Risk of Stroke among Patients with Chronic Rhinosinusitis: A Systematic Review and Meta-analysis

Phuuwadith Wattanachayakul, MD,* Pongprueth Rujirachun, MD,* and Patompong Ungprasert, MD, MS†

Background: Recent studies have suggested that patients with chronic rhinosinusitis (CRS) may have a higher risk of stroke although the data are still limited. The current systematic review and meta-analysis was conducted with the aims to identify all studies that investigated this relationship and summarize their results together to better characterize the risk of stroke among patients with CRS. *Methods:* A comprehensive literature review was conducted by searching for published articles in MEDLINE and EMBASE databases from inception to October 2018 to identify all observational studies that compared the risk of stroke among patients with CRS to individuals without CRS. Pooled risk ratio (RR) and 95% confidence interval (CI) were calculated using random-effect, generic inverse variance method of DerSimonian and Laird. *Results:* A total of 5 studies with 447,065 participants met the eligibility criteria and were included into the meta-analysis. The risk of stroke among patients with CRS was significantly higher than individuals without CRS with the pooled RR of 1.79 (95% CI, 1.34-2.40, $I^2 = 84\%$). *Conclusions:* The current study found that CRS is associated with higher risk stroke. Whether this relationship is causal and how it should be addressed in clinical practice require further investigations.
Key Words: Stroke—chronic rhinosinusitis—risk factor—meta-analysis

Introduction

Chronic rhinosinusitis (CRS) is a common chronic inflammatory disorder characterized by the presence of persistent inflammation of sinonasal mucosa lasting for more than 12 weeks.[1] Common symptoms of CRS include rhinorrhea, nasal blockage, postnasal drip, and facial pain. The reported prevalence of CRS was 11.8% in the United States and 10.9% in Europe.[2,3] The exact etiology and pathogenesis of CRS remain unknown but studies have suggested the roles of both genetic and environmental factor.[4,5]

Stroke is one of the leading causes of morbidity and mortality worldwide.[6] In 2013, it was estimated that 10.3 million new patients suffered from stroke (about two thirds were ischemic stroke).[7] Well-established risk factors of stroke include hypertension, diabetes mellitus, atrial fibrillation, dyslipidemia, and physical inactivity.[8-9] Interestingly, recent studies have suggested a relationship between CRS and an increased risk of stroke, although the data are still relatively limited.[10-14] The current systematic review and meta-analysis were conducted with the aims to identify all studies that investigated this relationship and summarize their results together to better characterize the risk of stroke among patients with CRS.

Materials and Methods

Data Sources and Searches

Two investigators (P.W. and P.R.) independently searched for published articles indexed in MEDLINE and EMBASE databases from inception to October 6, 2018 using the search strategy that included the terms for CRS and stroke. The search strategy is available as

Supplementary Data 1. References of the included studies were also manually reviewed for additional eligible studies. This study was undertaken in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement, which is available as Supplementary Data 2.

Inclusion Criteria

To be eligible for the meta-analysis, the study could be either cohort study, case-control study, or cross-sectional studies that investigate if CRS is associated with a higher risk of stroke. Eligible cohort study must start with recruitment of cases with CRS and comparators without CRS and, then, follow them until the occurrence of stroke or the end of study. Eligible case-control study must start with cases with stroke and controls without stroke and, then, investigate for their prior history of CRS. Eligible cross-sectional study must recruit subjects and investigate for the presence of stroke and CRS at the same time. Eligible study must also provide the magnitude of association, which could be either relative risk (RR), hazard ratio, or odds ratio (OR) along with its corresponding confidence interval (CI).

