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Risk of stroke in patients with congenital heart disease: a systematic review and meta-analysis

Ramez M. Odat[1], Muhammad Idrees[2], Hritvik Jain[3], Sakhr Alshwayyat[4,5,6], Husam Aldean H. Hussain[1], Basma Badrawy Khalefa[7], Ali O. Aldamen[8], Abdel Rahman K. Bani Yaseen[1], Bassel Alrabadi[1], Mohammad-Amer A. Tamimi[9], Ayham Mohammad Hussein[10], Hamdah Hanifa[11*] and Osama Aloudat[12]

Abstract

Background Patients with congenital heart disease (CHD) are more likely to experience ischemic and hemorrhagic stroke due to factors such as arrhythmias, residual shunts and related cardiovascular complications. However, guidelines for identifying CHD patients at the highest risk of stroke remain unclear. In this study, we aimed to evaluate the risk of developing stroke in patients with CHD.

Methods A systematic literature search was performed on PubMed, Scopus, Cochrane, and Embase databases to retrieve studies that evaluated stroke risk in patients with CHD. Random effects model was used to pool the hazard ratios (HR) with 95% confidence intervals (CI). Subgroup analysis was conducted on age, type of stroke, type of study and region. Publication bias was assessed by Egger's regression test. Statistical significance was set at $p < 0.05$. All the analysis was performed using R studio V4.3.1.

Results Eleven studies (5,490,412 participants) were included in this systematic review and meta-analysis. Patients with CHD were at a higher risk of stroke [Pooled HR: 3.25; 95% CI: 2.25, 4.68; $p < 0.01$; I^2: 100%] than the control group. In subgroup analysis, patients with CHD were at a higher risk of ischemic stroke [Pooled HR: 4.45; 95% CI: 2.24, 8.85; $p < 0.01$; I^2: 100%] and hemorrhagic stroke [Pooled HR: 4.70; 95% CI: 1.70, 12.96; $p < 0.01$; I^2: 99%] than the control group.

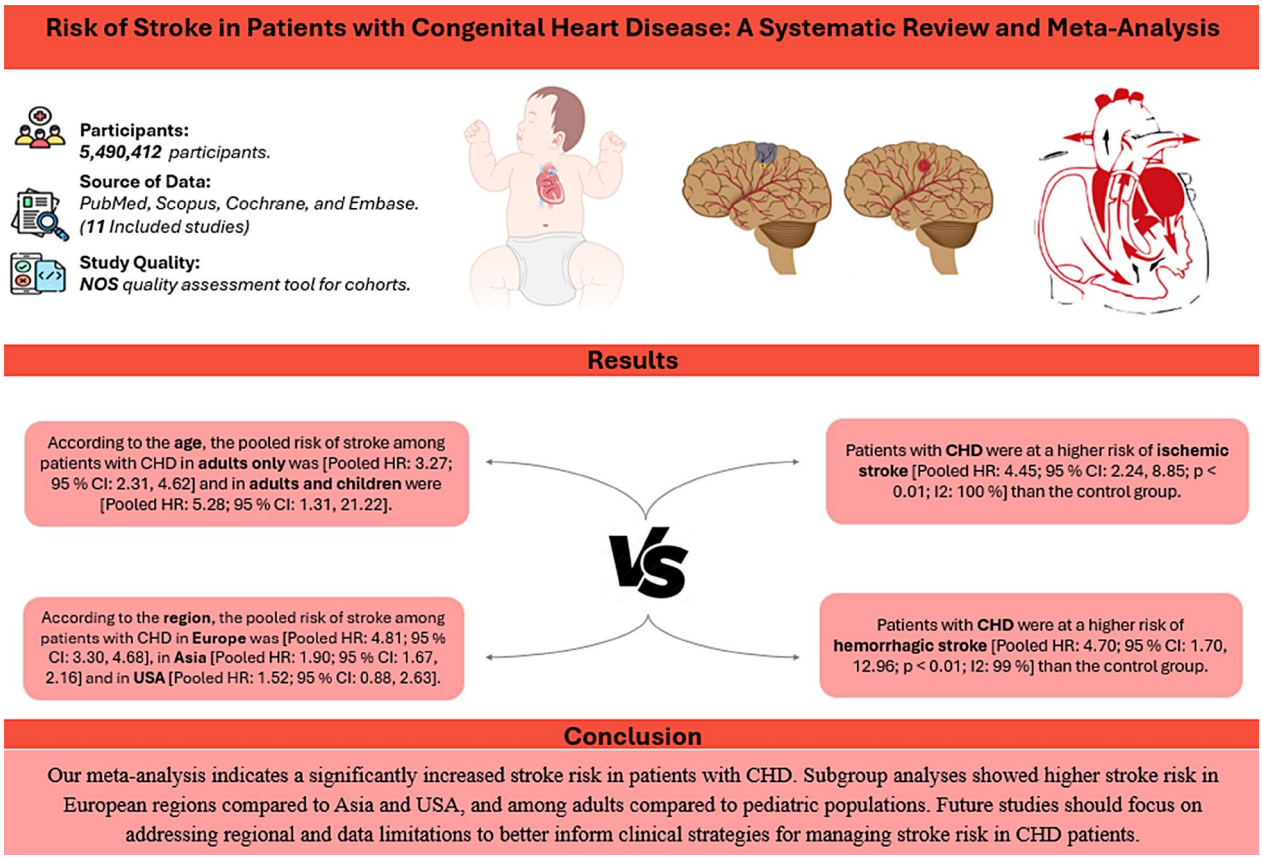
Conclusion Our meta-analysis indicates a significantly increased stroke risk in patients with CHD. Subgroup analyses showed higher stroke risk in European regions compared to Asia and USA, and among adults compared to pediatric populations. Future studies should focus on addressing regional and data limitations to better inform clinical strategies for managing stroke risk in CHD patients.

