adults with CHD (Table 3) were mental disorders (OR, 7.00 [95% CI, 2.66–18.4]), malignancy (OR, 4.05 [95% CI, 1.23–13.3]), increasing Charlson's comorbidity scores, especially scores ≥2 (OR, 5.15 [95% CI, 1.88–14.1]), and a recent 90-day history of cardiac/high-risk surgery (OR, 14.9 [95% CI, 1.59–139]). Endocarditis (OR, 4.65 [95% CI, 0.66–32.8]), pulmonary embolism/deep vein thrombosis (OR, 4.42 [95% CI, 0.54–36.5]), peripheral vascular disease (OR, 3.85 [95% CI, 0.74–20.1]), hypertension (OR, 2.52 [95% CI,

Table 1. Stroke Incidence Rate Per 100000 Person-Years by Sex, Congenital Heart Lesion, and Stroke Type

Age-group, y	All stroke		Ischemic stroke		Ischemic or Unspecified stroke*		Hemorrhagic stroke		Intracerebral hemorrhage		Subarachnoid hemorrhage	
	ASR	95% CI	ASR	95% CI	ASR	95% CI	ASR	95% CI	ASR	95% CI	ASR	95% CI
All												
18–44	237	191–283	190	149–232	215	171–259	22	8–36	14	3–25	8	0–16
45–64	513	429–598	361	290–432	429	352–507	84	50–118	51	24–78	33	11–54
18–64	346	302–389	258	220–295	299	259–340	46	31–62	29	16–41	18	8–28
Male sex												
18–44	272	201–343	217	153–280	249	180–317	23	3–44	15	0–32	8	0–20
45–64	532	418–647	363	269–458	440	336–544	92	44–141	59	20–98	33	4–63
18–64	375	312–437	274	221–328	324	266–382	51	28–73	32	14–51	18	5–32
Female sex												
18–44	204	145–263	166	113–220	183	127–239	21	3–40	13	0–28	8	0–19
45–64	491	366–617	358	251–465	416	301–532	75	26–124	41	5–77	34	1–67
18–64	317	256–378	242	189–295	275	218–332	42	20–65	24	7–41	18	3–33
Severe												
18–44	176	52–300	99	4–194	160	40–280	16	0–46	0	…	16	0–46
45–64	314	5–622	157	0–375	242	0–518	71	0–211	71	0–211	0	…
18–64	230	87–373	122	18–225	192	62–323	38	0–96	28	0–83	9	0–28
Shunt												
18–44	310	233–387	267	195–339	288	213–362	22	2–43	19	0–38	4	0–11
45–64	771	598–945	598	445–750	670	508–832	101	39–164	60	12–109	41	1–81
18–64	492	409–574	397	323–472	438	360–516	54	26–81	35	13–57	18	2–35
Left-sided												
18–44	186	93–279	147	66–229	171	83–260	14	0–42	0	…	14	0–42
45–64	437	312–563	286	185–386	360	247–473	77	24–131	38	1–75	40	1–78
18–64	285	210–360	202	138–265	246	176–315	39	12–66	15	0–30	24	1–47
Right-sided												
18–44	182	3–362	86	0–206	134	0–287	48	0–143	48	0–143	0	…
45–64	132	0–390	132	0–390	132	0–390	0	…	0	…	0	…
18–64	162	13–311	104	0–229	133	0–271	29	0–87	29	0–87	0	…
Other												
18–44	183	63–303	140	36–244	140	36–244	43	0–103	22	0–64	22	0–64
45–64	283	134–431	134	35–234	199	75–323	83	2–165	65	0–138	19	0–56
18–64	222	129–315	138	63–212	163	83–243	59	10–107	38	0–77	20	0–50

ASR indicates age-standardized rates relative to the Australian population in June-2016.
*Sensitivity analysis.

0.87–7.31]), and an increasing CHA_2DS_2VASc score (OR, 1.27 [95% CI, 0.71–2.28]) were positively associated with hemorrhagic stroke but were not statistically significant. Unlike ischemic stroke, CHD-specific variables were not associated.

