

Asthma and Risk of Stroke: A Systematic Review and Meta-analysis

Li-ying Wen, MSc,* Hong Ni, MSc,† Ke-sheng Li, MSc,* Hui-hui Yang, MSc,*
Jian Cheng, MSc,* Xu Wang, MSc,* De-sheng Zhao, MSc,* Ming-yu Xie, MSc,*
and Hong Su, PhD*

Background: Several studies have suggested that asthma is associated with an increased risk of stroke. However, the results are inconsistent. The aim of this study is to investigate the relation of asthma and the risk of stroke through a systematic review and meta-analysis of published research. **Methods:** Pertinent studies were identified by a search of the PubMed and the Web of Science databases to June 2015. Study-specific hazard ratios (HRs) with 95% confidence intervals (CIs) were pooled using fixed-effect or random-effect models when appropriate. Associations were tested in subgroups representing different participants and study characteristics. Publication bias was assessed with Egger's test. **Results:** Five articles comprising 524,637 participants and 6031 stroke cases were eligible for inclusion. Asthma was associated significantly with increased risk of stroke, and the pooled HR was 1.32 (95% CI: 1.13, 1.54, $I^2 = 80.4\%$). Subgroup analyses revealed that the association between asthma and stroke risk was stronger among female patients (HR = 1.42, 95% CI: 1.15-1.76) and prospective cohort study design (HR = 1.52, 95% CI: 1.21-1.91). **Conclusion:** Asthma is associated with a significantly increased risk of stroke. This finding may have clinical and public health importance. **Key Words:** Asthma—stroke—inflammatory—meta-analysis—systematic review.
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From the *Department of Epidemiology and Health Statistics, School of Public Health, Anhui Medical University, Hefei, Anhui, China; and †Department of Science and Education, Anhui Province Children's Hospital, Hefei, Anhui, China.

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Address correspondence to Hong Su, Department of Epidemiology and Health Statistics, School of Public Health, Anhui Medical University, 81 Meishan Road, Hefei 230032, Anhui Province, China. E-mail: suhong5151@sina.com.

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Introduction

Stroke has long been a significant public health problem. The Global Burden of Diseases, Injuries, and Risk Factors 2010 study ranked stroke as the second most common cause of death,^{1,2} and the third leading cause of disability in 2010.^{3,4} Although age-adjusted rates of stroke mortality have decreased worldwide in the past 2 decades, the absolute number of stroke patients per year, stroke survivors, related deaths, and the overall global burden of stroke (disability-adjusted life years lost) are serious and increasing.⁵ Although the age-standardized incidence of stroke has declined significantly in high-income countries, the incidence has increased considerably in developing countries.⁵

Asthma has been also a big issue in the public health. The World Health Organization estimates that approximately 300 million people worldwide suffer asthma and projects that an additional 100 million persons will have this disease by 2025.^{6,7} Asthma accounts for about 1% of all disability-adjusted life years lost worldwide, reflecting the severity and prevalence of this disease.⁶ The Global Initiative for Asthma figures out that the prevalence of asthma in different countries ranges from 1% to 18%.⁸

Chronic inflammation is thought to play a fundamentally important role in stroke development,^{9,10} whereas asthma is a common chronic inflammatory disease of the airways characterized by variable and recurring symptoms, reversible airflow obstruction, and bronchospasm.¹¹ And previous studies have found the association between asthma and stroke, prompting that they might occur on a background of inflammation.^{12,13}

In view of the severity of stroke damages, the relationship between asthma and stroke has attracted increasing attention. However, the conclusions remain controversial. This inconsistency not only hinders in the understanding of the mechanism of stroke but also impacts the targeted intervention. In addition, to the best of our knowledge, no meta-analysis has been performed to examine the specific association between asthma and stroke risk.

Therefore, we performed a systematic review and meta-analysis of all available cohort studies to examine the association between asthma and the risk of stroke.

