BMC Gastroenterology

SYSTEMATIC REVIEW Open Access

Risk of stroke in patients with inflammatory bowel disease: a systematic review and meta-analysis

Chao Luo[1], Lingpei Liu[1], Di Zhu[1], Zuanmin Ge[1], Yuehua Chen[1] and Feng Chen[2,3*]

Abstract

Background Current studies suggest a potential link between inflammatory bowel disease (IBD), comprising Crohn's disease (CD) and ulcerative colitis (UC), and cardiovascular diseases, such as stroke. This study aimed to assess the risk of stroke in IBD patients compared to general population.

Methods Systematic search was done in PubMed, Embase, CENTRAL, Scopus, and CINAHL databases for studies published till September 2023. Using a random-effects model, the hazard ratios (HRs) with 95% confidence intervals (CIs) for stroke occurrence were calculated. Subgroup analyses were done to estimate pooled HR with 95%CI for CD, UC, and overall IBD cases separately. Publication bias assessment was done by Begg's and Egger's tests.

Results Thirteen studies with 2,802,955 participants were included. IBD patients in general had significantly higher risk of stroke, with HR of 1.30 [95% CI 1.21–1.39]. Subgroup analysis demonstrated an HR of 1.35 [95% CI 1.22–1.49] for CD and 1.15 [95% CI 1.09–1.22] for UC. Substantial heterogeneity was detected across studies, with no substantial publication bias. Sensitivity analyses affirmed the stability of findings.

Conclusion IBD in general, and Crohn's disease in particular are associated with significantly higher risk of stroke. Our findings further emphasize the importance of cardiovascular risk assessment and management strategies in IBD care.

Protocol registration PROSPERO, CRD42023470602.

Keywords Crohn's disease, Inflammatory bowel disease, Meta-analysis, Stroke, Ulcerative colitis

Introduction

Inflammatory bowel disease (IBD), which includes Crohn's disease (CD) and ulcerative colitis (UC), is a chronic and often relapsing inflammatory gastrointestinal condition. Over the past few decades, research has provided a more comprehensive understanding of the multifaceted interplay between genetic, environmental, microbial, and immunological factors contributing to the pathogenesis of IBD [1, 2]. While the primary manifestations of IBD are localized to the gastrointestinal tract, IBD patients are at higher risk of developing numerous systemic complications [3]. Recent studies suggested that IBD patients may be at high risk of developing

*Correspondence:
Feng Chen
lcyiyi@163.com
[1]Department of General Practice, Affiliated Jinhua Hospital, Zhejiang University School of Medicine, Jinhua Municipal Central Hospital, Jinhua, Zhejiang 321000, China
[2]Department of Neurosurgery, Affiliated Jinhua Hospital, Zhejiang University School of Medicine, Jinhua Municipal Central Hospital, Jinhua, Zhejiang 321000, China
[3]Department of Neurosurgery, Affiliated Jinhua Hospital, Zhejiang University School of Medicine, Jinhua Municipal Central Hospital, No. 365, Renmin East Road, Jinhua City, Zhejiang Province 321000, China

cardiovascular diseases (CVD) and ischemic stroke [4, 5], one of the leading causes of morbidity and mortality worldwide [6]. Several proposed mechanisms by which IBD might contribute to the elevated stroke risk include chronic systemic inflammation, coagulation abnormalities, and the use of certain medications that have cardiovascular side effects [7, 8].

Chronic systemic inflammation, a hallmark of IBD, plays a pivotal role in the development and progression of atherosclerosis, which is a primary underlying cause of ischemic stroke [9]. The chronic inflammatory state in IBD has been associated with the increase in the levels of circulating proinflammatory cytokines, acute phase reactants, and endothelial dysfunction, all of which play key roles in atherogenesis [10, 11]. In addition, patients with IBD often present with hypercoagulability, attributed to increased platelet activation, elevated levels of fibrinogen, and various other clotting factors, further predisposing them to thrombotic events, including stroke [12]. Moreover, current IBD therapies, such as immunomodulators, corticosteroids, anti-tumour necrosis factor-α (TNFα) therapies, have potential cardiovascular side effects. Corticosteroids, for instance, are associated with hypertension, hyperglycemia, and dyslipidemia– all of which are established risk factors for stroke [13]. Studies provided mixed results between anti-TNFα therapies and risk of thromboembolic events (both increased and reduced risk) [14, 15]. Therefore, understanding the potential relationship between IBD and stroke is of paramount importance, not only for clinicians managing patients with IBD but also for public health planning and preventative strategies. While previous meta-analyses have consistently reported a modest increase in the risk of cerebrovascular diseases among patients with IBD, the findings from individual studies have shown considerable variability. While some studies report a significant increase in stroke risk among IBD patients, others have found no such association [16–18]. Such disparities could be attributed to differences in study design, sample size, confounding variables, or geographic and population differences.

The need for this systematic review stems from the critical gaps and inconsistencies in the current evidence regarding the association between IBD and stroke risk. While prior evidence syntheses have explored this relationship, they often fail to provide a clear and comprehensive understanding of the distinct contributions of CD and UC to stroke risk. Our work extends the current literature in two key ways. First, By incorporating a broader range of studies and a large pooled sample of over 2.8 million participants, our review provides robust estimates of stroke risk stratified by IBD subtypes. Second, we employ rigorous statistical methods to account for heterogeneity across studies and ensure the reliability of our findings. Unlike previous reviews that primarily reported associations, our meta-analysis synthesizes these findings with a focus on clinical implications, emphasizing the need for cardiovascular risk assessment in routine IBD management. This nuanced understanding not only addresses discrepancies in the existing literature but also provides actionable insights for clinicians and policymakers. Hence, this study aims to establish whether patients with IBD have an increased risk of stroke compared to the general population.