Keywords Congenital heart disease, CHD, Stroke, Ischemic, Hemorrhagic

*Correspondence:
Hamdah Hanifa
hamdahhanifa@gmail.com

Full list of author information is available at the end of the article

Graphical Abstract



Introduction

Stroke is one of the leading causes of impairments and global health issues [1]. Heart diseases, particularly heart failure, are significant contributors to the development of stroke [2]. The impaired cardiac function in heart failure often leads to reduced cerebral perfusion, arrhythmias, and the formation of blood clots, all of which increase the risk of ischemic stroke [2]. Congenital heart disease (CHD) is the most prevalent congenital disorder affecting approximately 1% of live births globally [3]. CHD includes mild to severe conditions, with a global prevalence varying due to healthcare access, diagnostic technologies, and genetic or environmental factors. Asia has the highest prevalence at 9.3 per 1,000 live births, followed by North America and Europe at 8.1 and 8.2 per 1,000 live births, respectively [4]. CHD significantly contributes to infant morbidity and mortality, with delayed diagnosis being critical in lower-income regions, such as Latin America and parts of Asia [5].

Survival rates for individuals born with CHD have significantly improved, with approximately 97% of children now reaching adulthood [6]. Advances in surgery, cardiology, and healthcare have shifted the prevalence towards adulthood. In the 1950s, only 15% of children with CHD survived to adulthood; today, over 90% survive, including individuals in their 60s [7]. Despite these advancements, adults with CHD have a 3.2-fold higher mortality risk than the general population [8]. The increasing adult CHD population presents challenges, such as managing comorbidities, complex interventions, and lifelong care needs.

Adults with congenital heart disease (ACHD) are at increased risk for multiple comorbidities, including heart failure, coronary artery disease, mental health challenges, and other chronic conditions that exacerbate their overall health outcomes [9, 10]. Patients with CHD have a higher risk of stroke owing to heart failure, arrhythmias, and defect complexity. Atrial fibrillation (AF) significantly increases this risk, with CHD patients having a five-fold higher probability of ischemic stroke than non-CHD patients with AF. Those with Tetralogy of Fallot and other complex anomalies are especially prone to atrial arrhythmias, increasing the likelihood of thromboembolic events, including stroke and transient ischemic attack [11, 12].

New-onset arrhythmias, particularly when accompanied by heart failure, aggravate the stroke risk by increasing hemodynamic instability and encouraging thromboembolism. Previous studies highlighted an elevated risk of stroke in young adults aged 20–29, especially in those with multiple atherosclerotic risk factors [13, 14]. Stroke risk in CHD patients is estimated to be 10–100 times greater than that in the general population. Furthermore, a case–control study conducted in Taiwan demonstrated a 2.2 times higher likelihood of stroke in adults with five common types of CHD compared to healthy controls [15, 16].

Stroke outcomes frequently result in significant neurological impairment and require substantial rehabilitation. This study investigated the existing evidence on stroke risk among CHD patients, identifying specific risk patterns within CHD subgroups and pinpointing areas needing further research to enhance care and patient outcomes.

Materials and methods

This systematic review and meta-analysis were made and reported in line with the guidelines of Preferred Reporting Items for Systematic Review and Meta-Analysis Statement (PRISMA 2020) [17–19].

Search strategy

A systematic search was conducted in several databases including Medline (via PubMed), Embase, the Cochrane Library, Scopus, was conducted from their inception to August 2024, using a combination of keywords related to the stroke and congenital heart disease: ("stroke" OR "Cerebrovascular Accident" OR "Vascular Accident" OR "CVA" OR "ischemic stroke" OR "transient ischemic attack" OR "TIA" OR "hemorrhagic stroke") AND ("congenital heart disease" OR "congenital heart defects" OR "CHD" OR "Heart Abnormality" OR "Heart Defect" OR "Malformation Of Heart"). The search strategy was adjusted according to the demands of specific databases.

Study selection and eligibility criteria

To determine the studies to be included in this review, the following inclusion criteria were used: (i) studies assessing the risk of stroke development in heart defects and (ii) randomized controlled trials or observational studies. Studies were included regardless of patient age, sex, race, socioeconomic background, and geographical location. Inaccessible full texts, abstracts, review articles, letters to editors, case reports, and case series were excluded. Two examiners (H.B. and R.M.) independently screened introductory studies based on their titles and abstracts. A third examiner (A.A.) was consulted for cases of disparity.

