Meta-Analysis of the Association Between Asthma and the Risk of Stroke

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Introduction: Asthma and stroke share many risk factors. Previous meta-analysis has indicated that asthma is associated with an increased risk of stroke. However, this study were limited by the small number of articles included and the lack of subgroup analyses of different stroke types and different populations. This meta-analysis aimed to synthesize evidence systematically to investigate the impact of asthma on stroke.

Methods: We searched Medline (via PubMed), Web of Science and EMBASE databases and manually identified eligible studies (inception dates to December 25, 2021) that analyzed the association between asthma and stroke. We conducted quality assessment to evaluate the risk of bias of studies and sensitivity analyses to test the robustness of results.

Results: We included 8 cohort studies and 10 cross-sectional studies comprised 3,011,016 participants. We found patients with asthma had a higher risk of stroke than patients without asthma [relative risk (RR): 1.34, 95% confidence interval (CI): 1.21–1.47]. Moreover, asthma significantly increased the risk of ischemic stroke (RR: 1.25, 95% CI: 1.06–1.47) without increasing the risk of hemorrhagic stroke (RR: 1.08, 95% CI: 0.87–1.34). Asthma increased the risk of stroke in both men (RR: 1.20, 95% CI: 1.10–1.32) and women (RR: 1.29, 95% CI: 1.12–1.48) with no significant difference between the sexes. We also found that patients with inactive asthma, child-onset asthma, or no smoking history did not have an increased risk of stroke.

Conclusions: These results supported the finding that asthma could significantly increase the risk of stroke, but this impact was not consistent in different populations.

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INTRODUCTION

Asthma is a common chronic inflammatory disease. Globally, it is estimated that 334 million people have asthma, including children and adults (1). The incidence of asthma continues to increase, particularly in places with a western lifestyle (2), which aggravates the health and financial burden of society.
Patients with asthma have reduced lung function and a high risk of comorbidities. Essentially, asthma is due to chronic airway inflammation, and the main features are airway hyper-reactivity and reversible airway limitation. However, chronic asthmatic inflammation is not limited to the airway, but affects the whole body (3, 4). Consequently, asthma is a risk factor for stroke (5). In addition, asthma and stroke share other risk factors, including smoking and obesity (6, 7).

Stroke is responsible for over 5.5 million deaths annually, and it is estimated that 166 million healthy-life years are lost due to stroke (8). The question of whether asthma increases the risk of stroke is currently unresolved, and it has become a hot topic at the intersection of respiratory medicine and neurology (9, 10).

Considering the growing incidence of asthma and the high disability rate and mortality associated with stroke, there is an urgent need to determine how asthma affects the risk of stroke. Moreover, knowledge about the degree of stroke risk induced by asthma in different populations will assist in developing population-wide interventions. In addition, this knowledge could inform the clinical management of patients with asthma that have high stroke risk.

A previous meta-analysis of 5 cohort studies noted that asthma was associated with an increased risk of stroke (11). However, due to insufficient data in the studies included, that review failed to analyze the stroke risk in different populations with asthma. To avoid these limitations and provide reliable evidence, we conducted a meta-analysis that included cohort studies and cross-sectional studies to investigate the impact of asthma on stroke.

**MATERIALS AND METHODS**

This meta-analysis was conducted according the MOOSE (Meta-Analysis of Observational Studies in Epidemiology) and PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist (Supplementary Table 1), to ensure quality (12). This meta-analysis was previously registered on the International Prospective Registry of Systematic Reviews (PROSPERO Identifier: CRD 42021290745).

**Literature Search**

We searched electronic databases up to December 25, 2021 (PubMed, EMBASE). The detailed search terms are provided in Supplementary Table 2. In addition, to ensure the adequacy of the included studies, we conducted a manual search.

**Selection Criteria and Outcomes of Interest**

We included observational cohort studies with both prospective and retrospective designs. The inclusion criteria were: both asthma and control groups had to be included; the total number of subjects had to be >1,000, to reduce bias; outcome measures had to include an analysis of the association between asthma and stroke; and the data had to include hazard ratios (HRs), relative risks (RRs), odds ratios (ORs), or the number of stroke events in the asthma and control groups.