The eligibility of the retrieved studies was determined independently by the first 2 investigators (P.W. and P.R.). The third investigator (P.U.) reviewed all the included studied to ensure that the inclusion criteria were met and also served as the deciding vote when different determinations of study eligibility were made by the first 2 investigators. Newcastle-Ottawa quality assessment scale was used to assess the quality of the included cohort and case-control studies.[15] This scale evaluates the quality of the included studies in 3 areas including the recruitment of participants, the comparability between the groups and the ascertainment of the outcome of interest for cohort studies, and exposure of interest for case-control studies. The modified version of this scale was used to assess the quality of the included cross-sectional studies.[16]

Data Extraction

A standardized data collection form was used to extract the following information: last name of the first author, study design, year(s) of study, country of origin, year of publication, sample size, characteristics of included participants, methods used to identify and verify the diagnosis of CRS and stroke, and confounders that were adjusted and adjusted effect estimates with 95% CI. This data extraction was independently performed by the same 2 investigators (P.W. and P.R.) to minimize error. Any discrepancies found in the case record forms were resolved by referring back to the original articles.

Statistical Analysis

Review Manager 5.3 software from the Cochrane Collaboration was used for data analysis. Point estimates and standard errors were extracted from individual study and were combined together using the generic inverse variance method as described by DerSimonian and Laird.[17] Random-effect model, rather than a fixed-effect model, was used because the included studies were of different methodologies and background populations. ORs from case-control studies and cross-sectional studies were used as the estimates for RRs to combine with RRs from cohort studies for the calculation of pooled effect estimate. Statistical heterogeneity was assessed using the Cochran's Q test. This statistic is complemented with the I^2 statistic which quantifies the proportion of the total variation across studies that is due to heterogeneity rather than chance. A value of I^2 of 0%-25% represents insignificant heterogeneity, 26%-50% low heterogeneity, 51%-75% moderate heterogeneity and greater than 75% high heterogeneity.[18] Funnel plot was used to assess for the presence of publication bias.[19]
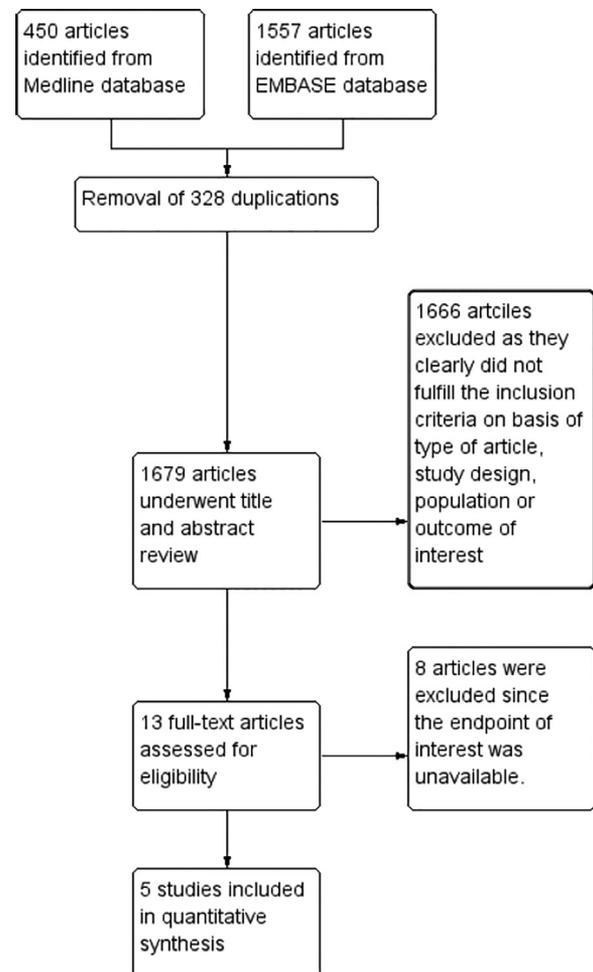