Data extraction and quality assessment

Data from acceptable studies, such as the first author, publication year, country, number of patients, risk factors, and clinical outcomes, were extracted into a tested Excel spreadsheet by two independent examiners (A.A. and R.M.). To ensure integrity and remove errors, the two examiners cross-checked and verified the extraction sheet. The Newcastle-Ottawa Scale (NOS) for cohort studies was used to assess the quality of the included studies [20]. A study with a total score between 10 and 15 is considered 'good quality'; a score between 6 and 9 is deemed 'fair quality,' whereas a score between 0 and 5 is indicative of a 'poor quality.' Two examiners (H.B. and A.B.) completed the quality assessment, and a third examiner (S.A.) was consulted in cases of contradiction in judgment.

Data analysis

Statistical analysis was conducted using R Studio [21]. The pooled hazard ratio (HR) with a 95% cnfidence interval was calculated using the DerSimonian-Laird random effects model. The pooled HR for outcomes was estimated using a multivariable model, with factors modified for age, sex, comorbidities, smoking status, and socioeconomic status. Statistical significance was determined if the 95% cnfidence interval for the pooled HR did not cross the neutral value "1" and the two-tailed p-value was less than 0.05. The Higgins I^2 metric was used to evaluate statistical heterogeneity, with 25–50% cnsidered mild, 50–75% idicating moderate heterogeneity, and >75% svere heterogeneity [22]. Sensitivity analysis was conducted to evaluate the effect of each study on the overall effect assessment by the "leave-one-out method" [23, 24]. Subgroup analysis was performed based on country, study type, and patient age to assess their influence on the overall effect. Publication bias was assessed using funnel plot visualization and Egger's regression test [24]. A p-value of >0.05 for publication bias assessment indicated insignificant publication bias.

Results

Search results

Our search strategy yielded 301 studies from PubMed, Scopus, Cochrane, and Embase. After eliminating duplicates, 155 studies were screened by title and abstract, leading to the exclusion of 144. The remaining 11 full-text articles were assessed by the same authors, and 11 [25–35]were deemed eligible for inclusion (Fig. 1).

Characteristics of included studies

A total of 5,490,412 participants were included in the analysis, with 491,930 in the CHD group and 4,998,482 in the control group. The publication years spanned from 2008 to 2023. Two studies were conducted in Asia [32,