**Data Abstraction**

The titles and abstracts of eligible studies were analyzed independently by two independent investigators (Z-FL and Z-YA). Disagreements were settled by discussing with a third investigator (Z-HL) to reach a consensus. Then, the reviewers independently assessed the full text of all studies for inclusion, based on the criteria related to population selection, study design, and outcome. The investigators also attempted to contact the corresponding author for information on missing data.

**Assessment of the Risk of Bias**

The risk of study bias and quality were assessed with the Newcastle-Ottawa Scale (NOS) for cohort studies. NOS scores below 6 indicated low quality, NOS scores of 6 or 7 indicated medium quality, and NOS scores above 7 indicated high quality. Two authors (S-CH and M-DH) independently completed the quality assessments. In cases of disagreement, a third investigator (Z-FL facilitated the discussion and made the final decision).

**Data Analysis**

We pooled the data and calculated adjusted HRs, RRs, or ORs with 95% confidence intervals (95% CI). When adjusted estimates were unavailable, we included unadjusted estimates and the number of events to calculate stroke incidence in the asthma and control groups. The $I^2$ statistic was used to evaluate the heterogeneity of the included studies. To address the variability of each outcome of interest, an $I^2 > 50\%$ was defined as significant heterogeneity (13), and we used the random-effects model. Data were analyzed with Stata version 14.0 (Stata Corp., College Station, TX) or Review Manager 5.3 software (2014; The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark).

**Additional Analyses**

We conducted subgroup analyses investigating the risk of stroke of people with asthma in different stroke types (including ischemic stroke and hemorrhagic stroke) and different populations including asthma status, smoking status, gender and age of asthma onset. We also conducted sensitivity analyses to test the robustness of results.

**RESULTS**

Our searches identified 254 articles. After applying the inclusion and exclusion criteria, we included 18 observational studies (9, 14–30) (Figure 1). Among these, 2 studies (21, 22) were identified in the manual search and 16 studies (9, 14–20, 23–30) were identified in the electronic search.
Description of Studies
Among 18 the observational studies included, 10 were cross-sectional studies (21–30). Of these, 2 were cohort studies (21, 28) that did not have outcomes of interest, but reported cross-sectional data on the association between asthma and stroke in the baseline characteristics of the population. The other 8 cross-sectional cohort studies (9, 14–20) included 2 retrospective studies (17, 19) and 6 prospective studies (9, 14–16, 18, 20).

We collected baseline patient characteristics from each study (Table 1). The combined populations of these studies yielded a total of 3,011,016 participants. Six studies were conducted in Asia, 6 were conducted in North America, 4 were conducted in Europe, and 2 were conducted in Oceania. The quality assessments with the NOS (Supplementary Table 3) showed that 4 studies were high quality, 10 were medium quality, and 4 were low quality. Six studies presented data about the risk of ischemic stroke in patients with asthma, and 3 studies presented data about the risk of hemorrhagic stroke in patients with asthma. Some studies examined the impact of asthma on stroke in different subgroups, based on sex, smoking status, asthma status, and age of asthma onset.

Association Between Asthma and Stroke
We analyzed 18 studies and 26 subsets with a random-effects model. That analysis revealed that patients with asthma had a 34% higher risk of stroke than individuals without asthma (RR: 1.34, 95% CI: 1.21–1.47, p < 0.00001; I²: 89%, p < 0.00001). Most of the subsets (22 of 26) showed an increased risk of stroke in patients with asthma, but the heterogeneity was pronounced. Moreover, the risk of stroke was significantly increased with asthma, in both the cohort studies (RR: 1.24, 95% CI: 1.08–1.42, p = 0.003) and the cross-sectional studies (RR: 1.55, 95% CI: 1.27–1.88, p < 0.00001), and no difference was found between analysis results of cohort studies and cross-sectional studies (p = 0.07 for between-group difference) (Figure 2).