DISCUSSION

This is the first study describing the incidence of stroke and investigating associated predictors in a whole-population Australian cohort of people with CHD with mean follow-up time of 11 ± 6 years. By 65 years of age, 2.35% of patients had developed an incident ischemic stroke and 0.42% had an incident hemorrhagic stroke. As expected,[3,4,12–14,16,17,37,38] the absolute risk of stroke was low among adults with CHD, but substantially higher relative to the general population for CHD lesions of all severity/complexity, especially at younger ages. In our cohort, adults with CHD with shunt or left-sided lesions and those with recent cardiac surgery had higher rates of stroke than those with severe lesions. We identified that mental disorders and comorbidity and vascular risk scores were strong predictors of stroke among adults with CHD, along with CHD-specific and traditional risk factors of stroke; sociodemographic variables, including

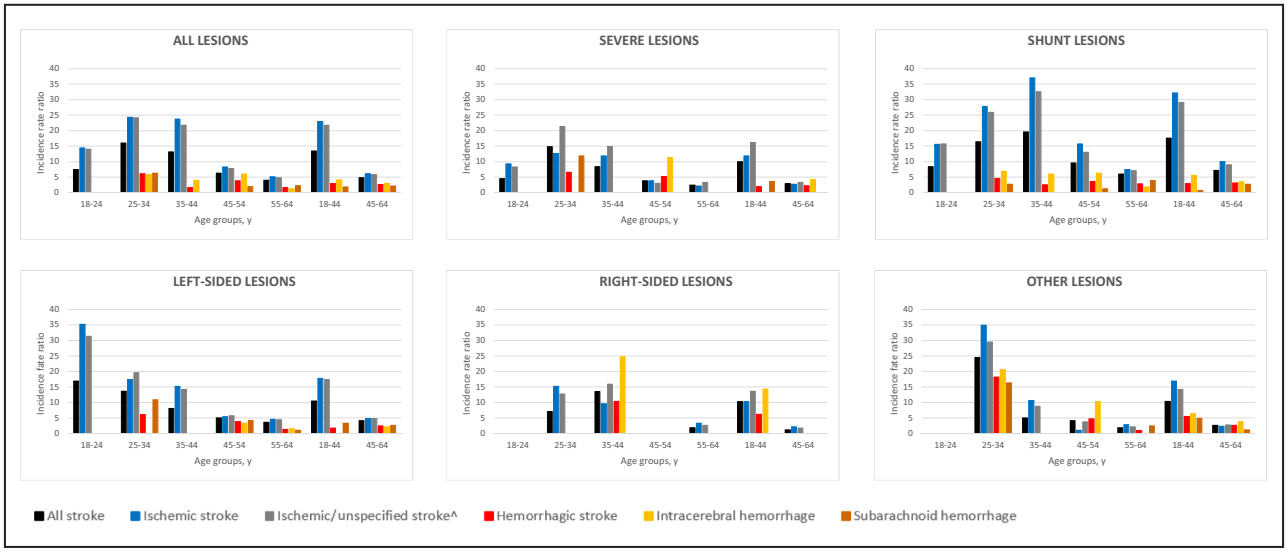

Figure 2. Standardized incidence rate ratios comparing stroke rates in cohort of adults with congenital heart disease with the Western Australian general population by lesion type, age group, and stroke type. ^ indicates sensitivity analysis.

sex, being Indigenous, or living in remote or disadvantaged areas, were not associated.

Incidence Rates Among Adults With CHD

Adults with CHD had annual rates of 0.26% for ischemic stroke, 0.029% for ICH, and 0.018% for SAH. Although absolute rates for hemorrhagic stroke were similar to other studies, ischemic stroke rates were nearly 2-fold higher than Canadian,[14] Swedish,[16] and Danish[38] cohorts. This may partly be due to methodological differences, such as our more inclusive definition of incident stroke events including both principal and secondary diagnoses to improve stroke capture and sensitivity.[21] We addressed this by undertaking a sensitivity analysis by excluding 48 strokes identified only via secondary diagnosis fields, which resulted in slight reduction of annual incidence rates to 0.21% for ischemic stroke, 0.019% for ICH, and 0.014% for SAH (Table S5).