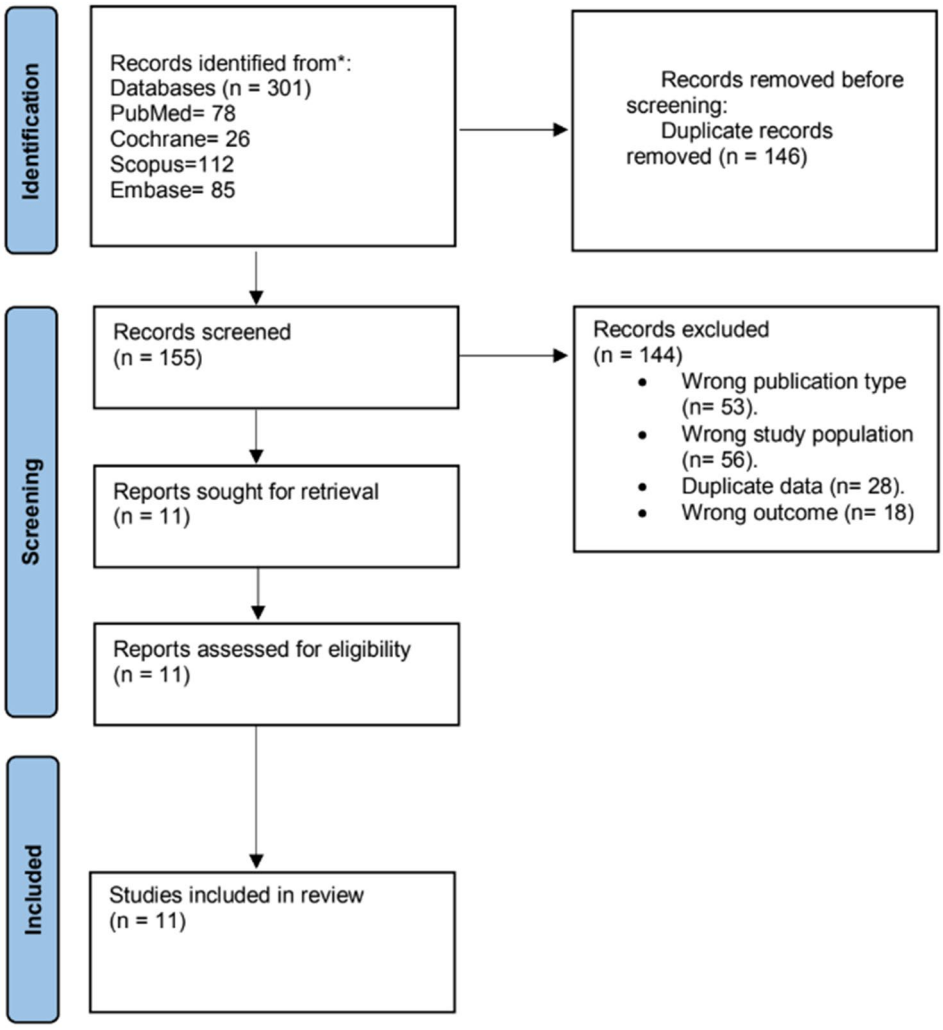


Fig. 1 Flow chart of the selection process

35], two in the United States [26, 31], seven in Europe [25, 27–30, 33, 34]. The baseline characteristics of all the studies included in this meta-analysis are illustrated in (Table 1).

Outcomes

The risk of stroke was reported in all eleven studies. Patients with CHD were at a higher risk of stroke [Pooled HR: 3.25; 95% CI: 2.25, 4.68; $p<0.01$; I^2: 100%] than the control group (Fig. 2). A leave-one-out analysis was performed to address the high heterogeneity. However, excluding any single study did not result in significant changes in the direction of the overall effect (Figure S1). Publication bias was insignificant on Egger's regression test ($P=0.333$) with no concern for funnel plot asymmetry (Figure S2). A subgroup analysis was conducted to determine the influence of region, study type, age. The combined risk of stroke among patients with CHD was found to be significantly elevated in various regions: in Europe, the pooled hazard ratio (HR) was 4.81 (95% confidence interval [CI]: 3.30 to 4.68; $p<0.01$; I^2: 95%); in Asia, the pooled HR was 1.90 (95% CI: 1.67 to 2.16; $p<0.01$; I^2: 96%); and in the USA, the pooled HR was 1.52 (95% CI: 0.88 to 2.63; $p<0.01$; I^2: 99%) (Figure S3a).

In the subgroup analysis based on study type, the pooled risk of stroke among patients with CHD varied significantly: in prospective studies, the pooled HR was 5.33 (95% confidence interval [CI]: 1.32 to 21.43; $p<0.01$; I^2: 98%); in retrospective studies, the pooled HR was 2.79 (95% CI: 1.71 to 4.55; $p<0.01$; I^2: 98%); and in case-control studies, the pooled HR was 3.63 (95% CI: 1.91 to 6.90; $p<0.01$; I^2: 98%) (Figure S3b). In the subgroup analysis according to age, the pooled risk of stroke among patients with CHD revealed significant findings: for adults only, the pooled HR was 3.27 (95% confidence interval [CI]: 2.31 to 4.62; $p<0.01$; I^2: 100%); whereas for studies including both adults and children, the pooled

Table 1 Characteristics of the included studies. * median & IQR

Study	Country	Type	Patients	Stroke type	CHD patients	Control number	Total participants	Mean age (years)	Aim	Conclusion
Videbaek et al., 2015	Europe	Prospective	Adults only	-	1241	12,254	13,495	47.4 years (IQR: 43.5–50.9) *	To study the long-term prognosis of simple CHD	Patients diagnosed with simple CHD in the 1960s have substantially increased long-term mortality and cardiac morbidity compared with the general population. Further studies on the effectiveness of systematic medical follow-up programs appear warranted.
Mandalenakis., 2016	Europe	Prospective	Adults and children	ischemic	25,985	259,750	285,735	9.51	Study the relative risk and potential factors for developing ischemic stroke in children and young adults with CHD in Sweden.	The risk of developing ischemic stroke was almost 11 times higher in young patients with CHD than in the general population, although absolute risk is low. Cardiovascular comorbidities were strongly associated with the development of ischemic stroke in young CHD patients.
Lin et al., 2014	Asia	Retrospective	Adults only	-	3,267	6534	9,801	36.5	To identify the long-term major adverse cardiovascular events (MACE) in adult congenital heart disease (CHD) patients in Taiwan.	Taiwanese patients with CHD were at an increased risk of life-long cardiovascular MACE, including heart failure, stroke, acute coronary syndrome, and malignant dysrhythmia. Surgical correction may help to decrease long-term MACE in CHD patients, especially those with ASD.
Maxwel et al., 2013	United States	Retrospective	Adults only	-	10,004	37,581	47,585	57.85	To describe the risk of patients with congenital heart disease having noncardiac surgery	Compared with a matched control cohort, CHD patients undergoing noncardiac surgery experienced increased perioperative morbidity and mortality. Within the limitations of a retrospective analysis of a large administrative dataset, this finding demonstrates that this is a vulnerable population and suggests that better efforts are needed to understand and improve the perioperative care they receive.
Billett et al., 2008	Europe	Retrospective	Adults and children	Stroke and transient ischaemic attack	9952	29,837	39,789	28.1	To determine the prevalence of comorbidities, patterns of healthcare utilization and primary care recording of clinical indicators in patients with congenital heart disease	There is a significant burden of comorbidity associated with congenital heart disease, and levels of primary care utilization and referral to secondary care are high in this patient group. The predicted future expansion in the numbers of adults with congenital heart disease owing to improvements in survival will have implications for primary and secondary care, and not just tertiary centers offering specialist care.