We also measured the effects of asthma on ischemic and hemorrhagic stroke. Patients with asthma had 25% more risk of ischemic stroke compared to people without asthma, and this difference was significant (RR: 1.25, 95% CI: 1.06–1.47, p < 0.00001; I²: 93%, p < 0.00001). In contrast, the probability of hemorrhagic stroke did not increase significantly in patients with asthma (RR: 1.08, 95% CI: 0.87–1.34, p = 0.49; I²: 87%, p < 0.00001) (Figure 3).
TABLE 1 | Baseline characteristics of participants assessed in the studies included in the meta-analysis.

| References          | Population | Participant number | Study Type                      | Follow-up, mean or (range) | Age, range or (mean ± SD) | Gender (female, %) | Diagnosis criteria of asthma | Diagnosis criteria of stroke | Comorbidities, n (%) | Confounding factors adjusted for in the analyses | NOS score |
|---------------------|------------|--------------------|---------------------------------|-----------------------------|---------------------------|--------------------|-----------------------------|--------------------------|-------------------|-----------------------------------------------|-----------|
| Onufrait et al. (15) | Community  | 14,567             | Cohort study, prospective      | 12–14                       | 45–64                     | 56.9%              | Self-reported               | Doctor diagnosis          | DM:10.9%, HTN:33.5%, CB:8.4%, emphysema:1.6% | NA                                             | 7         |
| Chung et al. (17)    | Community  | 72,587             | Cohort study, retrospective     | 7.2                         | 52.1 ± 17.6               | 54.3%              | Electronic medical record   | Electronic medical record | AF:0.5%, HTN:29.1%, HPL: 16.2%, HF:2.0%, COPD: 9.9%, DVT:0.1%, CHD:13.7% | Age, sex and comorbidities of AF, HTN, HPL, HF, alcoholism, obesity, COPD, DVT and CHD | 7         |
| Çolak et al. (18)    | Community  | 94,079             | Cohort study, prospective      | <9.4                        | 56.1                      | 59.2%              | Doctor diagnosis            | Doctor diagnosis          | Pneumonia or acute bronchitis:22.5%                       | Age, sex, BMI, leisure time physical activity, education, annual household income, alcohol, cumulative tobacco consumption, BP, TC, LDL-C, HDL-C, TG, use of cholesterol-lowering medication, and DM | 7         |
| Kim et al. (19)      | Community  | 234,728            | Cohort study, retrospective     | <12                         | >20                       | 63.7%              | Electronic medical record   | Electronic medical record | HTN:38.8%, DM:20%, IHD:6.8%, depression:10.4%, dyslipidemia:28.2%          | Age, sex, income, region of residence, HTN, DM, HPL, IHD, depression histories | 8         |
| Cepelis et al. (16)  | Community  | 57,104             | Cohort study, prospective      | 17.2 ± 5.4                  | >20                       | 52.9%              | Self-reported               | Electronic medical record | DM:2.2%, HTN:37.5%                                                 | Age, birth year cohort, sex, BMI, smoking status, alcohol use, education level, TC:HDL ratio, HTN, DM | 8         |
| Iribarren et al. (20) | Community | 407,190            | Cohort study, prospective      | 2.3–9.3                     | ≥18                       | 66.0%              | Electronic medical record   | Electronic medical record | HTN:7.2%, DM:5.6%, HPL:6.1%                                                | DM, HTN, HPL, BMI, smoking status and history of any allergy | 7         |
| Schanen et al. (14)  | Community  | 13,501             | Cohort study, prospective      | ≥14                         | 54 ± 5.9                  | 57.0%              | Self-reported               | Electronic medical record | DM:10.7%, HTN:23.5%                                                | Age, sex, race/center, HLD-C, BP, HTN medication use, smoking status, pack years, WHR, DM, and sport score | 8         |
| Tattersal et al. (9)  | Community  | 6,792              | Cohort study, prospective      | 9.1 ± 2.8                   | 62.1 ± 10.2               | 52.9%              | Self-reported               | Electronic medical record | DM:12.6%                                                   | Age, race, sex, TC, HLD-C, BP, smoking, DM, anti-HTN and lipid-lowering medication use, BMI, family history of CVD, income | 8         |
| Wee et al. (29)      | Community  | 162,570            | Cross-sectional study          |                             | 53.3 ± 8.4                | 65.7%              | Self-reported               | Electronic medical record | HTN:22.5%, DM:8.0%, HPL:13.4%, IHD:3.1%                                  | Age, sex, income, BMI, smoking, 7 alcohol, HTN,DM,HPL, other allergic rhinitis histories, nutritional intake | 7         |