Rates of ischemic stroke were highest among adults with CHD with shunt and left-sided lesions. Most studies have reported highest incidence of ischemic stroke among severe (ie, "complex"/"cyanotic") and left-sided lesions, followed by shunt or valve lesions.[13,14,38] Consistent with our findings, Swedish patients with CHD aged 18 to 44 years with atrial septal defects had higher risk of ischemic stroke than those with severe lesions (23% versus 14%–16%).[16] Our findings are further supported by other studies with higher prevalence of stroke in adults with "simple"/"noncomplex" CHD lesions than "intermediate"/"complex" CHD lesions (14.9% versus 5%–9%).[25,37] This could be due to the greater health surveillance, lower prevalence of systemic comorbidities, or lower life-expectancy (survivor bias) in those with moderate-to-severe than less severe CHD lesions.[7,24,25]

For hemorrhagic stroke, absolute rates in our cohort were highest for "other," shunt, and left-sided lesions. This is different from the sole other comparable study in a Swedish cohort that reported highest rates in "severe nonconotruncal defects" (which are a subset of our "severe" lesions) for ICH and in coarctation of aorta for SAH.[17] Absence of data on antithrombotic prescriptions makes it difficult to determine if this increased risk of ICH was mediated by differences in antithrombotic prescription or other factors. Perhaps left-sided lesions included valve replacements and therefore greater number of systemically anticoagulated patients with higher risk of left-sided valve thromboembolism. However, multivariable regression did not identify any significant differences in risk of hemorrhagic stroke by type of CHD lesion.

Comparison of Incidence in Adults With CHD With the General Population

Despite their lower prevalence of most comorbidities and risk factors, stroke rates were substantially elevated in adults with CHD relative to the WA general population for both sexes, all stroke types, and all CHD lesions. This is potentially explained by CHD-related risk factors such as corrective cardiac surgeries, use of antithrombotic medications[11] and, additionally for female patients with CHD, the physiological changes of pregnancy that predispose to stroke,[39] such as hypertensive disorders, hypercoagulability and increased cardiac stroke volume. Stroke incidence increased with age although the differential with the general

Table 2. Predictors of Ischemic Stroke Among Adults With Congenital Heart Disease (18–64 y)