Materials and methods

Inclusion criteria

The included studies focused on individuals diagnosed with IBD, regardless of their demographic characteristics such as age, gender, ethnicity, or region. The exposed cohort consisted of patients diagnosed with any type of IBD (CD and UC). The comparison cohort incorporated patients without IBD. The primary objective was to compare the incidence of stroke between IBD and non-IBD patients. The included studies were cohort or case-control study in English, published from the inception of database until September 2023.

Information sources and search strategy

An extensive search was conducted in PubMed, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), Scopus, and CINAHL databases. Reference sections of relevant studies and reviews were manually searched. We combined terms related to "inflammatory bowel disease", "Crohn's disease", "ulcerative colitis", and "stroke", harnessing both Medical Subject Headings (MeSH) and applicable keywords. The search strategy for individual databases are provided in Supplementary File. The search was done as per PRISMA guidelines [19].

Study selection and data extraction

Two independent reviewers screened titles and abstracts of the retrieved articles, followed by full-text examination of the selected studies. Consensus was achieved either via discussions or by consulting a third reviewer. A predefined template was used by the same set of reviewers to independently extract relevant data including attributes of the study (authorship, year, design, context), participant details (sample size, age range, gender distribution, disease severity), intervention specifics, and results. Information related to funding and potential conflicts of interest were also noted.

Risk of bias assessment

Newcastle Ottawa Scale [20] was used to assess the risk of bias in observational studies. Studies scoring between 0 and 3 were deemed high-risk, 4–6 indicated moderate risk, and 7–9 were viewed as low risk of bias.

Statistical analysis

We analyzed data from studies that exhibited sufficient uniformity in terms of methodology, subjects, interventions, and results, and used a random-effects model to compensate for potential variations across the studies. The pooled effect measures were presented as hazard ratios (HRs) with 95% confidence interval (CI) for the outcome, and data were visualized by forest plots. Subgroup analysis was performed to estimate pooled HR with 95%CI separately for CD and UC patients.

Heterogeneity was quantified by I^2 statistic [21], which describes the percentage of variation across studies that is due to heterogeneity rather than chance. The interpretation of I^2 followed standard thresholds: low heterogeneity ($I^2 \leq 25\%$), moderate heterogeneity (I^2 between 26% and 50%), substantial heterogeneity (I^2 between 51% and 75%), and considerable heterogeneity ($I^2 > 75\%$). Publication bias was assessed by funnel plots and Begg's and Egger's regression tests.

Sensitivity analyses were conducted to evaluate the robustness and stability of the findings by systematically excluding individual studies one at a time and reassessing the pooled HRs. This approach was used to identify whether any single study disproportionately influenced the overall effect size. Additionally, sensitivity analyses were performed to explore the impact of study quality, by comparing results after excluding studies with moderate or high risk of bias. These analyses were pre-specified in the protocol to ensure transparency and to address potential sources of heterogeneity and bias in the pooled estimates. The results of the sensitivity analyses were graphically represented, highlighting the consistency of the findings across various scenarios. All the analysis was performed using STATA version 14.2.

Results

Study screening

Initial search across databases identified 1,083 records. Of them, 321 were removed as duplicates. Of the 762 records screened, additional 704 were excluded. Resulting 58 full-text articles were assessed for eligibility. Ultimately, 13 studies met the inclusion criteria, while 45 were excluded due to varying participants, exposures, or overlapping data (Fig. 1) [16, 17, 22–32].

Characteristics of the included studies

The included studies were published between 1984 and 2019 in various countries including Spain, Canada, South Korea, the UK, Taiwan, France, Denmark, the USA, Sweden, and Germany. Of 13 studies, 10 were cohort studies, 2 retrospective cohort studies, and 1 nested case-control study, encompassing a total sample size of over 2.8 million participants. The follow-up duration varied among studies, ranging from 3.4 to 71.16 years. The mean age of participants across studies ranged from 36.5 to 56 years. Gender distribution was consistent in most studies (45.1–58.5% females) (Table 1). Risk of bias was low in most (7 out of 13) included studies (Table 2).

Risk of stroke between IBD and non-IBD patients

Data from 13 studies with a total of 2,802,955 participants were analyzed. The pooled HR for stroke in IBD patients compared to non-IBD cohort was 1.30 [95%CI: 1.21–1.39; $p < 0.001$], suggesting a statistically significant increase in the risk of stroke among IBD patients (Fig. 2). The analysis revealed substantial heterogeneity among the studies, as evidenced by the Cochran's Q value of 81.79 (df = 12, $p < 0.001$) and the I^2 of 85.3%.

Subgroup analysis

The pooled HR for stroke in CD patients compared to general population group was 1.35 [95% CI 1.22–1.49; $p < 0.001$], suggesting that CD is associated with a statistically significant increase in the risk of stroke (Fig. 3). The analysis revealed substantial heterogeneity among the studies, as evidenced by the Cochran's Q value of 62.22 (df = 8, $p < 0.001$) and the I^2 of 87.1%.