(Continued)
### TABLE 1 | Continued

| References            | Population type | Study Type            | Follow-up, mean or (range) | Age, range or (mean ± SD) | Gender (female, %) | Diagnosis criteria of asthma | Diagnosis criteria of stroke | Comorbidities, n (%) | Confounding factors adjusted for in the analyses | NOS score |
|-----------------------|-----------------|-----------------------|-----------------------------|---------------------------|--------------------|-------------------------------|---------------------------|------------------------|-----------------------------------------------|-----------|
| Enright et al. (22)   | Community       | Cross-sectional study |                            | 72.8 ± 5.6                | 57.0%              | Self-reported                | Electronic medical record  | NA                    | NA                                            | 5         |
| Lee et al. (24)       | Community       | Cross-sectional study |                            | 49.5 ± 10.0               | 51.7%              | Self-reported                | Doctor diagnosis           | DM:7.7%, MI:3.2%, CHD:5.6% | Age, BP, HDL-C, BMI, Hs-CRP, smoking, and DM | 6         |
| Adams et al. (30)     | Community       | Cross-sectional study | ≥ 18                       | 49.1%                     |                    | Self-reported                | NA                        | Age and sex             | 5                                             |           |
| Appleton et al. (23)  | Community       | Cross-sectional study | ≥ 18                       | NA                        |                    | Doctor diagnosis             | Self-reported             | DM:13.0%, Age (<50 years), sex, smoking, MI | 6         |
| Bozek et al. (26)     | Community       | Cross-sectional study |                            | 67.9 ± 5.6                | 53.6%              | Doctor diagnosis             | Electronic medical record | HTN:44.5%, HPL:48.0%, CHD:23.6%, arrhythmias:2.6%, HF:18.6%, hyperuricemia:6.0%, dementia: 4.1%, depression: 17.5%, delirium:4.1%, anxiety:9.9% |           |
| Park et al. (25)      | Community       | Cross-sectional study | 46-68                      | 58.4%                     |                    | Electronic medical record    | Arthritis:28.6%, HTN:37.7%, Dyslipidemia:32.7%, DM:12.6%, Depression:16.6%, Obesity:11.9% | NA                    | 6                                             |           |
| Weatherburn et al. (27)| Community     | Cross-sectional study | ≥ 18                       | 50.9%                     |                    | Electronic medical record    | Electronic medical record  | COPD:3.7%, HF:1.3%, CHD:5.7%, DM:5.3%, HTN:18.5%, AF:15.7% | Age, sex, deprivation, smoking | 6         |
| Strand et al. (20)    | Community       | Cross-sectional study | 40.0 ± 13.5                | 50.9%                     |                    | Self-reported                | Self-reported             | DM:8.8%, CHD:3.3%, cancer:24.1% | NA                                            | 5         |
| He et al. (21)        | Community       | Cross-sectional study | ≥20                        | 51.9%                     |                    | Self-reported                | Electronic medical record  | DM:8.9%, CHD:3.3%, cancer:9.3%, arthritis:21.4% | NA                                            | 6         |

AF, atrial fibrillation; BMI, body mass index; BR, blood pressure; CB, chronic bronchitis; CVD, cardiovascular disease; CHD, coronary heart disease; DM, diabetes mellitus; DVT, deep vein thrombosis; HDL, high-density lipoprotein; HDL-C, high-density lipoprotein cholesterol; HPL, hyperlipidemia; HTN, hypertension; HF, heart failure; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; NA, not available; TC, total cholesterol; TG, triglycerides; WHR, waist-hip ratio.
Association Between Asthma and Stroke in Different Populations

Next, we examined the risk of stroke in different populations. The risk of stroke was significantly increased in both men (RR: 1.20, 95% CI: 1.10–1.32, \( p < 0.0001 \); \( I^2 \): 24%, \( p = 0.22 \)) and women (RR: 1.29, 95% CI: 1.12–1.48, \( p = 0.0005 \); \( I^2 \): 61%, \( p = 0.007 \)) with asthma, compared to individuals without asthma (Figure 4). However, no significant difference was found between the sexes (\( p = 0.07 \) for between-group differences).

We also analyzed whether smoking status influenced the association between asthma and stroke risk. The subgroups of smoking included ever smokers (those that had smoked in the past or were smoking currently), and non-smokers (those that had never smoked). The reference subgroups were individuals with the same smoking status, but without asthma. We found that, among patients that did not have a history of smoking, those with asthma did not have an elevated risk of stroke, compared to those without asthma (RR: 1.18, 95% CI: 1.03–1.37, \( p = 0.02 \); \( I^2 \): 0%, \( p = 0.39 \)). Conversely, we found that, among patients with a smoking history, those with asthma had an elevated risk of stroke, compared to those without asthma (RR: 0.99, 95% CI: 0.81–1.22, \( p = 0.95 \); \( I^2 \): 42%, \( p = 0.18 \); Figure 5).