Table 1 (continued)

Study	Country	Type	Patients	Stroke type	CHD patients	Control number	Total participants	Mean age (years)	Aim	Conclusion
Dellborg et al., 2015	Europe	Bidirectional cohort	Adults only	-	833	4165	4998	70	the prevalence of ACHD in combination with T2DM to estimate the associated clinical risk, outcome and patient characteristics	Congenital heart disease and secondary risk factors for cardiovascular disease frequently coexist and the development of T2DM also in the ACHD population is not uncommon with an estimated prevalence of between 4 and 8%. Treatment of conventional cardiovascular risk factors in patients with congenital heart disease could be considered secondary prevention given the relatively high morbidity and high risk for mortality observed in patients with the combination of ACHD and T2DM.
Lee et al., 2023	Asia	Retrospective	Adults only	ischemic, hemorrhagic stroke	232,203	3,024,633	3,256,836	-	The incidence and risk of ischemic stroke (IS) and hemorrhagic stroke (HS) in Korean patients with CHD	Korean patients with CHD have a high risk of stroke. A personalized preventive approach is needed to reduce the incidence of stroke in this population.
Giang et al., 2021	Europe	Retrospective	Adults only	ischemic	88,700	890,450	979,150	CHD: 52.1 (IQR, 39.8–63.6)* Controls: 66.0 (IQR, 57.1–73.4) *	Study the long-term outcomes after IS, including IS recurrence and mortality risk	Patients with CHD had a 5-fold higher risk of developing index IS compared with matched controls. However, the risk of recurrent IS stroke and all-cause mortality were 34% and 47% lower, respectively, in patients with CHD compared with controls
Yelton et al., 2023	United States	Retrospective	Children only	ischemic and hemorrhagic stroke (combination)	80,927	345,102	426,029	months Stroke = 8(0-216) No stroke = 28(0-216) **	To delineate prevalence of stroke in the pediatric intensive care unit and to determine risk factors for stroke and association of stroke with mortality in patients with congenital heart disease	Children with congenital heart disease are at increased risk for developing stroke, which is associated with increased mortality. Early identification of the most vulnerable patients may enable providers to implement preventative measures or rapid treatment strategies to prevent neurologic morbidity.
Pedersen et al., 2019	Europe	Retrospective	Adults only	ischemic	16,836	168,360	185,196	Ischemic: 53 years (IQR: 40–67) * Hemorrhagic: 69 years (IQR: 55–78) *	Study and collect data regarding ischemic stroke risk and associated mortality in adults with CHD.	Both younger and older CHD adults have an increased risk of ischemic stroke and by 60 years of age 7.4% of CHD adults will have had an ischemic stroke. Post-stroke mortality was also increased in CHD adults compared with the general population

Table 1 (continued)

Study	Country	Type	Patients	Stroke type	CHD patients	Control number	Total participants	Mean age (years)	Aim	Conclusion
Giang et al., 2018	Europe	Retrospective	Adults only	intracerebral hemorrhagic stroke and subarachnoid hemorrhage	21,982	219,816	241,798	27	To study the risk of hemorrhagic stroke, including intracerebral hemorrhage (ICH) and subarachnoid hemorrhage (SAH) in CHD patients	The relative risk of hemorrhagic stroke among children and young adults with CHD was almost 8× higher than that of matched controls from the general population, although the absolute risk was low. The highest risk of ICH and SAH occurred in patients with severe nonocturnal defects and coarctation of the aorta

HR was 5.28 (95% CI: 1.31 to 21.22; $p<0.01$; I^2: 99%) (Figure S3c).

According to type of stroke, four studies assessed the risk of ischemic stroke among patients with CHD. Patients with CHD were at a higher risk of ischemic stroke [Pooled HR: 4.45; 95% CI: 2.24, 8.85; $p<0.01$; I^2: 100%] than the control group (Fig. 3). A subgroup analysis was conducted to determine the influence of region, study type, age. The pooled risk of ischemic stroke among patients with CHD in Europe was 5.85 (95% CI: 3.21 to 10.67; $p<0.01$; I^2: 96%) (Figure S4a).

In retrospective studies, the pooled risk of ischemic stroke among patients with CHD was 2.72 (95% CI: 1.42 to 5.20; $p<0.01$; I^2: 99%) (Figure S4b). For adults only, the pooled risk of ischemic stroke among patients with CHD was 3.34 (95% CI: 1.93 to 5.78; $p<0.01$; I^2: 100%) (Figure S4c).

Only two studies assessed the risk of hemorrhagic stroke among patients with CHD [25, 35]. Lee et al., 2023 [35]defined the hemorrhagic stroke as intracerebral, subarachnoid, and subdural hemorrhagic stroke. However, Giang et al., 2018 [25]assessed the risk of intracerebral hemorrhagic stroke and subarachnoid hemorrhagic stroke separately. Patients with CHD were at a higher risk of hemorrhagic stroke [Pooled HR: 4.70; 95% CI: 1.70, 1296; $p<0.01$; I^2: 99%] than the cotrol group (Fig. 3).