The pooled HR for stroke in UC patients compared to non-UC individuals was 1.15 [95%CI: 1.09–1.22; $p < 0.001$], indicating a statistically significant increase in the risk of stroke in the UC cohort (Fig. 4). Moderate heterogeneity was detected among the studies, as reflected by the Cochran's Q value of 23.56 (df = 8, $p = 0.003$) and the I^2 statistic, which was 66%.

Publication bias assessment

Begg's test that assesses funnel plot asymmetry, was conducted to evaluate the publication bias using an adjusted Kendall's Score. The test resulted in a score (P-Q) of 26 with a standard deviation of 16.39, the calculated z-value of 1.59 and a corresponding p-value of 0.113. After continuity correction, the z-value was adjusted to 1.53 with a p-value of 0.127, suggesting no strong evidence of publication bias based on the Begg's test.

The Egger's test was also employed to assess small-study effects which could be indicative of publication bias (Fig. 5). Coefficient value was 0.124 (Standard Error = 0.04) with a statistically significant t-value of 2.90 ($p = 0.014$). Coefficient value was 2.27 (Standard Error = 1.09) with a t-value of 2.08. The p-value for this coefficient was 0.06, suggesting no significant bias. The significant slope coefficient in the Egger's test indicates the presence of small-study effects. However, one should be cautious as this could be attributed to factors other than publication bias, such as true heterogeneity.

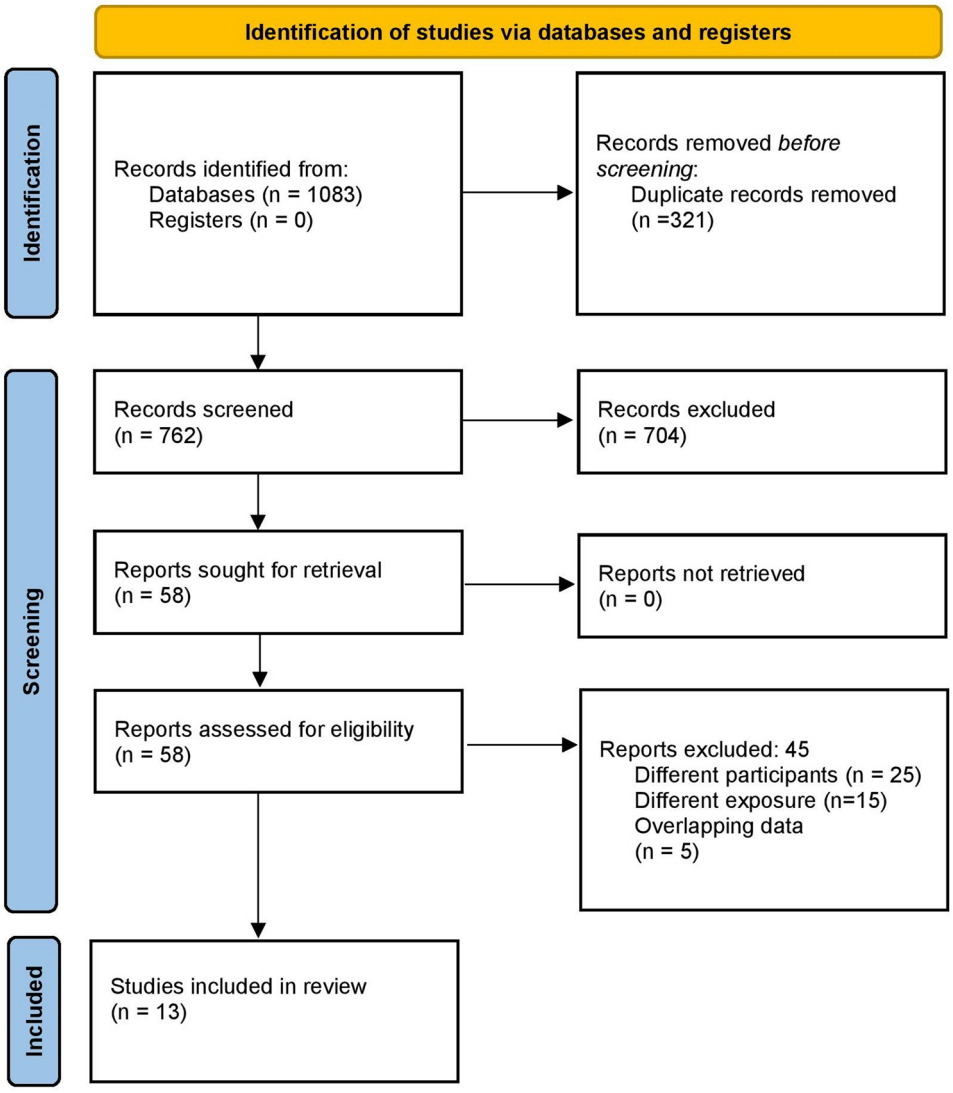

Fig. 1 PRISMA flowchart

Sensitivity analysis

In the sensitivity analysis, each study was individually omitted to assess its impact on the overall effect estimate. When each study was omitted, the pooled estimates ranged from 1.20 to 1.24, indicating moderate variability. Despite this, the overall combined effect, with all studies included, was 1.22 [95% CI: 1.19–1.24], showing consistently elevated risk across the analysis (Fig. 6).

Discussion

This comprehensive meta-analysis aimed to investigate the association between IBD and the risk of stroke, and further stratified the analysis based on the IBD subtypes. Our results have demonstrated a statistically significantly increased risk of stroke in patients with IBD compared to those without this condition. Specifically, IBD patients had 30% higher risk of stroke compared to the general population. The risk was even higher for CD patients (35%) while UC subgroup demonstrated only 15% increase in the risk of stroke.