Figure 1. *Flowchart of literature review process.*

Table 1. *Baseline characteristics of studies included in this meta-analysis*

	Li et al[10]	Wu et al[11]	Kang et al[12]	Rosenthal et al[13]	Lee et al[14]
Year of publication	2007	2012	2013	2016	2018
Country of origin	China	Taiwan	Taiwan	United States	Korea
Study design	Case-control study	Retrospective cohort study	Retrospective cohort study	Cross-sectional study	Retrospective cohort study
Study subjects	Cases: Cases were patients with ischemic stroke (diagnosed based on based on clinical presentation and imaging study) who were seen at the Second hospital of Hebei Medical University from October 2006 to August 2007. Controls: Controls were healthy volunteers without a history of stroke who were recruited from the same hospital.	Cases: Cases were patients with CRS who were identified from the database of the Taiwan Longitudinal Health Insurance Database in the year 2005 (LHID2005) which randomly collected health data of approximately 1 million patients through the records of the National Health Insurance program. Patient with prior history of stroke and age <18 years old were not included. Comparators: Comparators were individuals without CRS who were identified from the same database. Individuals with prior history of stroke were not included. Comparators were age, sex, and calendar year-matched to cases.	Cases: Cases were patients with CRS who were identified from the database of the Taiwan Longitudinal Health Insurance Database in the year 2010 (LHID2010) which randomly collected health data of approximately 1 million patients through the records of the National Health Insurance program. Patient with prior history of stroke and age <18 years old were not included. Comparators: Comparators were individuals without CRS who were identified from the same database. Individuals with prior history of stroke were not included. Comparators were age, sex, urbanization, and calendar year-matched to cases.	Study subjects were patients who underwent brain MRs at the Johnson Veteran Affair Medical Affairs in Charleston, South Carolina from January to December 2009. Their MRs were reviewed for the presence of CRS and their medical records were reviewed for the presence of stroke.	Cases: Cases were patients who were diagnosed with CRS from 2002 to 2013. Cases were identified from the database of the Korean Health Insurance Review and Assessment Service-National Sample Cohort which randomly collected health data of approximately 1 million patients through the National Health Insurance Sharing Service. Patients with prior history of stroke were not included. Comparators: Comparators were individuals without diagnosis of CRS who were identified from the same database during the same time period as cases. Comparators were age, sex, income, region, and past medical history-matched to cases. Individuals with prior history of stroke were not included.
Number of subjects	Cases: 218 Controls: 218	Cases: 53,653 Comparators: 214,624	Cases: 15,846 Comparators: 47,538	Overall: 173	Cases: 22,959 Comparators: 91,836
Baseline characteristics of subjects	Mean age: Cases: 60.0 ± 13.1 years Controls: 51.5 ± 15.1 years Percentage of female: Case: 50% Controls: 50%	Mean age: NA Percentage of female: Cases: 59.8% Comparators: 59.8% Urbanization: Cases: 63.8% urban 27.6% suburban 8.6% rural Comparators:	Mean age: Cases: 41.6 ± 15.4 years Comparators: 41.6 ± 15.4 years Percentage of female: Cases: 53.6% Comparators: 53.6% Urbanization: Cases: 33.9% most urbanized	Mean age: Overall: 62.4 years Percentage of female: Overall: 9.8%	Mean age: NA Percentage of female: Cases: 58.2% Comparators: 58.2% Urbanization: Cases: 49.2% urban Comparators: 49.2% urban

Table 1 (*Continued*)