Quality assessment

We performed a quality assessment for nine cohorts and two case-control studies. Following the NOS Study Quality Assessment Tool guidelines, eight studies were considered of high quality and one of moderate quality. For case control studies, one was considered of high quality, and one was low quality (Table S1).

Discussion

Rising mortality and morbidity due to neurovascular decline in patients with CHD has garnered attention. However, statistical evidence supporting a definitive protocol is limited [36]. Given CHD's complexity of CHD, addressing research gaps necessitates statistical analysis of existing data, which this meta-analysis aimed to validate. Our findings show a significantly increased stroke risk in patients with CHD, with ischemic strokes being more common than hemorrhagic strokes. Subgroup analysis indicated a higher occurrence in adults than in the combined adult and pediatric groups, and a greater prevalence in Europe than in Asia.

Among neurological manifestations, we observed a heightened stroke risk in the CHD population. A recent Danish study (1977–2018) reported stroke risk in 18.9% of males and 11.4% of females with CHD, particularly in those with atrial septal defects (ASD) [37]. Contrary to Danish findings, Bokma et al. identified CHD type

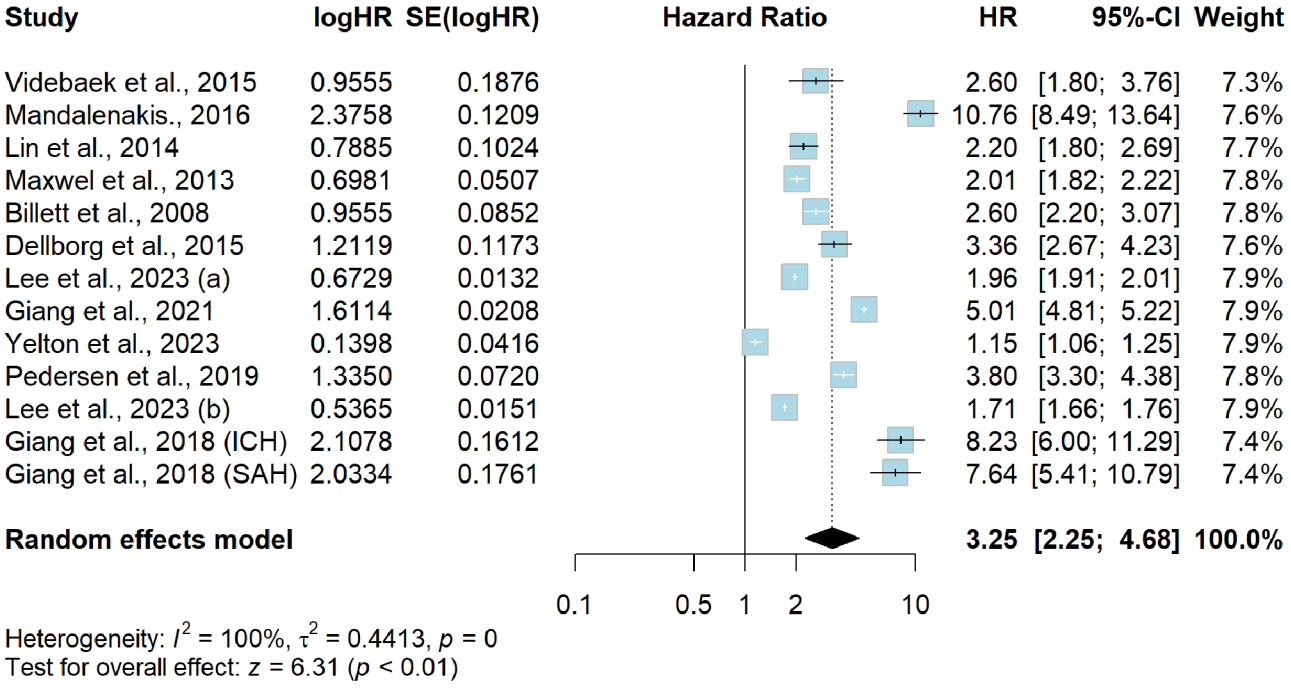


Fig. 2 Meta analysis of the risk of stroke (ischemic and hemorrhagic) in patients with CHD