Our findings align with the growing body of literature highlighting the systemic implications of IBD beyond the confines of the gastrointestinal tract. A large-scale study by Schicho et al. [33] have underlined the increased cardiovascular risks among IBD patients, which is consistent with our results and further strengthen the importance of comprehensive care in IBD patients. While cardiovascular implications of IBD were a focus of several studies, the nature and magnitude of this effect is still unclear. A recent meta-analysis by Jaiswal et al. [34] demonstrated that although IBD was associated with the overall higher risk of CVD, the tendency towards specific events, such as stroke or myocardial infarction, varied considerably based on the study design and populations. Our findings

Table 1 Characteristics of included studies (*N* = 13)

Author and year	Location	Study period	Study design	Study setting	Sample size	Study participants (exposure group)	Follow-up duration (in years)	Mean age at the time of study recruitment (in years)	Gender distribution Female (%)	Risk of bias
Baena-Díez 2018	Spain	2007–2012	Prospective Cohort study	Population based	962,033	Any IBD	NR	56	56	Low
Bernstein 2008	Canada	1984–2003	Retrospective Matched cohort study	Population based	88,561	Both CD & UC patients	19	36.5	58.5	High
Choi 2019	South Korea	2006–2009	Retrospective Cohort study	Population based	149,908	Both CD & UC patients	8.4	44	46.2	Low
Dregen 2014	United Kingdom	2002–2013	Prospective cohort study	Population based	393,682	Both CD & UC patients	NR	47	49	High
Huang 2014	Taiwan	1998–2011	Retrospective Cohort study	Population based	92,360	Both CD & UC patients	71.16	44.8	45.1	Low
Keller 2014	Taiwan	2001–2005	Retrospective Cohort study	Population based	2579	UC patients only	NR	51.64	47.8	High
Keller 2015	Taiwan	2001–2005	Retrospective Cohort study	Population based	16,545	CD patients only	NR	51.15	53.47	High
Kirchgesner 2017	France	2008–2013	Retrospective Cohort study	Population based	10,395	Both CD & UC patients	3.4	49	50.5	High
Kristensen 2014	Denmark	1996–2011	Retrospective Cohort study	Population based	260,774	Both CD & UC patients	NR	NR	NR	Low
Setyawan 2022	USA	2014–2018	Retrospective cohort study	Population based	69,374	Any IBD	NR	49	54.4	High
Sun 2023	Sweden	1969–2019	Retrospective cohort study	Population based	491,993	Both CD & UC patients	12	43.3	48.4	Low
Tanislav 2021	Germany	2000–2015	Retrospective cohort study	Population based	23,894	Both CD & UC patients	15	47.2	45.5	Low
Zoller 2012	Sweden	1987–2008	Prospective Cohort study	Population based	250,686	Both CD & UC patients	NR	NR	55.1	Low

IBD– Inflammatory bowel disease; CD– Crohn's disease; UC– Ulcerative Colitis NR-Not reported; USA– United States of America

Table 2 Risk of bias

Author and year	Selection	Comparability	Outcome	Risk of bias
Baena-Díez 2018	Low	Low	Low	Low
Bernstein 2008	High	Low	High	High
Choi 2019	Low	Low	Low	Low
Dregen 2014	Low	High	High	High
Huang 2014	Low	Low	Low	Low
Keller 2014	High	High	High	High
Keller 2015	High	High	Low	High
Kirchgesner 2017	High	High	High	High
Kristensen 2014	Low	Low	Low	Low
Setyawan 2022	High	High	High	High
Sun 2023	Low	Low	Low	Low
Tanislav 2021	Low	Low	Low	Low
Zoller 2012	Low	Low	Low	Low

IBD– Inflammatory bowel disease; CD– Crohn's disease; UC– Ulcerative Colitis NR-Not reported; USA– United States of America

specifically focused on the risk of stroke, thereby filling this critical gap in the literature.

The increased risk of stroke in IBD patients may be explained by different mechanisms. Inflammation remains central to the pathogenesis of both IBD and atherosclerosis. Elevated levels of inflammatory markers like C-reactive protein, which have been consistently reported in IBD patients [35], play a pivotal role in endothelial dysfunction, accelerating atherogenesis. In addition to inflammation, the prothrombotic state induced by chronic inflammation in IBD might also contribute the increased risk of stroke. This risk may be further exacerbated by the elevated homocysteine levels, observed in some IBD patients due to malabsorption [36]. Additionally, current studies suggest the role of gut microbiota in the pathogenesis of both IBD and vascular diseases. Emerging evidence points towards microbial dysbiosis in IBD patients as a potential factor aggravating systemic inflammation and, consequently, atherosclerotic processes. Previous study indicated a potential link between specific gut bacteria, enhanced gut permeability, and subsequent low-grade systemic inflammation that may predispose IBD patients to vascular diseases [37]. Such findings pave the way for investigating therapeutic interventions targeting gut microbiota to alleviate cardiovascular risks in IBD patients.