Methods

A meta-analysis was performed in accordance with the Meta-Analysis of Observational Studies in Epidemiology protocol.¹⁴

We conducted a search of the PubMed and the Web of Science databases for studies published through June 2015 and used the keywords “asthma,” “asthmatic,” “stroke,” “cerebrovascular disease” and “cardiovascular disease.” In addition, we conducted manual searches of the reference lists of all the included relevant articles to identify additional eligible publications. Only articles published in the English language were considered.

Studies that satisfied the following criteria were included in our meta-analysis: (1) published cohort studies; (2) the exposure of interest was asthma, including child-onset asthma and adult-onset asthma; (3) the outcome was the incidence of total stroke, ischemic stroke, hemorrhagic stroke, or stroke mortality; (4) the authors reported effect estimates (hazard ratio [HR]) and 95% confidence intervals (CIs) for comparisons of asthma versus nonasthma. The study selection process is depicted diagrammatically in Figure 1.

During screening, we excluded cross-sectional studies, nonhuman studies, and nonoriginal studies (e.g., reviews, editorials, and commentaries). Studies of other exposures and end points were also excluded.

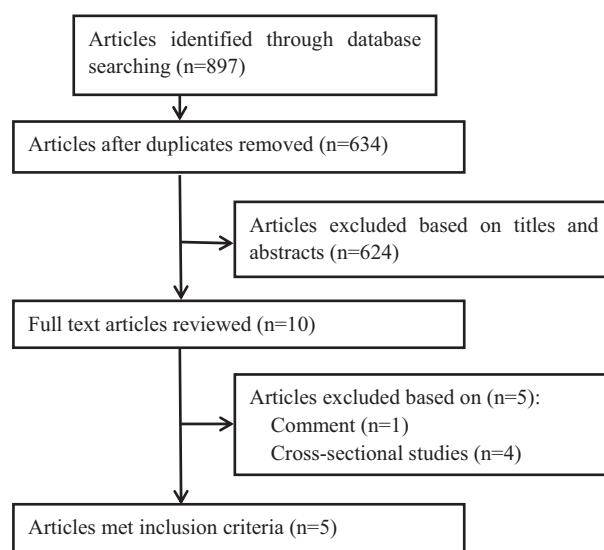


Figure 1. Flow diagram of literature search and study selection.

Two authors (L.Y.W. and M.Y.X.) extracted detailed information from each included article independently. Any disagreements were discussed until consensus was reached. For each study that satisfied the selection criteria, the following information was extracted: basic information (e.g., the name of the first author, publication year, age and gender of the cohort, and number of participants/cases); study characteristics (e.g., the name and geographic location of the study and the follow-up duration); assessment of asthma; stroke assessment; and risk estimates with 95% CIs. If the risk estimates were reported in several multivariable-adjusted models in the original study, the most thoroughly adjusted model (and its covariates) was extracted.

The quality assessment of each study was conducted independently by 2 authors (L.Y.W. and D.S.Z.) in accordance with the Newcastle–Ottawa Scale for nonrandomized studies.¹⁵ The Newcastle–Ottawa Scale assigns a maximum of 9 points to each study: four for selection, two for comparability, and three for the assessment of outcomes and adequacy of follow-up. Scores of 0–3, 4–6, and 7–9 were regarded as low, moderate, and high quality, respectively.

The HRs were used as the common measure of association across studies. The HR was pooled using fixed-effect or random-effect models when appropriate. Forest plots were produced to visually assess the HRs and corresponding 95% CIs across studies.

Subgroup analyses were conducted by gender (male or female), study design (prospective and retrospective), follow-up duration (<10 years or ≥10 years), and whether or not controlling smoking status in the models.

The sensitivity analysis was also performed to evaluate whether the results could have been affected markedly by a single study by removing it one by one from the meta-analysis.

Heterogeneity of HRs among studies was evaluated by the I^2 statistic, with values of 25%, 50%, and 75% representing low, medium, and high degrees of heterogeneity, respectively.¹⁶ The possibility of publication bias was evaluated using the visual inspection of a funnel plot and the Egger's regression test.¹⁷ All tests were 2-sided and differences were considered to be significant if the P value is less than .05, with the exception of the heterogeneity assessment, which was considered statistically significant at a P value less than .10. All statistical analyses were performed using Stata software (version 12.0; StataCorp LP, College Station, TX).