	Li et al[10]	Wu et al[11]	Kang et al[12]	Rosenthal et al[13]	Lee et al[14]
		60.1 % urban 29.3% suburban 10.6% rural Geographic region: Cases: 49.0% Northern 25.3% Central 24.3% Southern 1.5% Eastern Comparators: 49.1% Northern 22.7% Central 26.0% Southern 2.2% Eastern	Comparators: 33.9% most urbanized		
Diagnosis of CRS	Presence of inflammatory lesion on imaging examination including mucosal thickening, inflammatory fluid accumulation and submucosal cyst in frontal, ethmoid, sphenoid, and maxillary sinus	Presence of ICD-9 codes for CRS	Presence of ICD-9 code for CRS	Presence of significant sinusitis on MRs (defined as score of ≥6 by sinusitis scoring system)	Presence of ICD-10 code for CRS at least twice in the database plus history of at least one CT of head and neck without the presence of the ICD-10 code for nasal polyps
Diagnosis of stroke	Fulfillment of the diagnostic criteria developed by the Fourth National Cerebrovascular Diseases Conference in 1995 and confirmed by imaging study	Presence of ICD-9 codes for stroke in the database (both cases and comparators were reviewed for diagnostic codes of stroke until the end of 2009)	Presence of ICD-9 codes for stroke (both cases and comparators were reviewed for diagnostic codes of stroke until the end of 2005)	Presence of diagnosis of stroke (made by physicians who saw them in routine practice) in medical records	Presence of ICD-10 codes for stroke (both cases and comparators were reviewed for diagnostic codes of stroke until the end of 2012)
Confounder adjusted in the multivariate analysis	None	Age, sex, income, urbanization level, geographic region, coronary heart disease, diabetes, hypertension, and hyperlipidemia	Age, sex, income, geographic region, urbanization level, hypertension, diabetes, coronary heart disease, heart failure, atrial fibrillation, hyperlipidemia, alcohol abuse/alcohol dependence syndrome, obesity, and tobacco use disorder	Race and smoking	Age, sex, income, region of residence, hypertension, diabetes, dyslipidemia, ischemic heart disease, migraine, chronic kidney disease, depression, sleep disorder, and chronic obstructive pulmonary disorder
Newcastle-Ottawa score	Selection: 3 stars Comparability: 1 star Outcome: 3 stars	Selection: 4 stars Comparability: 2 stars Outcome: 3 stars	Selection: 4 stars Comparability: 2 stars Outcome: 3 stars	Selection: 3 stars Comparability: 1 star Outcome: 3 stars	Selection: 4 stars Comparability: 2 stars Outcome: 3 stars

Abbreviations: CRS, chronic rhinosinusitis; ICD, international classification of diseases; MRs magnetic resonance scan; NA, not available.

Results

The literature search yielded 2007 potentially relevant articles (1557 articles from EMBASE and 450 articles from MEDLINE). After the exclusion of 328 duplicated articles, 1679 articles underwent title and abstract review. A total of 1666 articles were excluded at this stage as they clearly did not fulfill the eligibility criteria based on the type of article, study design, participants, and outcome of interest. A total of 13 articles underwent full-length article review and 8 articles were excluded at this stage since they did not report the association of interest. Finally, 5 observational studies[10-14] (3 cohort studies, 1 case-control study, and 1 cross-sectional study) comprising 447,065 patients were included into the meta-analysis. The literature retrieval, review and selection process are shown in Figure 1. The characteristics of the included studies and their quality assessment are described in Table 1.

The pooled analysis found a significantly increased risk of stroke among patients with CRS with the pooled RR of 1.79 (95% CI, 1.34-2.40). High between-study heterogeneity was detected ($I^2 = 84\%$). Figure 2 demonstrates the forest plot of this meta-analysis. Funnel plot was used to evaluate for the presence of publication bias as shown in Figure 3. The graph was asymmetric and may suggest the presence of publication bias in favor of studies with positive results.

Sensitivity Analysis

To strengthen the validity of the pooled result, a sensitivity analysis was performed by including only cohort studies into the meta-analysis (ie, the only case-control study and cross-sectional study were excluded from the meta-analysis). Only cohort studies were included in this sensitivity analysis because it is the only design (among
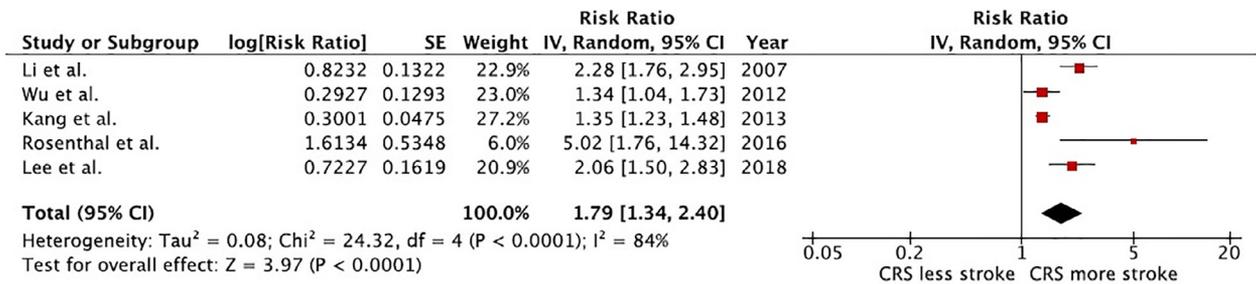