Next, we compared patients with active asthma to patients with inactive asthma. Active asthma was defined as either a negative response to the question, “Do you still have asthma?” (14, 21), or evidence that the patient had not recently used asthma
medication (9, 16). The risk of stroke was elevated in patients with active asthma (RR: 1.48, 95% CI: 1.12–1.95, \( p = 0.006; I^2: 72\%\), \( p = 0.01\)), but not in patients with inactive asthma (RR: 0.95, 95% CI: 0.80–1.13, \( p = 0.58; I^2: 10\%\), \( p = 0.34\)) (Figure 6). Thus, asthma activity had a significant effect on the association between asthma and stroke (\( p = 0.008 \) for the between-group difference).

We also analyzed the age of asthma onset and patient sex. Child-onset and adult-onset asthma were defined by the age of the first asthma onset. In two studies (15, 24), the cut-off ages were 18 and 21 years. The results showed that only women with adult-onset asthma had an increased risk of stroke, compared to individuals without asthma (RR: 2.30, 95% CI: 1.51–3.52, \( p = 0.001; I^2: 0\%\), \( p = 0.81\)) (Figure 7).

**Sensitivity Analyses**

We performed sensitivity analyses to test the robustness of the main outcomes (Supplementary Figures 1–5). By omitting one study at a time and re-computing the pooled effect estimates, we did not find any significant difference in the results. We also analyzed the data with studies which did not adjust for blood lipid levels (or hyperlipidemia), blood pressure levels (or hypertension), or diabetes mellitus were omitted, and the result was robust (Supplementary Figure 6). Two studies with only an association between asthma and stroke but not have the study outcomes and 4 low quality studies might reduce the quality of the data. We analyzed the data with these studies omitted and the result was robust (Supplementary Figure 7).

**Publication Bias**

The publication bias was evaluated with a funnel plot. The funnel plot was visually symmetrical overall (Supplementary Figure 8).

**DISCUSSION**

This study assessed the effects of asthma on stroke by including previous studies comprehensively, particularly those with data for different populations. Our results showed that patients with asthma had a 34% higher risk of stroke than those without asthma. Furthermore, active asthma significantly increased the risk of stroke compared to inactive asthma (RR: 1.48 vs. RR: 0.95, \( p = 0.008 \)). These results were consistent with previous studies, which showed that asthma, particularly active asthma, significantly increased the risk of stroke (11).

The chronic inflammatory state of asthma accelerates the process of atherosclerosis, which can lead to the development of stroke (9). Asthma and stroke share many common risk factors, including advanced age, smoking, obesity, air pollution, and stress. Thus, the association between asthma and stroke is, to some extent, affected by confounding factors (18, 31). Previous studies have pointed out that asthma was an independent risk factor for stroke. Asthma induced endothelial damage, accelerated atherosclerosis progression, and even caused thrombosis, due to decreased lung function and hypoxemia (4, 29). Previous studies have shown that elevated eosinophils (32),

### FIGURE 3

Forest plot shows association between asthma and the risk of ischemic or hemorrhagic stroke. SE, standard error; IV, Inverse Variance method; df, degrees of freedom; c-s, current smoking; f-s, former smoking; ICH, Intracerebral hemorrhage; SAH, Subarachnoid hemorrhage.
FIGURE 4 | Forest plot shows association between asthma and the risk of stroke in male or female. SE, standard error; IV, Inverse Variance method; df, degrees of freedom; a/f, adult female; a/m, adult male; c/f, child female; c/m, child male.