	Distribution		Unconditional logistic regression	
	Cases (%)	Controls (%)	Univariate	Multivariable
Potential predictors	n=186	n=16 019*	Odds ratio (95% CI)	Odds ratio (95% CI)
Sociodemographic variables				
Median age (y) (Q1–Q3)†	44.6 (32.9–55.8)	46.8 (37.2–57.0)	1.01 (1.00–1.03)	1.00 (1.00–1.00)
Younger adults, 18–44 y	46.2	51.8	0.80 (0.60–1.07)	…
Male sex	144.1	147.3	1.14 (0.85–1.52)	…
Indigenous	4.8	4.9	0.99 (0.50–1.93)	…
Metro/inner regional residence	87.1	89.9	0.89 (0.60–1.30)	…
Socioeconomic disadvantage				
Quintile 1—most	11.3	12.7	1.06 (0.62–1.80)	…
Quintile 2	25.8	22.5	1.37 (0.90–2.09)	…
Quintile 3	19.4	20.6	1.12 (0.71–1.76)	…
Quintile 4	21.5	18.2	1.41 (0.91–2.19)	…
Quintile 5—least (ref)	21.5	25.7	Ref	…
CHD specific/associated variables				
Lesion type				
Severe	3.8	8.2	0.89 (0.36–2.20)	1.00 (0.39–2.58)
Shunt	63.4	44.7	2.76 (1.58–4.81)	3.22 (1.83–5.68)
Left-sided	23.7	28.3	1.62 (0.89–2.97)	1.36 (0.74–2.52)
Right-sided	1.6	4.2	0.75 (0.22–2.62)	0.89 (0.25–3.13)
Other (ref)	7.5	14.6	Ref	Ref
Cardiac/high-risk surgery	13.4	8.0	1.79 (1.17–2.73)	0.24 (0.09–0.62)
Recent, within past 90 d	6.5	0.2	28.3 (14.6–54.9)	41.1 (15.4–110)
Left-sided valve repair/replacement	7.5	1.3	5.96 (3.40–10.4)	4.35 (1.31–14.4)
Right-sided valve repair/replacement	0.0	0.4	…	…
Common complications of CHD associated with stroke				
Heart failure	4.3	0.9	5.17 (2.50–10.7)	1.51 (0.54–4.21)
Endocarditis	3.8	0.4	9.46 (4.28–20.9)	4.89 (1.88–12.7)
Atrial fibrillation	4.3	2.0	2.17 (1.06–4.44)	0.62 (0.24–1.57)
Pulmonary hypertension	1.1	0.5	2.09 (0.51–8.55)	…
Secondary erythrocytosis	0.5	0.1	4.13 (0.55–30.8)	…
Other comorbidities and procedures associated with stroke				
Hypertension	10.2	2.4	4.57 (2.81–7.43)	2.49 (1.33–4.66)
Diabetes	5.4	1.2	4.63 (2.41–8.90)	1.87 (0.84–4.13)
Coronary heart disease	4.8	2.0	2.49 (1.26–4.90)	0.76 (0.31–1.89)
Peripheral vascular disease	4.3	1.0	4.35 (2.11–8.97)	2.83 (1.17–6.86)
Pulmonary embolism/deep vein thrombosis	1.1	0.3	3.69 (0.89–15.3)	0.98 (0.21–4.65)
Chronic kidney disease	3.2	1.0	3.43 (1.50–7.87)	0.79 (0.27–2.34)
Chronic obstructive pulmonary disease	4.3	1.7	2.54 (1.24–5.20)	1.10 (0.47–2.58)
Malignancy	2.7	1.0	2.76 (1.12–6.79)	1.92 (0.75–4.96)
Mental disorder	11.3	4.2	2.91 (1.84–4.61)	1.93 (1.03–3.61)
Tobacco abuse	18.8	7.4	2.90 (2.00–4.21)	1.99 (1.27–3.13)
Alcohol or drug abuse	4.8	1.9	2.65 (1.34–5.22)	0.80 (0.33–1.95)
Pacemaker procedures	3.2	0.9	3.86 (1.68–8.87)	0.86 (0.27–2.74)
Life-support procedures	9.1	3.1	3.12 (1.88–5.17)	1.50 (0.44–5.14)
Catheter-based procedures	8.1	5.6	1.48 (0.87–2.52)	…

(*Continued*)

Table 2. Continued

Potential predictors	Distribution		Unconditional logistic regression	
	Cases (%)	Controls (%)	Univariate	Multivariable
	n=186	n=16 019*	Odds ratio (95% CI)	Odds ratio (95% CI)
Risk-scoring systems‡				
CHA_2DS_2VASc score				
0 (ref)	80.1	94.2	Ref	Ref
1	11.8	4.4	3.14 (2.00–4.95)	2.20 (1.28–3.79)
≥2	8.1	1.4	6.72 (3.89–11.6)	4.01 (1.82–8.84)
Continuous	…	…	2.14 (1.76–2.61)	1.66 (1.20–2.30)
Charlson's comorbidity score				
0 (ref)	74.2	94.5	Ref	Ref
1	6.5	3.7	2.24 (1.24–4.07)	1.80 (0.96–3.38)
≥2	19.4	1.8	13.6 (9.24–19.9)	10.1 (6.62–15.3)
Continuous	…	…	1.89 (1.67–2.15)	1.74 (1.52–1.98)

CHD indicates congenital heart disease.
*All eligible controls were selected for each case and a fixed case-to-controls ratio was not assigned to increase power and precision.
†Age at time of stroke for cases and age at time of selection for matched controls.
‡Two separate multivariable models including the Charlson's comorbidity index[29] and CHA_2DS_2VASc score[28] together (both as class and both as continuous variables) were also evaluated as potential predictors of stroke. These models excluded the following covariates for comorbidities that they already incorporated namely, heart failure, endocarditis, atrial fibrillation, pulmonary hypertension, hypertension, diabetes, coronary heart disease, diabetes, peripheral vascular disease, pulmonary embolism/deep vein thrombosis, chronic kidney disease, chronic obstructive pulmonary disease, and malignancy.