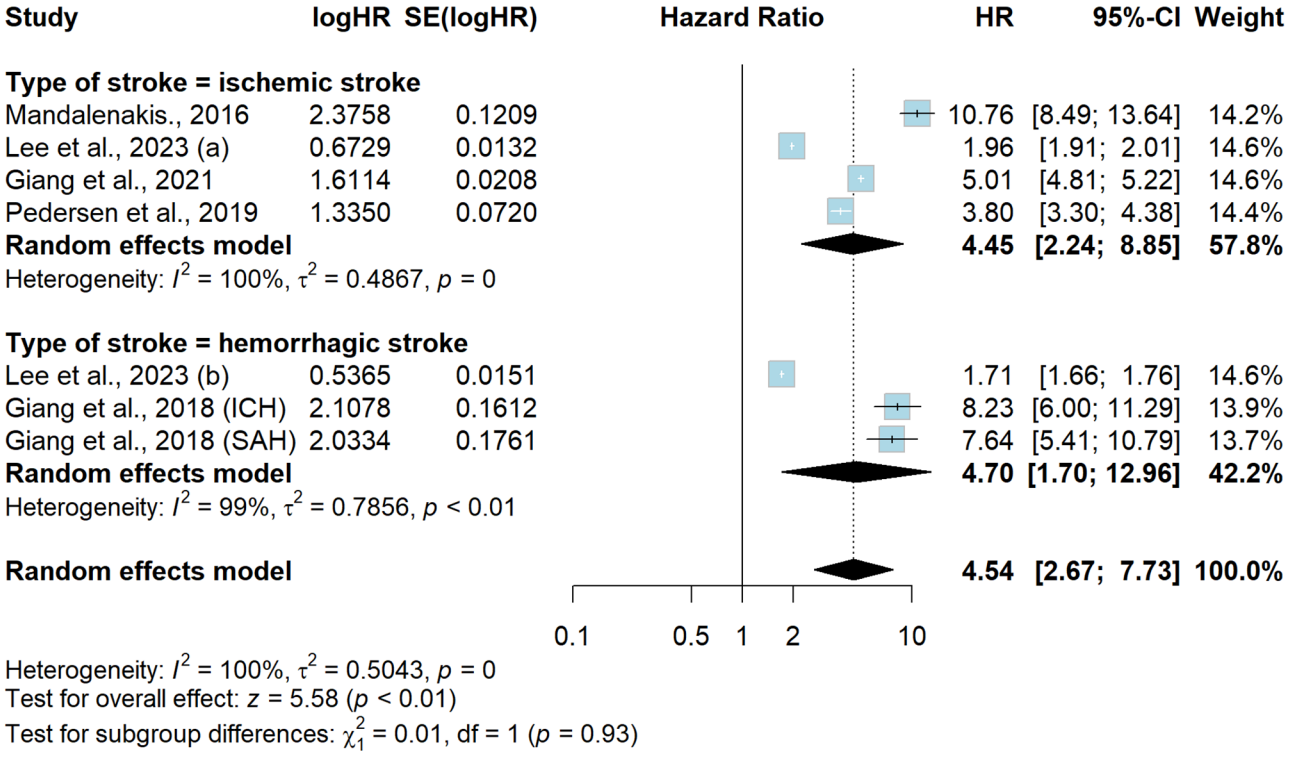


Fig. 3 Subgroup analysis of by the type of stroke

(simple or severe) as a predictor of stroke rather than thromboembolic phenomena [38]. Our current analysis indicates a 4.5-fold increase in ischemic stroke risk, consistent with Pedersen et al. [28]. However, Holmgren et al. attributed the risk primarily to atrial fibrillation, excluding shunt or valvular issues, resulting in a relatively lower HR in their depiction. Fox et al. further emphasized the issue, finding a 19-fold increase in stroke risk among CHD patients, corroborating our results [39].

Escalated stroke risk affiliated with dysrhythmias in CHD was anomalous disarray in the conduction system and anatomical variation offering competitive challenges for its dissolution. Not limited to this, turbulent blood flow in dilated heart chambers provokes pro-coagulants prevailing thromboembolism which is postulated to be a root cause for anoxic brain injury with an ultimate stroke presentation [40]. With hyperviscosity cascade valvular endothelium under stress of congenital malformation accumulates the predisposition for infective endocarditis followed by slow but progressive cerebrovascular changes ending with a stroke of newer onset [41, 42]. The alternating shorter recovery period with successive stroke events may offset the qualitative life, raising mortalities among such patients. Volume pressure variations based on the congenital evolution of cardiac structures may impose compensatory mechanisms in the vascular territory of the brain enhancing the stroke risk as well [31]. Despite an aggressive pre-amptive anti-coagulation scheme, co-existing mechanistic links secondary to paradoxical embolism heighten stroke events claiming to be of anatomical origin. Persistent shunts, coarctation of the aorta, and various surgical or medical interventions introduced at the earliest to apprehend morbidity were forecasted to mount hemorrhagic stroke among CHD patients [25]. Several mechanisms and risk factors associated with developing stroke in patients with CHD.

An Australian cohort study indicated that ischemic stroke (2.3%) is more common than hemorrhagic stroke (0.4%) in young adults, supporting our findings on the incidence of hemorrhagic stroke [43]. Our analysis suggested a higher risk of ischemic stroke in the young CHD population. Shunts and left-sided lesions are associated with an increased stroke incidence in CHD patients compared to those without CHD [38]. CHD patients exhibit a younger age of ischemic stroke onset, with a risk factor of 3.8 as per Pedersen et al. [28], rising by 1.6 times with age (>60 years), which is consistent with Pedersen et al. [28]. The risk of ischemic stroke increases with age and is less pronounced in older than in younger patients. Lanz et al. reported a 9- to 12-fold higher risk in patients under 55, with a smaller increase of 2 to 4 times for those aged 55–64 [44]. Additional studies showed a tenfold risk increase in younger age groups [29] and a 16-fold increase in findings by Giang et al., supporting our pooled analysis [27]. While the higher risk at younger ages aligns with our data, Lanz et al.'s results lack cohort comparison, and Mandalenakis et al. focused on children and young adults.