FIGURE 5 | Forest plot shows association between asthma and the risk of stroke in smoking or non-smoking people. SE, standard error; IV, Inverse Variance method; df, degrees of freedom.
FIGURE 6 | Forest plot shows association between different asthma status (including active asthma and inactive asthma) and the risk of stroke. SE, standard error; IV, Inverse Variance method; df, degrees of freedom.

| Study or Subgroup | log(Risk Ratio) | SE   | Weight | IV, Random, 95% CI | IV, Random, 95% CI |
|-------------------|-----------------|------|--------|-------------------|-------------------|
| 1.4.1 active asthma |                 |      |        |                   |                   |
| Cepels, active 2019 | 0.157           | 0.0956 | 16.6%  | 1.17 [0.97, 1.41] |                   |
| He, active 2021    | 0.5582          | 0.0773 | 17.2%  | 1.75 [1.50, 2.03] |                   |
| Schanen, active 2005 | 0.4383          | 0.2488 | 10.5%  | 1.55 [0.95, 2.53] |                   |
| Tattersal, active 2015 | 0.4947       | 0.42   | 5.9%   | 1.64 [0.72, 3.74] |                   |
| Subtotal (95% CI) | 50.3%           |       |        | 1.48 [1.12, 1.95] |                   |
| Heterogeneity: Tau² = 0.05; Chi² = 10.72, df = 3 (P = 0.01); I² = 72% |
| Test for overall effect: Z = 2.75 (P = 0.006) |

1.4.2 inactive asthma

| Study or Subgroup | log(Risk Ratio) | SE   | Weight | IV, Random, 95% CI | IV, Random, 95% CI |
|-------------------|-----------------|------|--------|-------------------|-------------------|
| Cepels, inactive 2019 | -0.0513        | 0.1139 | 16.0%  | 0.95 [0.76, 1.19] |                   |
| He, inactive 2021    | -0.1785         | 0.1336 | 15.2%  | 0.84 [0.64, 1.09] |                   |
| Schanen, inactive 2005 | 0.3646         | 0.275 | 9.6%   | 1.44 [0.84, 2.47] |                   |
| Tattersal, inactive 2015 | 0.0583       | 0.2969 | 8.9%   | 1.06 [0.59, 1.90] |                   |
| Subtotal (95% CI) | 49.7%           |       |        | 0.95 [0.80, 1.13] |                   |
| Heterogeneity: Tau² = 0.00; Chi² = 3.33, df = 3 (P = 0.34); I² = 10% |
| Test for overall effect: Z = 0.55 (P = 0.56) |

Total (95% CI) 100.0% 1.22 [0.96, 1.56]

Heterogeneity: Tau² = 0.08; Chi² = 35.61, df = 7 (P < 0.00001); I² = 80%

Test for overall effect: Z = 1.64 (P = 0.10)

Test for subgroup differences: Chi² = 6.93, df = 1 (P = 0.008). I² = 85.6%

FIGURE 7 | Forest plot shows association between asthma and the risk of stroke in different age of asthma onset and different gender. SE, standard error; IV, Inverse Variance method; df, degrees of freedom.

| Study or Subgroup | log(Risk Ratio) | SE   | Weight | IV, Random, 95% CI | IV, Random, 95% CI |
|-------------------|-----------------|------|--------|-------------------|-------------------|
| 1.6.1 adult-onset male |                  |      |        |                   |                   |
| Lee, a/m 2012     | 0.5068          | 0.6225 | 10.0%  | 1.66 [0.49, 5.62] |                   |
| Onufra, a/m 2008  | -1.0498         | 0.6929 | 8.7%   | 0.35 [0.09, 1.36] |                   |
| Subtotal (95% CI) | 18.7%           |       |        | 0.79 [0.17, 3.61] |                   |
| Heterogeneity: Tau² = 0.78; Chi² = 2.79, df = 1 (P = 0.09); I² = 64% |
| Test for overall effect: Z = 0.31 (P = 0.76) |

1.6.2 child-onset male

| Study or Subgroup | log(Risk Ratio) | SE   | Weight | IV, Random, 95% CI | IV, Random, 95% CI |
|-------------------|-----------------|------|--------|-------------------|-------------------|
| Lee, c/m 2012     | 0.2546          | 0.8372 | 6.6%   | 1.29 [0.25, 6.66] |                   |
| Onufra, c/m 2008  | -0.4308         | 0.4118 | 15.9%  | 0.65 [0.29, 1.46] |                   |
| Subtotal (95% CI) | 22.4%           |       |        | 0.74 [0.36, 1.53] |                   |
| Heterogeneity: Tau² = 0.00; Chi² = 0.54, df = 1 (P = 0.46); I² = 0% |
| Test for overall effect: Z = 0.80 (P = 0.42) |