population during younger versus older ages was substantially higher for ischemic stroke (23.0 versus 6.1), slightly higher for ICH (4.1 versus 3.0), and similar for SAH (1.9 versus 2.1). These findings indicate a lower age of stroke incidence in adults with CHD than the general population. This is aligned with (but greater than) estimates for ischemic stroke comparing younger with older adults with CHD from: Canada (9–12 versus 2–4 times),[14] Sweden (12 versus 4 times),[16] and Denmark (3.4 versus 1.7 times).[38] However, our IRRs for ICH among younger adults with CHD (18–44 years) are lower than Swedish (8 times)[17] and Canadian (5–6 times) cohorts.[14] Variations in the magnitude of findings can be explained by the heterogeneity in cohort definitions (eg, differing age cutoffs and inclusion of children or older adults) and differing criteria for selection of comparison groups, identification/selection of stroke events, classification of lesion types, and study periods.

Predictors of Stroke in Adults With CHD

Few studies investigate risk factors associated with stroke in adults with CHD. In our cohort, we confirmed positive associations of traditional cardiovascular risk factors of ischemic stroke (namely hypertension, peripheral vascular disease, infective endocarditis, and tobacco use) commonly associated with stroke in adults in the general population[10] and other adult cohorts with CHD.[4,13,14] However, Bokma et al.[15] and Saha et al.[37] did not find any associations of ischemic stroke in adults with CHD with traditional atherosclerotic risk factors (such as hypertension, diabetes, or smoking), suggesting a potential cardioembolic mechanism of most stroke. Most studies report higher risk in adults with "severe"/"cyanotic" CHD lesions associated with hypercoagulability.[4,14] However, we identified greater risk of stroke among adults with shunt lesions, left-sided repair/replacement procedures, or recent surgery on the heart/major arteries.[12,15,37] This is noteworthy for clinicians as shunt lesions (inclusive of ventricular septal defects and atrial septal defects) comprise over one third of all CHD lesions in adulthood[4,23,40] and give rise to stroke through paradoxical embolism from the venous to the systemic circulation (but can be prevented with anticoagulant therapy and with the use of air trap filters on intravenous lines used for infusions). Other explanations for stroke risk in our cohort include atrial arrythmias, atrial cardiopathy, or left ventricular thrombus formation, which would all be more likely to occur following left-sided lesion repair. It may also be that patients with "severe"/"cyanotic" disease have either had defects repaired or have not survived to adulthood.

The association of cardiac surgery with stroke in adult patients with CHD is complex. A markedly elevated risk of stroke was observed in the 90-day period after cardiac surgery in our study. Yet, these estimates are based on a small number of stroke cases and need to be interpreted cautiously. Additionally, despite our best efforts to capture disease severity and patient comorbidities via multivariable models, there remains a

Table 3. Predictors of Hemorrhagic Stroke Among Adults With Congenital Heart Disease (18–64 y)