A major strength of our review is large sample size with various demographics that increases ggeneralizability of our results. Moreover, we evaluated the risk based on

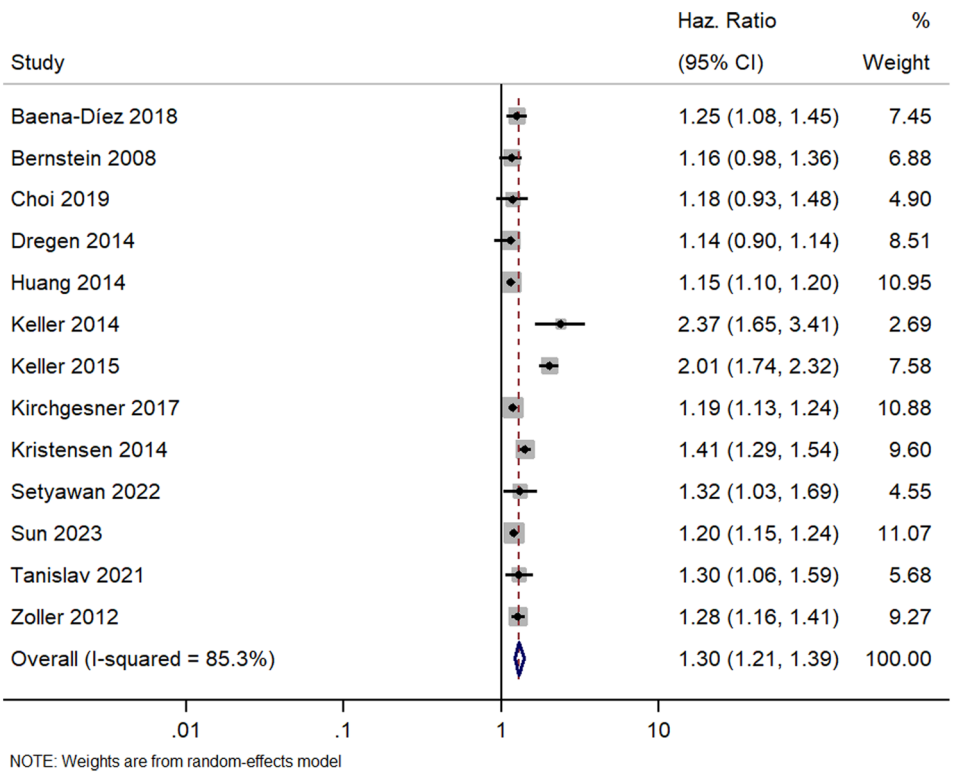

Fig. 2 Forest plot showing the risk of stroke between inflammatory bowel disease and non-inflammatory bowel disease patients

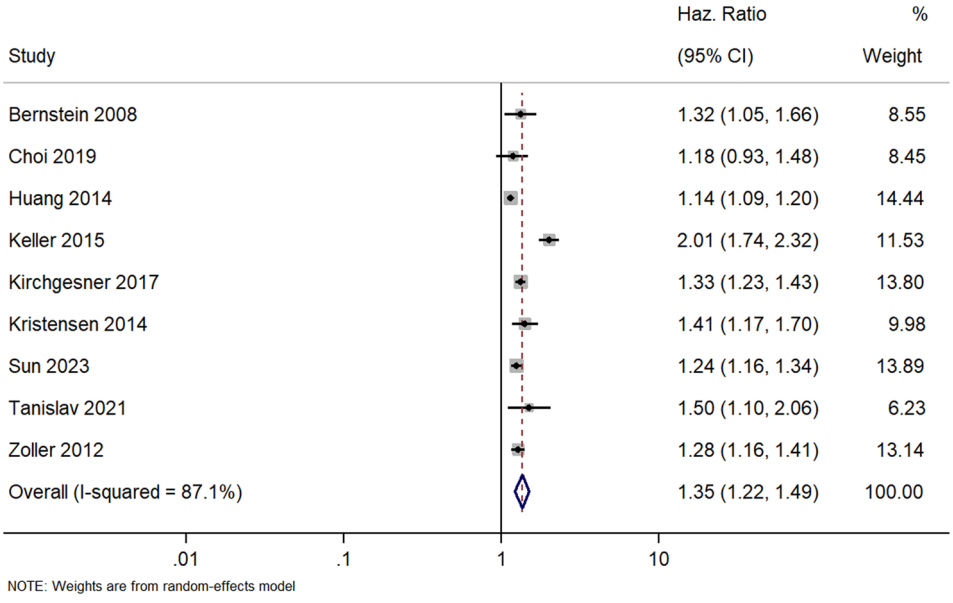

Fig. 3 Forest plot showing the risk of stroke between Crohn's disease and non-Crohn's disease patients

IBD subtypes, offering granularity to the overall understanding of the association between IBD and stroke. Our review offers a more comprehensive evaluation of CDI-associated outcomes in IBD patients by incorporating a broader range of outcomes, including hospitalization duration, colectomy rates, and specific complications, which have not been synthesized in prior reviews. However, our study has limitations. The substantial heterogeneity among the included studies underscores the potential presence of other confounding factors, not adjusted universally across the studies. Despite a comprehensive search strategy, publication bias cannot be