1.6.3 adult-onset female

| Study or Subgroup | log(Risk Ratio) | SE   | Weight | IV, Random, 95% CI | IV, Random, 95% CI |
|-------------------|-----------------|------|--------|-------------------|-------------------|
| Lee, a/f 2012     | 0.7227          | 0.5155 | 12.6%  | 2.06 [0.75, 5.66] |                   |
| Onufra, a/f 2008  | 0.8587          | 0.2361 | 22.8%  | 2.36 [1.48, 3.76] |                   |
| Subtotal (95% CI) | 35.4%           |       |        | 2.30 [1.51, 3.52] |                   |
| Heterogeneity: Tau² = 0.00; Chi² = 0.06, df = 1 (P = 0.81); I² = 0% |
| Test for overall effect: Z = 3.86 (P = 0.0001) |

1.6.4 child-onset female

| Study or Subgroup | log(Risk Ratio) | SE   | Weight | IV, Random, 95% CI | IV, Random, 95% CI |
|-------------------|-----------------|------|--------|-------------------|-------------------|
| Lee, c/f 2012     | -0.6539         | 1.0231 | 4.7%   | 0.52 [0.07, 3.86] |                   |
| Onufra, c/f 2008  | 0.3853          | 0.3366 | 18.7%  | 1.47 [0.76, 2.84] |                   |
| Subtotal (95% CI) | 23.4%           |       |        | 1.33 [0.71, 2.49] |                   |
| Heterogeneity: Tau² = 0.00; Chi² = 0.93, df = 1 (P = 0.33); I² = 0% |
| Test for overall effect: Z = 0.89 (P = 0.37) |

Total (95% CI) 100.0% 1.27 [0.79, 2.04]

Heterogeneity: Tau² = 0.20; Chi² = 13.67, df = 7 (P = 0.06); I² = 49%

Test for overall effect: Z = 0.97 (P = 0.33)

Test for subgroup differences: Chi² = 8.32, df = 3 (P = 0.04). I² = 63.9%
C-reactive protein (33), eosinophil cationic protein (34), and eotaxin (35) were involved in the development of atherosclerosis in patients with asthma. These features might explain why active asthma increases the risk of stroke: in active asthma, inflammation is severe and hypoxemia is prolonged, and these factors accelerate the atherosclerotic process.

Previous studies have suggested that asthma caused similar increases in the risks of ischemic and hemorrhagic stroke. In contrast, the present study showed that asthma mainly increased the risk of ischemic stroke and had less effect on the risk of hemorrhagic stroke. Our findings were supported by the association between asthma and atherosclerosis. Indeed, atherosclerosis directly drives thrombosis, which leads to ischemic stroke, and it is much less related to hemorrhagic stroke. In contrast, the main risk factors for hemorrhagic stroke are trauma and congenital vascular developmental malformations, which are more weakly associated with asthma.

The greatest strength of this study was that it included the largest sample size of any study to date that aimed to analyze the relationship between asthma and stroke. Moreover, we characterized the effect of smoking status on this association with a sufficiently sized subgroup analysis.

Limitations
However, this study also had some limitations. First, unfortunately, we could not obtain sufficient data on patient asthma treatments to analyze their effects on stroke risk. Previous studies have shown that asthma treatment medications, like β receptor-agonists and glucocorticoids, could influence stroke outcomes (36–39). Moreover, we only included observational studies; therefore, we could not infer any direct causal relationships. Additionally, observational studies are susceptible to confounding factors that may bias the results. Finally, the heterogeneity of the included studies was not negligible; therefore, our results should be interpreted with caution.

Conclusions
In conclusion, this meta-analysis provided evidence to support the notion that asthma is an important risk factor for stroke. This information is important for the development of strategies for preventing and treating asthma and stroke. In the future, well-designed, large, multicenter cohort studies should be conducted with a particular focus on a quantitative assessment of the effects of asthma on patients during stroke treatment.

DATA AVAILABILITY STATEMENT
The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS
Z-FL: analysis of data, interpretation results, drafting, and editing the article. Z-HF, Z-YA, S-CH, M-DH, and W-XZ: design of study, solution of problem, and reviewing the article. S-CH and M-DH: extraction of data and assessment of articles quality. All authors contributed to the article and approved this version of article.

SUPPLEMENTARY MATERIAL
The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2022.900438/full#supplementary-material

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