	Distribution		Unconditional logistic regression	
	Cases, %	Controls, %	Univariate	Multivariable
Potential predictors	n=33	n=2596*	Odds ratio 95% CI	Odds ratio 95% CI
Sociodemographic variables				
Median age (y) (Q1–Q3)†	49.7 (38.6–54.8)	49.7 (38.6–55.8)	1.00 (0.97–1.04)	…
Younger adults, 18–44 y	30.3	30.0	1.01 (0.48–2.14)	…
Male sex	142.4	146.5	1.18 (0.59–2.37)	…
Indigenous	12.1	4.0	3.34 (1.15–9.67)	2.32 (0.74–7.32)
Metro/inner regional residence	75.8	88.9	0.57 (0.26–1.28)	…
Socioeconomic disadvantage				
Quintile 1—most	12.1	10.2	1.65 (0.48–5.67)	1.27 (0.38–4.32)
Quintile 2	9.1	19.9	0.63 (0.16–2.46)	0.47 (0.13–1.70)
Quintile 3	39.4	20.4	2.67 (1.06–6.73)	2.45 (0.97–6.17)
Quintile 4	18.2	19.8	1.27 (0.42–3.79)	1.28 (0.45–3.59)
Quintile 5—least (ref)	21.2	29.3	…	Ref
CHD specific/associated variables				
Lesion type				
Severe	6.1	6.7	0.81 (0.16–4.03)	…
Shunt	45.5	40.1	1.01 (0.39–2.62)	…
Left-sided	27.3	32.9	0.74 (0.26–2.09)	…
Right-sided	3.0	4.1	0.66 (0.08–5.49)	…
Other (ref)	18.2	16.2	Ref	…
Cardiac/high-risk surgery	27.3	9.6	3.54 (1.63–7.69)	1.01 (0.26–3.86)
Recent, within past 90 d	6.1	0.2	33.4 (6.25–179)	14.9 (1.59–139)
Left-sided valve repair/replacement	12.1	1.8	7.32 (2.48–21.6)	3.49 (0.51–23.8)
Right-sided valve repair/replacement	0.0	0.3	…	…
Common complications of CHD associated with stroke				
Heart failure	9.1	1.5	6.39 (1.87–21.8)	0.94 (0.23–3.85)
Endocarditis	6.1	0.4	15.2 (3.23–71.3)	4.65 (0.66–32.8)
Atrial fibrillation	9.1	3.4	2.85 (0.85–9.52)	0.76 (0.21–2.81)
Pulmonary hypertension	0.0	0.7	…	…
Secondary erythrocytosis	0.0	0.2	…	…
Other comorbidities and procedures associated with stroke				
Hypertension	21.2	4.6	5.60 (2.38–13.2)	2.52 (0.87–7.31)
Diabetes	12.1	1.8	7.48 (2.53–22.1)	1.51 (0.42–5.48)
Coronary heart disease	9.1	3.3	2.95 (0.88–9.87)	0.35 (0.08–1.45)
Peripheral vascular disease	6.1	1.2	5.34 (1.22–23.3)	3.85 (0.74–20.1)
Pulmonary embolism/deep vein thrombosis	6.1	0.2	27.9 (5.41–143)	4.42 (0.54–36.5)
Chronic kidney disease	3.0	1.3	2.29 (0.30–17.2)	…
Chronic obstructive pulmonary disease	6.1	2.2	2.87 (0.67–12.3)	…
Malignancy	12.1	1.9	7.17 (2.43–21.2)	4.05 (1.23–13.3)
Mental disorder	33.3	4.6	10.4 (4.93–22.0)	7.00 (2.66–18.4)
Tobacco abuse	24.2	9.3	3.11 (1.39–6.98)	0.96 (0.35–2.59)
Alcohol or drug abuse	12.1	1.5	8.82 (2.96–26.3)	1.09 (0.26–4.60)
Pacemaker procedures	6.1	1.2	5.34 (1.22–23.3)	2.14 (0.41–11.2)
Life support procedures	15.2	3.8	4.55 (1.72–12.0)	0.78 (0.10–5.77)
Catheter-based procedures	15.2	7.7	2.13 (0.81–5.57)	…

(*Continued*)

Table 3. Continued

Potential predictors	Distribution		Unconditional logistic regression	
	Cases, %	Controls, %	Univariate	Multivariable
	n=33	n=2596*	Odds ratio 95% CI	Odds ratio 95% CI
Risk-scoring systems‡				
CHA_2DS_2VASc score				
0 (ref)	60.6	91.4	Ref	Ref
1	24.2	5.8	6.33 (2.74–14.6)	3.61 (1.33–9.80)
≥2	15.2	2.9	8.01 (2.93–21.9)	1.91 (0.44–8.21)
Continuous	…	…	2.36 (1.69–3.31)	1.27 (0.71–2.28)
Charlson's comorbidity score				
0 (ref)	72.7	93.4	Ref	Ref
1	6.1	4.0	1.96 (0.46–8.41)	0.96 (0.24–3.77)
≥2	21.2	2.7	10.3 (4.27–24.6)	5.15 (1.88–14.1)
Continuous	…	…	1.72 (1.41–2.10)	1.56 (1.22–1.99)

CHD indicates congenital heart disease.