Results

The literature search yielded 897 articles. After duplicate studies and studies that did not meet the inclusion criteria were excluded, 10 potentially eligible studies were selected. After detailed evaluations, 5 cohort studies were included for the final meta-analysis.^{12,13,18-20}

Characteristics of 5 selected studies are shown in Table 1. The total number of participants included in this meta-analysis was 524,637, with 6031 reported stroke outcomes. The studies varied with regard to how results were presented. Two studies reported the results of total stroke,^{18,20} 2 studies reported the results separately by asthma subtypes,^{12,13} and 1 study provided results separately by different stroke subtypes.¹⁶ With regard to study location, 4 studies were conducted in the United States,^{12,13,18,19} and one in Taiwan.²⁰ The study samples ranged from 6792 to 417,190, and the follow-up durations ranged from 7.3 to 14 years. All of the studies comprised both men and women. All of the selected studies had a high quality.

With respect to exposure assessment, 2 studies relied on self-report of physician diagnosed asthma^{12,18}; 1 study included asthma medication use as a component of asthma definition²⁰; 1 study was based on medical records¹⁹; and 1 study combined self-reported measures with asthma medication use based on different subtypes.¹³ As regards outcome evaluation, stroke was assessed by death certificates or medical records in each study.

Adjusted HRs could be determined for all studies. Most of the studies were adjusted for age (4 studies) and smoking status (3 studies).

The association between asthma and stroke risk reached statistical significance; the pooled HR was 1.32 (95% CI: 1.13, 1.54; Fig. 2). Although high heterogeneity ($I^2 = 80.4\%$) was detected, no publication bias was observed based on either the funnel plot or Egger's test ($P = .387$).

A sensitivity analysis of omitting 1 study in each turn showed that the study by Iribarren et al¹⁹ had the largest influence on the results: the pooled HR without this study was 1.38 (95% CI: 1.29, 1.49), and no heterogeneity was detected in the sensitivity analyses. We also conducted subgroup analysis to explore potential sources of

Table 1. Characteristics of studies included in the meta-analysis

Source	No. of participants	No. of cases	Follow-up years	Sex	Baseline age (years)	Asthma measures	Stroke measures	HR (95% CI)	Study quality
Schanen et al ¹⁸ United States	13,501	438	14	Male and female	45-64	Self-reported, doctor diagnosed	Hospital and death certificates	1.50 (1.04, 2.15)	9
Onufrak et al ¹² United States	14,567	531	14	Male and female	45-64	Self-reported, physician-diagnosed	Follow-up, hospital discharge lists, state vital statistics, hospital records, and death certificates	1.76 (1.20, 2.58)	9
Iribarren et al ¹⁹ United States	417,190	708	13	Male and female	18 or older	Hospitalization, outpatient and emergency department visits	Medical records	1.13 (1.07, 1.20)	9
Chung et al ²⁰ Taiwan	72,587	4,184	7.3	Male and female	18 or older	Newly diagnosed asthma, had received treatment	Hospitalization records	1.37 (1.27, 1.48)	9
Tattersall et al ¹³ United States	6,792	170	9.1	Male and female	Mean 62.2	Self-reported, physician diagnosed	Death certificates and medical records	1.23 (.76, 1.99)	9

Abbreviations: CI, confidence interval; HR, hazard ratio.