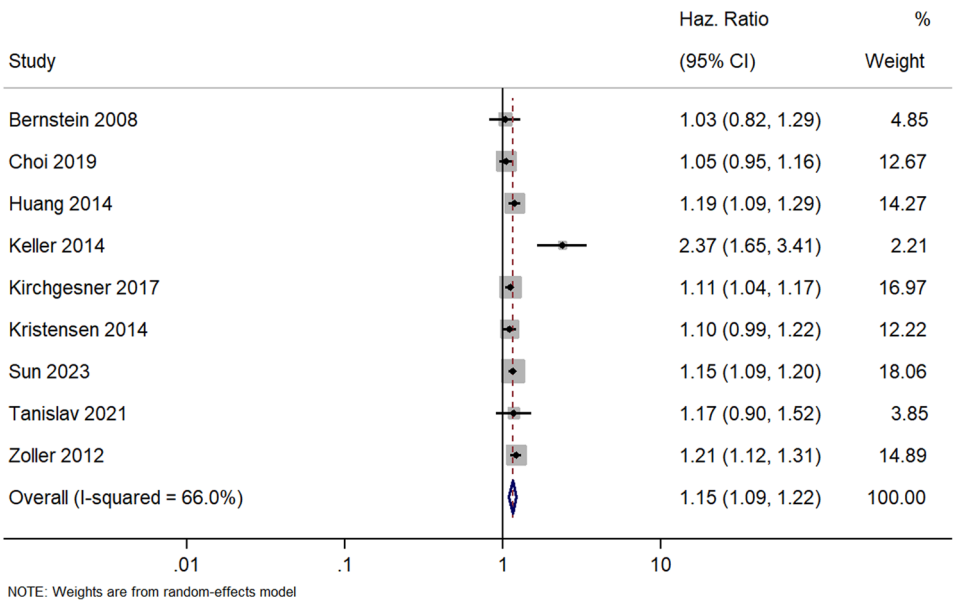

Fig. 4 Forest plot showing the risk of stroke between ulcerative colitis and non-ulcerative colitis patients

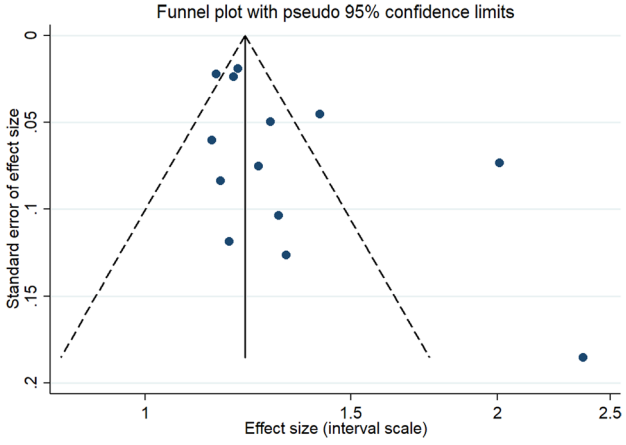

Fig. 5 Funnel plot for publication bias

entirely ruled out. Lastly, the absence of patient-level data prevented us from conducting a more detailed subgroup analysis based on age, gender, or comorbidities. Moreover, while our review encompassed a significant number of participants, the geographical distribution of the included studies was not explicitly stated, potentially leaving certain populations underrepresented. The diversity of healthcare systems, variations in IBD management strategies, and differing baseline cardiovascular risks across populations can introduce additional layers of complexity, which our study was not equipped to dissect. Additionally, past research suggested that long-lasting IBD and recurrent flares might contribute to the increased risk of vascular events [38]. Due to the lack of such granular data in the included studies, our meta-analysis did not account for the impact of disease duration on the risk of stroke. Future studies are needed to further investigate this relationship.

Our study has important implications for clinicians, as it underscores the importance of a holistic approach to managing IBD. Given the elevated risk of stroke, routine cardiovascular risk assessments might be beneficial for these patients. Patients may be advised of lifestyle changes, including increased physical activity, balanced diet, and smoking cessation. Furthermore, the use of certain medications like corticosteroids, which have been associated with an elevated cardiovascular risk [39], should be judicious, weighing their benefits against potential long-term risks.

Our results suggest several possible directions for future research, such as understanding the temporal relationship between IBD diagnosis and the onset of stroke, and the role of specific IBD therapies in modulating this risk. Multicentre trials with a more standardized approach to adjusting for potential confounders will further consolidate our findings and aid in framing more evidence-based guidelines for IBD management.

Our findings also signal the need for interdisciplinary collaboration. Gastroenterologists should perhaps work in tandem with cardiologists to develop a more integrated care model for IBD patients. Such collaborations could facilitate more comprehensive screening protocols and even joint clinics where cardiovascular risk mitigation becomes an integral part of IBD management. This approach is not novel; integrated care models have shown promising results in diseases like diabetes, where endocrinologists and cardiologists collaborate to manage the multifaceted risks effectively.