*All eligible controls were selected for each case, and a fixed case-to-controls ratio was not assigned to increase power and precision.

†Age at time of stroke for cases and age at time of selection for matched controls.

‡Two separate multivariable models including the Charlson's comorbidity index[29] and CHA_2DS_2VASc score[28] together (both as class and both as continuous variables) were also evaluated as potential predictors of stroke. These models excluded the following covariates for comorbidities that they already incorporated namely, heart failure, endocarditis, atrial fibrillation, pulmonary hypertension, hypertension, diabetes, coronary heart disease, diabetes, peripheral vascular disease, pulmonary embolism/deep vein thrombosis, chronic kidney disease, chronic obstructive pulmonary disease, and malignancy.

potential for confounding from unmeasured or unrecorded clinical variables. Nevertheless, it highlights a highly vulnerable period for adult patients with CHD, which is consistent with the perioperative risk of stroke reported in the general population[41] and in another study on these patients.[14] Conversely, the "protective" effect of long-term cardiac surgery may reflect a healthy survivor bias.

Atrial fibrillation and heart failure were more prevalent in adults with CHD with stroke than those without. A confluence of clinical factors combined with an aging population of adults with CHD has led to a steep increase in the prevalence of atrial fibrillation over recent decades.[42] However, we did not find a significant association between these conditions and risk of ischemic (or ischemic/unspecified) stroke, despite atrial fibrillation being an established risk factor for ischemic stroke (and heart failure) in the general population and adults with CHD.[10,13,14,38,43] It may be that these conditions are underdiagnosed or underrecorded on administrative data, or generally well managed in our cohort. Alternatively, it may suggest a different mechanism of ischemic stroke in adults with CHD.

The use of a composite comorbidity score, such as Charlson's, can serve as a more meaningful summative risk estimate for people with multiple chronic comorbidities (like hypertension, diabetes, chronic kidney disease, atrial fibrillation, and heart failure). Indeed, on a continuous scale, risk of ischemic and hemorrhagic stroke increased by 1.6-fold for every 1-point increase in comorbidity score. Similarly, although the CHA_2DS_2VASc score has been developed and validated on older populations without CHD, it was identified as a predictor of ischemic stroke in adults with CHD, similar to a Danish study.[38] There may thus be potential for its use as a preliminary screening tool among adult patients with CHD until a more specific tool is developed.

The emergence of mental disorders as an independent predictor of both ischemic and hemorrhagic stroke in the cohort of adults with CHD is consistent with the strong evidence of the association of mental disorders and risk of stroke in the general population for all ages.[44,45] Mental disorders affect between 30% and 50% of all adult patients with CHD, being substantially higher than the general population prevalence of ~20%.[6,46–48] However, because mental disorders are largely underdiagnosed or undertreated in adults with CHD,[46,47] our results may have underestimated the true effect size. High prevalence of atherosclerotic comorbidities, side effects of medications (especially via obesity and insulin resistance), and lifestyle-related risk factors (like smoking, medication nonadherence, obesity, or inactivity) predispose people with mental disorders to increased risk of cardiovascular conditions, including stroke.[44] Nevertheless, younger people with mental disorders in the general population still have a higher risk of stroke in the absence of these comorbidities or lifestyle issues.[45] As such, consistent with the American Heart Association recommendations[46] and guidelines,[48] psychiatric conditions should be actively screened for and considered in the management

of adult patients with CHD due to their elevated risk of stroke. This indicates a potential interplay of atherosclerotic, cardioembolic, and psychosocial risk factors in the pathogenesis of ischemic stroke among adults with CHD.