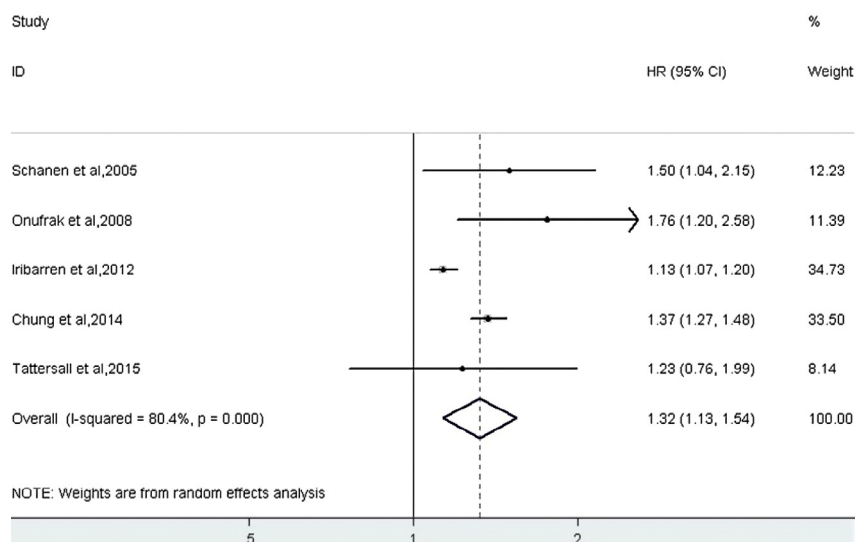


Figure 2. Hazard ratios of stroke for asthmatic participants compared with nonasthmatic participants.

heterogeneity and to perform comparison between groups. As shown in Table 2, we noted that asthma was associated with an increased risk of stroke if the participants were women. In addition, the increased risk was more evident in several strata of study characteristics, not adjusting for smoking status and prospective study design.

No heterogeneity was found in lower follow-up duration and prospective study design ($I^2 = .0\%$). There existed low heterogeneity in the subgroups of controlling ($I^2 = 16.0\%$) and not controlling smoking status ($I^2 = 36.8\%$) in the model. Moderate to high heterogeneity was found in other subgroups. No publication bias was observed in all subgroups.

Discussion

The results of our systematic review and meta-analysis demonstrated that asthma was associated with a significantly increased risk of developing stroke. Fur-

thermore, the association persisted and remained statistically significant across several subgroups stratified by various study and participant characteristics.

Asthma may contribute to stroke through a variety of mechanisms. First, asthma has known immunological/inflammation effects,²¹ which could influence stroke risk. Previous studies suggest that asthma is positively associated with C-reactive protein,^{22,23} and the later study have been thought to be associated with an increased risk of stroke.^{24,25} Second, asthma is associated with smoking,²⁶ physical inactivity,²⁷ unhealthy diet,²⁸ and obesity,²⁹ which might increase the risk of stroke. Adjusting for smoking status somewhat attenuated the association between asthma and stroke, indicating that smoking may confound or mediate the association between asthma and stroke. The magnitude of the asthma-stroke association observed in the current study is similar to the associations between smoking and stroke (HR = 1.51; 95% CI: 1.45, 1.58; from a meta-analysis).³⁰ Tobacco smoke contains more than 7000

Table 2. Subgroup analyses of HR of stroke according to asthma status

Subgroup	No. of reports	HR (95% CI)	I^2 value (%)	Egger's test
Sex				
Female	4	1.42 (1.15, 1.76)	83.3	.203
Male	3	1.19 (.09, 1.43)	74.6	.818
Study design				
Prospective	3	1.52 (1.21, 1.91)	.0	.465
Retrospective	2	1.24 (1.03, 1.50)	93.6	—
Duration of follow-up				
10 years or more	3	1.37 (1.02, 1.84)	72.1	.122
Less than 10 years	2	1.37 (1.27, 1.47)	.0	—
Controlled smoking status in models				
Yes	3	1.14 (1.08, 1.20)	16.0	.379
No	2	1.38 (1.28, 1.49)	36.8	—

Abbreviations: CI, confidence interval; HR, hazard ratio.

different chemicals and compounds,^{31,32} including hundreds of toxins that stimulate the development of free radicals, causing vascular endothelial dysfunction and exacerbating vascular inflammation, thereby accelerating the degeneration of atherosclerotic lesions.³³ Structural damage to the arterial wall may also play a role in the development of hemorrhagic and intracerebral stroke.³⁴ Third, asthma is correlated with other major comorbidities, such as diabetes^{2,35} and hypertension,³⁶ both of which are major risk factors for stroke. Fourth, lung function impairment is associated with stroke risk in general and in white subjects.^{37,38} Participants with reduced lung function have increased inflammatory markers (such as C-reactive protein, interleukin-1 β , and interleukin-6),³⁹ which predict future atherosclerosis and cardiovascular events.^{40,41} The long-term airway remodeling from the inflammatory response and subsequent repair in asthma can produce irreversible airway obstruction and conduce to a decline in pulmonary function over time.¹⁸ In addition, severe asthma exacerbations are associated with a more rapid decline in lung function.^{42,43} Finally, asthma medication use may contribute to the observed association. One selected study in our meta-analysis found a positive association between the medication use and stroke risk.¹⁹ However, the results should be interpreted cautiously because medication use can be a marker of asthma severity, and many studies lacked information about dose and duration of medication use.