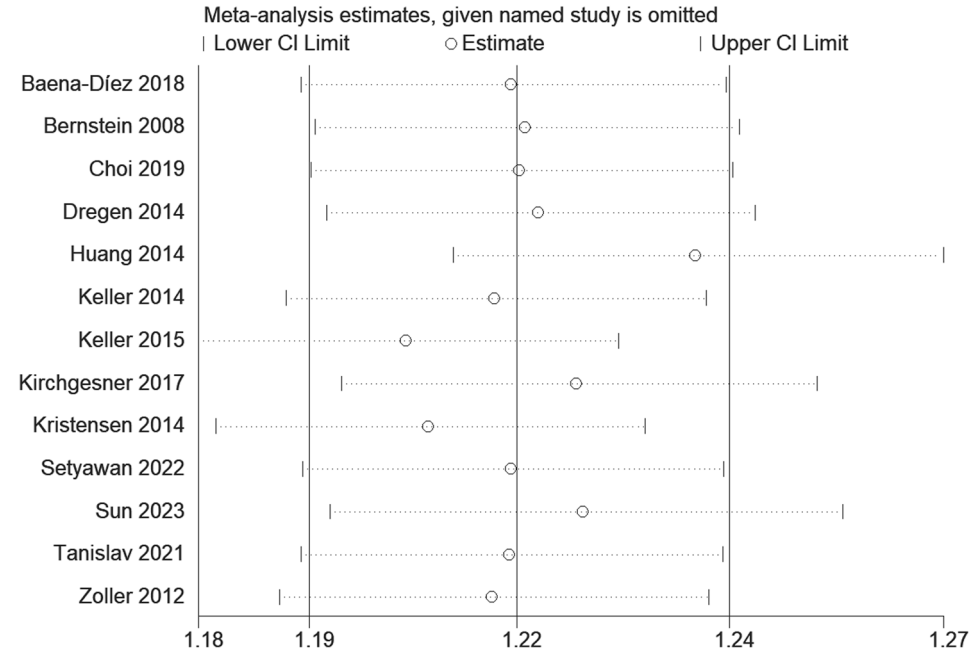

Fig. 6 Sensitivity analysis plot

Conclusion

In summary, our meta-analysis robustly confirms the increased risk of stroke in IBD patients, further underscoring the systemic implications of this primarily gastrointestinal disease. Comprehensive care of IBD patients, encompassing regular cardiovascular risk assessments, can be pivotal in mitigating this risk.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12876-025-03702-8.

Supplementary Material 1

Supplementary Material 2

Acknowledgements
Not applicable.

Author contributions
CL conceived and designed the study. LL, DZ, ZG, YC and FC collected the data and performed the analysis. CL was involved in the writing of the manuscript. All authors have read and approved the final manuscript.

Funding
This work was supported by Jinhua City Science and Technology Plan Project Social Development Key Project(2019-3-007).

Data availability
All data generated or analysed during this study are included in this published article and its 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.

Received: 11 July 2024 / Accepted: 17 February 2025
Published online: 25 February 2025

References

1. Jostins L, Ripke S, Weersma RK, Duerr RH, McGovern DP, Hui KY, et al. Host-microbe interactions have shaped the genetic architecture of inflammatory bowel disease. Nature. 2012;491:119–24.
2. Molodecky NA, Soon IS, Rabi DM, Ghali WA, Ferris M, Chernoff G, et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. Gastroenterology. 2012;142:46–54..e42; quiz e30.
3. Vavricka SR, Schoepfer A, Scharl M, Lakatos PL, Navarini A, Rogler G. Extraintestinal manifestations of inflammatory bowel disease. Inflamm Bowel Dis. 2015;21:1982–92.
4. Singh S, Singh H, Loftus EV, Pardi DS. Risk of cerebrovascular accidents and ischemic heart disease in patients with inflammatory bowel disease: a systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2014;12:382–93..e1: quiz e22.
5. Feng W, Chen G, Cai D, Zhao S, Cheng J, Shen H. Inflammatory bowel disease and risk of ischemic heart disease: an updated Meta-Analysis of cohort studies. J Am Heart Assoc. 2017;6:e005892.
6. Benjamin EJ, Muntner P, Alonso A, Bittencourt MS, Callaway CW, Carson AP, et al. Heart disease and stroke Statistics-2019 update: A report from the American heart association. Circulation. 2019;139:e56–528.
7. Zanoli L, Rastelli S, Inserra G, Lentini P, Valvo E, Calcagno E, et al. Increased arterial stiffness in inflammatory bowel diseases is dependent upon inflammation and reduced by Immunomodulatory drugs. Atherosclerosis. 2014;234:346–51.
8. Guan Q. A comprehensive review and update on the pathogenesis of inflammatory bowel disease. J Immunol Res. 2019;2019:7247238.
9. Libby P, Ridker PM, Hansson GK. Progress and challenges in translating the biology of atherosclerosis. Nature. 2011;473:317–25.