Strengths and Limitations

A major strength is the use of statewide hospitalization data over an extensive cohort ascertainment period of >30 years (1985–2017) that allowed the establishment of a near-complete whole-population cohort of adults with CHD, enabled by their high hospitalization rates.[12,24,25,37] Comprehensive CHD algorithms[22,23] permitted the classification of CHD lesions by anatomic complexity and physiological severity, reduced bias in cohort selection using administrative data, and allowed investigation of differences by lesion types. Yet, some misclassification of CHD lesions with variable severity is inevitable due to limited phenotypic information offered by *ICD* codes.[22,49] The presence of a dedicated *ICD-10-AM* code for patent foramen ovale (Q21.11) enabled differentiation from atrial septal defects, thereby reducing selection bias. Extensive data availability with a 15-year clearance period enabled accurate identification of incident hospitalized stroke events.[21] The nested case–control study design is an established and more efficient alternate to the conventional proportional hazards models for evaluating time-dependent exposures in cohort studies and offers the statistical power to investigate rare outcomes like hemorrhagic stroke.[50] Furthermore, using unconditional regression models allowed increase in precision and control of any potential confounding introduced by matching on age.[34] The relatively low contemporary incidence of stroke in Australia compared with other countries[18] may have partially mitigated the relative risk and incidence of stroke independently associated with CHD.

Some limitations also exist. Absence of clinical data, and exclusive reliance on administrative hospital data were associated with some information bias in this study. This includes underestimation of the prevalence of comorbidities (eg, dyslipidemia, anxiety/depression)[51] and lifestyle-related risk factors (eg, smoking, physical activity, diet) associated with stroke, or prescription medication use (e.g., antithrombotics, antihypertensives, lipid-lowering agents, or oral contraceptives). Furthermore, unmeasured confounding arising from absence of these data may hinder understanding of complex associations, such as with cardiac surgery, despite adjustment for a range of comorbidities and proxies for disease severity, such as the Charlson's and CHA_2DS_2VASc scores. Family history of stroke was unavailable but may have limited predictive value in adults with CHD.[15] There is potential misclassification of stroke type where ischemic, ICH, or SAH were listed on the same episode, but this affected a small number of cases (n=16). A sensitivity analysis where unspecified strokes were combined with ischemic strokes was undertaken for all analyses as prior validation work showed a high proportion of ischemic strokes to be miscoded as unspecified stroke on hospital data.[36] Further, the limited number of adults with CHD reduced the precision of risk estimates.

Future Directions

Our research answers some important questions about the risk of stroke among adults with CHD, yet some gaps in understanding remain, largely arising from the absence of clinical and prescription data. The establishment of a binational registry, the Congenital Heart Alliance of Australia and New Zealand,[1] opens a promising avenue for future research addressing these gaps in knowledge. In Australia, recent improvements in nationwide linkages between hospital, mortality, and medication databases, may also enable a better understanding of the impact of treatments for these patients on stroke incidence. For example, studies that investigate the risk of hemorrhagic stroke associated with antithrombotic medication use or that stratify by surgical methods will become feasible. Arguably, access to such databases may permit more timely identification of at-risk groups, enabling timely preventive or corrective interventions in the future.

CONCLUSIONS

This is the first whole-population Australian study to report incidence rates and incidence risk ratios of ischemic and hemorrhagic strokes in adults with CHD, comparing different lesion types within the cohort and with the broader population. We identify adults with CHD most likely to benefit from stroke risk surveillance and stroke prevention strategies, and find a potential interplay of atherosclerotic, cardioembolic, and psychosocial risk factors in the pathogenesis of stroke among adults with CHD that warrants further examination.

ARTICLE INFORMATION

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Affiliations

Cardiovascular Epidemiology Research Centre, School of Population and Global Health, The University of Western Australia, Crawley, WA, Australia (N.S., L.N., J.M.K.); Department of Cardiovascular Medicine, Mayo Clinic College of Medicine, Rochester, MN (L.J.B.); Department of Medicine, Royal Melbourne Hospital, University of Melbourne, Parkville, VIC, Australia (L.J.B.); Department of Neurology, Royal Adelaide Hospital, Adelaide, SA, Australia (T.J.K.); Cardiology Population Health Laboratory, Victor Chang Cardiac Research Institute, Sydney, NSW, Australia (L.N.); and Telethon Kids Institute, The University of Western Australia, Perth, WA, Australia (J.M.K.).

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Disclosures

None.

Supplemental Material

Tables S1–S9
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