Our results indicate that CHD-associated hemorrhagic stroke was statistically significant but occurred less frequently than ischemic stroke. Observational studies, such as those by Lanz et al., reported a hemorrhagic stroke incidence of only 14 per 100,000 person-years [44], while another study documented 1.18 per 10,000 person-years [25]. Swedish data have identified non-conotruncal defects and coarctation of the aorta as primary lesions for ICH and SAH, respectively [25]. Unlike IS, which occurs in young adults, hemorrhagic stroke was observed in children with ICH and SAH at ages 4 and 1 year, respectively [43].

In our study, adults showed a higher incidence than the combined incidence in adults and children. Advances in cardiac intervention have improved childhood survivability but have increased the risk of thromboembolic events [45]. Surgical interventions during childhood often lead to perioperative thromboembolic phenomena, with some strokes occurring early and others occurring after 5 years of age [46, 47]. This may explain our findings that heart failure, cardiomegaly, and hypertension become more pronounced in adulthood. A recent study also reported a 46% higher stroke incidence in adults, attributed to previous surgical interventions, especially shunt procedures (OR 4.20; 95% CI 1.36–12.9) and mechanical valve issues (OR 2.67; 95% CI 1.09–6.50) [38]. Previous studies also support a low absolute but high relative risk of stroke with advancing age [48].

Despite being statistically significant, European regions were hypothesized to have a higher stroke risk than Asia and USA as revealed by our subgroup analysis. The higher incidence of cerebrovascular accidents, up to 0.05% annually, in Europe could explain the increased stroke risk among patients with CHD [49]. Lifestyle, genetics, early diagnosis, economic status, and racial differences across regions may also contribute to stroke risk [50]. The inclusion of nearly six studies from Europe in our analysis may have skewed the results.

The limitations of our study must be acknowledged to pave the way for innovative future strategies; about 50% of the data in our analysis come from Europe, raising concerns about the generalizability of our findings. Also, the included studies did not specify the types of CHD in the patient populations, making it unfeasible to perform a subgroup analysis based on CHD type. Additionally, studies using inpatient registers without documenting variables such as blood pressure or medications may affect the assessment of individual stroke-related risk [25]. Misdiagnosis, variable classification, or coding issues in register-based data can distort the results,

raising concerns about its application. Survivorship bias due to insufficient follow-up data, as noted by Giang et al., is another limitation [25, 27].

Conclusion

In conclusion, this meta-analysis demonstrates a significantly elevated risk of stroke in patients with CHD compared to controls. The findings indicate that stroke risk varies regionally, with higher rates observed in Europe than in Asia and USA and highlights the need for targeted monitoring and management strategies in this vulnerable population. Further research is warranted to explore specific CHD types and their associated stroke risks, addressing limitations noted in existing studies.

Abbreviations

CHD	Congenital heart disease
HR	Hazard ratios
CI	Confidence intervals
ACHD	Adults with congenital heart disease
AF	Atrial fibrillation
NOS	Newcastle-Ottawa Scale
ASD	Atrial septal defects
ICH	Intracerebral hemorrhage
SAH	Subarachnoid hemorrhage

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12883-024-03967-8.

Supplementary Material 1

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Author contributions

R.M.O.: Study concept, Design, Data extraction, Analysis, Scientific writing and Drafting of the manuscript. M.I.: Analysis, Scientific writing and Drafting of the manuscript. H.J., S.A., H.H.H., B.B.K., A.O.A., A.K.B., B.A., M.A.T., A.M.H., H.H.: Scientific writing and Drafting of the manuscript. O.A.: Supervision, Validation, Editing.

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Data availability

Data is provided within the manuscript or supplementary information files.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Author details

[1]Faculty of medicine, Jordan University of Science and Technology, Irbid, Jordan
[2]Lahore General Hospital Lahore, Lahore, Punjab, Pakistan
[3]Department of Internal Medicine, All India Institute of Medical Sciences (AIIMS), Jodhpur, India
[4]King Hussein Cancer Center, Amman, Jordan
[5]Internship, Princess Basma Teaching Hospital, Irbid, Jordan
[6]Applied Science Research Center, Applied Science Private University, Amman, Jordan
[7]Faculty of Medicine, Ain Shams University, Cairo, Egypt
[8]Faculty of Medicine, Al Yarmouk University, Irbid, Jordan
[9]School of Medicine, University of Jordan, Amman, Jordan
[10]Faculty of Medicine, Al- Balqa' Applied University, Salt, Jordan
[11]Faculty of Medicine, University of Kalamoon, Al-Nabk, Syria
[12]Department of Pediatrics of Saint Louis University, School of Medicine, SSM Health Cardinal Glennon Children's Hospital, Missouri, MO, USA

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