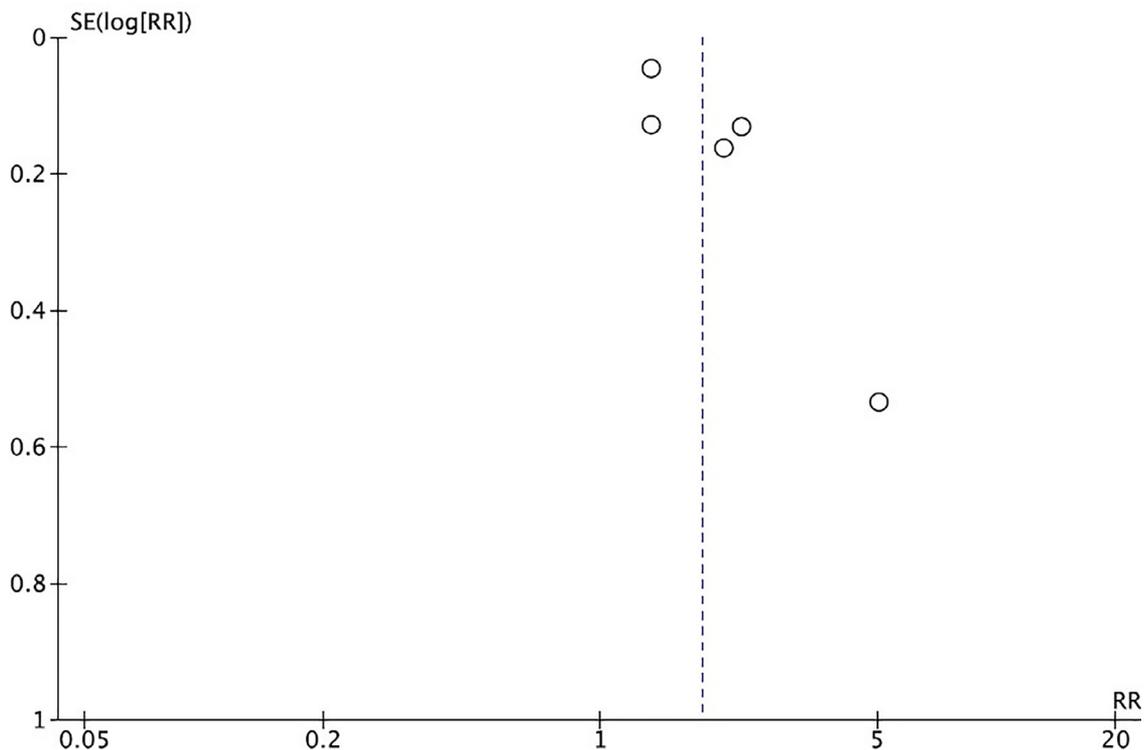**Figure 2.** *Forest plot of this meta-analysis.*

Figure 3. *Funnel plot of this meta-analysis.*

other observational designs) that can clearly demonstrate the temporal relationship between 2 variables, which is required for determination of causality. The pooled OR of the sensitivity analysis decreased slightly to 1.49 but remained statistically significant (95% CI, 1.20-1.86). Between-study heterogeneity also decreased to moderate level with I^2 of 69%.

Discussion

This current study is the first systematic review and meta-analysis that investigated the relationship between stroke and CRS. The results of the current study demonstrated that patients with CRS carried approximately 80% excess risk of stroke compared with individuals without CRS. The heightened risk was still observed even if only studies with more reliable design were included. There are some possible biological bases for this increased risk.