10. Scaldaferri F, Pizzoferrato M, Gerardi V, Lopetuso L, Gasbarrini A. The gut barrier: new acquisitions and therapeutic approaches. J Clin Gastroenterol. 2012;46(Suppl):S12–17.
11. Danese S, de la Motte Cd C, Fiocchi C. Platelets in inflammatory bowel disease: clinical, pathogenic, and therapeutic implications. Am J Gastroenterol. 2004;99:938–45.
12. Zezos P, Kouklakis G, Saibil F. Inflammatory bowel disease and thromboembolism. World J Gastroenterol. 2014;20:13863–78.
13. Ford AC, Bernstein CN, Khan KJ, Abreu MT, Marshall JK, Talley NJ, et al. Glucocorticosteroid therapy in inflammatory bowel disease: systematic review and meta-analysis. Am J Gastroenterol. 2011;106:590–9. quiz 600.
14. Olivera PA, Zuily S, Kotze PG, Regnault V, Al Awadhi S, Bossuyt P, et al. International consensus on the prevention of venous and arterial thrombotic events in patients with inflammatory bowel disease. Nat Rev Gastroenterol Hepatol. 2021;18(12):857–73. https://doi.org/10.1038/s41575-021-00492-8.
15. Grainge MJ, West J, Card TR. Venous thromboembolism during active disease and remission in inflammatory bowel disease: a cohort study. Lancet. 2010;375:657–63.
16. Baena-Díez JM, Garcia-Gil M, Comas-Cufí M, Ramos R, Prieto-Alhambra D, Salvador-González B, et al. Association between chronic immune-mediated inflammatory diseases and cardiovascular risk. Heart. 2018;104:119–26.
17. Dregan A, Charlton J, Chowienczyk P, Gulliford MC. Chronic inflammatory disorders and risk of type 2 diabetes mellitus, coronary heart disease, and stroke: a population-based cohort study. Circulation. 2014;130:837–44.
18. Card TR, Zittan E, Nguyen GC, Grainge MJ. Disease activity in inflammatory bowel disease is associated with arterial vascular disease. Inflamm Bowel Dis. 2021;27:629–38.
19. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;:n71.
20. Lo CK-L, Mertz D, Loeb M. Newcastle-Ottawa scale: comparing reviewers' to authors' assessments. BMC Med Res Methodol. 2014;14:45.
21. Higgins J, Thomas J, Chandler J, Cumpston M, Li T, Page M et al. Cochrane Handbook for Systematic Reviews of Interventions. https://training.cochrane.org/handbook. Accessed 18 Nov 2023.
22. Kristensen SL, Lindhardsen J, Ahlehoff O, Erichsen R, Lamberts M, Khalid U, et al. Increased risk of atrial fibrillation and stroke during active stages of inflammatory bowel disease: a nationwide study. Europace. 2014;16:477–84.
23. Keller JJ, Wang J, Huang Y-L, Chou C-C, Wang L-H, Hsu J-L, et al. Increased risk of stroke among patients with ulcerative colitis: a population-based matched cohort study. Int J Colorectal Dis. 2014;29:805–12.
24. Keller JJ, Wang J, Hwang Y-L, Chou C-C, Wang L-H, Hsu J-L, et al. Increased risk of stroke among patients with Crohn's disease: a population-based matched cohort study. Int J Colorectal Dis. 2015;30:645–53.
25. Tanislav C, Trommer K, Labenz C, Kostev K. Inflammatory bowel disease as a precondition for stroke or TIA: A matter of Crohn's disease rather than ulcerative colitis. J Stroke Cerebrovasc Dis. 2021;30:105787.
26. Huang W-S, Tseng C-H, Chen P-C, Tsai C-H, Lin C-L, Sung F-C, et al. Inflammatory bowel diseases increase future ischemic stroke risk: a Taiwanese population-based retrospective cohort study. Eur J Intern Med. 2014;25:561–5.
27. Sun J, Halfvarson J, Appelros P, Bergman D, Ebrahimi F, Roelstraete B, et al. Long-term risk of stroke in patients with inflammatory bowel disease: A Population-Based, Sibling-Controlled cohort study, 1969–2019. Neurology. 2023;101:e653–64.
28. Choi YJ, Lee DH, Shin DW, Han K-D, Yoon H, Shin CM, et al. Patients with inflammatory bowel disease have an increased risk of myocardial infarction: a nationwide study. Aliment Pharmacol Ther. 2019;50:769–79.
29. Zöller B, Li X, Sundquist J, Sundquist K. Risk of subsequent ischemic and hemorrhagic stroke in patients hospitalized for immune-mediated diseases: a nationwide follow-up study from Sweden. BMC Neurol. 2012;12:41.
30. Setyawan J, Mu F, Zichlin ML, Billmyer E, Downes N, Yang H, et al. Risk of thromboembolic events and associated healthcare costs in patients with inflammatory bowel disease. Adv Ther. 2022;39:738–53.
31. Bernstein CN, Wajda A, Blanchard JF. The incidence of arterial thromboembolic diseases in inflammatory bowel disease: a population-based study. Clin Gastroenterol Hepatol. 2008;6:41–5.
32. Kirchgesner J, Beaugerie L, Carrat F, Andersen NN, Jess T, Schwarzinger M, et al. Increased risk of acute arterial events in young patients and severely active IBD: a nationwide French cohort study. Gut. 2018;67:1261–8.
33. Schicho R, Marsche G, Storr M. Cardiovascular complications in inflammatory bowel disease. Curr Drug Targets. 2015;16:181–8.
34. Jaiswal V, Batra N, Dagar M, Butey S, Huang H, Chia JE, et al. Inflammatory bowel disease and associated cardiovascular disease outcomes: A systematic review. Med (Baltim). 2023;102:e32775.
35. Liu D, Saikam V, Skrada KA, Merlin D, Iyer SS. Inflammatory bowel disease biomarkers. Med Res Rev. 2022;42:1856–87.
36. Ratajczak AE, Szymczak-Tomczak A, Rychter AM, Zawada A, Dobrowolska A. Krela-Kaźmierczak I. Does folic acid protect patients with inflammatory bowel disease from complications?? Nutrients. 2021;13:4036.
37. Rahman MM, Islam F, -Or-Rashid MH, Mamun AA, Rahaman MS, Islam MM, et al. The gut microbiota (Microbiome) in cardiovascular disease and its therapeutic regulation. Front Cell Infect Microbiol. 2022;12:903570.
38. Czubkowski P, Osiecki M, Szymańska E, Kierkuś J. The risk of cardiovascular complications in inflammatory bowel disease. Clin Exp Med. 2020;20:481–91.
39. deFonseka AM, Tuskey A, Conaway MR, Behm BW. Antitumor necrosis Factor-α therapy is associated with reduced risk of thromboembolic events in hospitalized patients with inflammatory bowel disease. J Clin Gastroenterol. 2016;50:578–83.

Publisher's note