When it comes to the sex-specific subgroup analyses, asthma was strongly associated with stroke risk among women (HR = 1.42; 95% CI: 1.15, 1.76), whereas there was no significant association among men (HR = 1.19; 95% CI: .09, 1.43). The reason may be that sex hormones could play a crucial role in modulating immunological inflammation in asthma.⁴⁴ Additionally, this finding is consistent with experimental investigations showing that the pathogenesis of a variety of lung diseases is influenced by sex, which suggests that sex hormones play an important role in the modulation of immune response and chronic human lung diseases.^{45,46} With respect to study design, the risk of stroke from prospective cohort studies (HR = 1.52; 95% CI: 1.21, 1.91; I^2 = .0%) was stronger than that only from retrospective cohort studies (HR = 1.24; 95% CI: 1.03, 1.50; I^2 = 93.6%). This may be explained by the finding that all the events (such as exposure, latent period, and subsequent outcome) had already occurred in a retrospective cohort study, in which exposure and outcome assessments cannot be controlled but need to rely on others for accurate recordkeeping. Additionally, it can be very difficult to make accurate comparisons between the exposed and the nonexposed. What's more, there existed high heterogeneity in the retrospective cohort studies. Thus, more prospective cohort studies need to be conducted to further identify the relationship between asthma and stroke risk.

In addition, we intended to conduct subgroup analysis according to diabetes, hypertension, dyslipidemia, and atrial fibrillation; but hypertension and dyslipidemia were controlled in all selected articles, diabetes was adjusted in 4 articles, and atrial fibrillation was not controlled in the same 4 articles. Therefore, we conducted an analysis of the 4 articles, the pooled HR was 1.33 (1.06, 1.67), the value was slightly higher than the pooled HR value of the five articles, which could not consider that there was a significant difference between the 2 values. But the CI attenuated after controlling atrial fibrillation, which just indicated that the sampling error was smaller. Therefore, the relationship between atrial fibrillation and asthma and stroke still need to be further explored to elucidate the underlying mechanisms. Patients with diabetes exhibit accelerated progression of carotid intima-media thickness and atherosclerotic plaque formation, and are inclined to occlusive disease affecting small penetrating arteries in the brain.⁴⁷

A noteworthy strength of this meta-analysis is the cohort design of the included studies, which eliminated any possible recall bias that can occur in retrospective case-control studies. Furthermore, many of the studies in this meta-analysis had large sample sizes and long follow-up durations, which provided high statistical power to our assessment of the correlation between asthma and the risk of stroke.

Several limitations of this meta-analysis should be considered. First, because of the observational nature of the included studies, the existence of lost to follow-up is inevitable. Second, several studies suggested that medication use might mediate the association between asthma and stroke risk.⁴⁸⁻⁵⁰ However, most studies did not provide information on asthma treatment and medication use. The role of asthma treatment in modulating subsequent risk of stroke needs to be studied further. Moreover, Onufrak et al found that adult-onset asthma might be a significant risk factor for stroke in women but not in men. Nonetheless, only 1 selected study involved the above issue, so it cannot be identified between them. Thus, further studies should be implemented to explore the association between child-onset asthma or adult-onset asthma and the risk of stroke by gender stratification.

In conclusion, this systematic review and meta-analysis provides strong evidence that asthma is a significant risk factor for stroke. Given the high prevalence and incidence of asthma and stroke in the general population, the observed association between asthma and stroke has clinical and public health importance. More studies are needed to explore the underlying mechanisms and to elucidate the causal pathways that link asthma and stroke.

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