The first explanation is related to chronic inflammation generated by CRS. Studies have demonstrated that inflammation has hostile effects on the integrity and function of endothelial cell. Several inflammatory cytokines, such as C-reactive protein, interleukin-1, and interleukin-6, can activate immune cells and smooth muscle cells in the subendothelial layer, resulting in accelerated atherogenesis. This would eventually lead to premature atherosclerosis and cardiovascular diseases, including stroke.[20-21] In addition, inflammatory cytokines can cross-activate the coagulation cascade, leading to a higher chance of thrombus formation and thromboembolic events.[22-23] In fact, the increased risk of cardiovascular disease among patients with chronic inflammation is not unique to CRS and has been previously reported in other immune-mediated disorders.[24-27]

Second, several case reports have described patients with intracranial infection that occurred as a complication of CRS.[28-31] Intracranial infection can spread into intracranial artery, resulting in cerebral vasculitis which will compromise blood flow to brain parenchyma and cause cerebral ischemia.[12] Therefore, it is possible that some cases of CRS-related stroke were consequence of intracranial infection.

Third, medications used to treat CRS may also play a role in the increased risk of stroke. For instance, decongestants that are often used to relieve the symptom of nasal congestion can increase blood pressure, which is a prime risk factor for stroke.[32-33] Similarly, use of glucocorticoids, the commonly prescribed medications for the treatment of flare of CRS, is associated with several adverse metabolic effects that are predisposing factors for cardiovascular diseases, such as diabetes mellitus, hypertension, and dyslipidemia.[34]

It is also possible that the relationship between CRS and stroke is not causal but is a function of shared predisposing factor. One possible explanation is smoking which is a risk factor for both conditions.[35-36] The current meta-analysis cannot exclude the possibility of smoking as a confounder as most included studies did not adjust their effect estimates for smoking.

The current systematic review and meta-analysis had some limitations that may weaken the validity of the pooled analysis and, thus, the results should be interpreted with caution. First, the meta-analysis had high between-study heterogeneity. The differences in study design and methods used to diagnose CRS and stroke were the likely causes of this heterogeneity. Second, publication bias in favor of positive studies may have been present. Therefore, the pooled effect estimate may have been inflated. Third, all but 1 included study was conducted in Asia. Thus, generalizability of the observations to other population could be limited.

Conclusions

In conclusion, this study found that CRS is associated with a higher risk stroke. Whether this relationship is causal and how it should be addressed in clinical practice require further investigations.

Authors′ Contributions

All authors had access to the data and a role in writing the manuscript.

Supplementary Materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jstrokecerebrovasdis.2019.01.002.

References

1. Fokkens WJ, Lund VJ, Mullol J, et al. EPOS 2012: European position paper on rhinosinusitis and nasal polyps 2012. A summary for otorhinolaryngologists. Rhinology 2012;50:1-12.
2. Adams PF, Kirzinger WWK, Martinez ME. Summary health statistics for the U.S. population: National Health Interview Survey, 2012. National Center for Health Statistics. Vital Health Stat 2013;259:1-95.
3. Hastan D, Fokkens WJ, Bachert C, et al. Chronic rhinosinusitis in Europe—an underestimated disease. A GA2LEN study. Allergy 2011;66:1216-1223.
4. Lam K, Schleimer R, Kern RC. The etiology and pathogenesis of chronic rhinosinusitis: a review of Current Hypotheses. Curr Allergy Asthma Rep 2015;15:41.
5. Min JY, Tan BK. Risk factors for chronic rhinosinusitis. Curr Opin Allergy Clin Immunol 2015;15:1-13.
6. Centers for Disease Control and Prevention (CDC). Prevalence and most common causes of disability among adults—United States, 2005. MMWR Morb Mortal Wkly Rep 2009;58:421-426.
7. Barker-Collo S, Bennett DA, Krishnamurthi RV, et al. Sex differences in stroke incidence, prevalence, mortality and disability-adjusted life years: results from the Global Burden of Disease study 2013. Neuroepidemiology 2015;45:203-214.
8. Allen CL, Bayraktutan U. Risk factors for ischaemic stroke. Int J Stroke 2008;3:105-116.

9. The European Stroke Organisation (ESO) Executive Committee and the ESO Writing Committee. Guidelines for management of ischaemic stroke and transient ischaemic attack 2008. Cerebrovasc Dis 2008;25:457-507.

10. Li H, Liu HJ, Zhu QF, et al. Association between ischemic cerebrovascular disease and nasosinusitis evaluated by 3.0T MRI. J Clin Rehab Tissue Eng Res 2007;11:9722-9725.

11. Wu CW, Chao PZ, Hao WR, et al. Risk of stroke among patients with rhinosinusitis: a population-based study in Taiwan. Am J Rhinol Allergy 2012;26:278-282.

12. Kang JH, Wu CS, Keller JJ, et al. Chronic rhinosinusitis increased the risk of stroke: a 5-year follow-up study. Laryngoscope 2013;123:835-840.

13. Rosenthal PA, Lundy KC, Massoglia DP, et al. Incidental paranasal sinusitis on routine brain magnetic resonance scans: association with atherosclerosis. Int Forum Allergy Rhinol 2016;6:1253-1263.

14. Lee WH, Kim JW, Lim JS, et al. Chronic rhinosinusitis increases the risk of hemorrhagic and ischemic stroke: a longitudinal follow-up study using a national sample cohort. PLOS ONE 2018;13:e0193886.

15. Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality if non-randomized studies in meta-analyses. 2009. http://www.ohrica/programs/clinical_epidemiology/oxfordasp.

16. Herzog R, Alvarez-Pasquin MJ, Diaz C, et al. Are healthcare workers' intentions to vaccinate related to their knowledge, beliefs and attitudes? A systematic review. BMC Pub Health 2013;13:154.

17. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177-188.

18. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ 2003;327:557-560.

19. Easterbrook PJ, Berlin JA, Gopalan R, et al. Publication bias in clinical research. Lancet 1991;337:867-872.

20. Montecucco F, Mach F. Common inflammatory mediators orchestrate pathophysiological processes in rheumatoid arthritis and atherosclerosis. Rheumatology (Oxford) 2009;48:11-22.

21. Raggi P, Genest J, Giles JT, et al. Role of inflammation in the pathogenesis of atherosclerosis and therapeutic interventions. Atherosclerosis 2018;276:98-108.

22. Xu J, Lupu F, Esmon CT. Inflammation, innate immunity and blood coagulation. Hamostaseologie 2010;30:8-9.

23. Esmon CT. The interactions between inflammation and coagulation. Br J Haematol 2005;131:417-430.

24. Ungprasert P, Cheungpasitporn W, Wijarnpreecha K, et al. Risk of ischemic stroke in patients with polymyositis and dermatomyositis: a systematic review and meta-analysis. Rheumatol Int 2015;35:905-909.

25. Ungprasert P, Sanguankeo A, Upala S. Risk of ischemic stroke in patients with systemic sclerosis a systematic review and meta-analysis. Mod Rheumatol 2015;29:1-12.

26. Arkema EV, Svenungsson E, Von Euler M, et al. Stroke in systemic lupus erythematosus: a Swedish population-based cohort study. Ann Rheum Dis 2017;76:1544-1549.

27. Crowson CS, Liao KP, Davis JM, et al. Rheumatoid arthritis and cardiovascular disease. Am Heart J 2013;166:622-628. e1.

28. Perez Barreto M, Sahai S, Ameriso S, et al. Sinusitis and carotid artery stroke. Ann Otol Rhinol Laryngol 2000;109:227-230.

29. Rochat P, von Buchwald C, Wagner A. Sinusitis and ischemic stroke. Rhinology 2001;39:173-175.

30. Macdonald RL, Findlay JM, Tator CH. Sphenoethmoidal sinusitis complicated by cavernous sinus thrombosis and pontocerebellar infarction. Can J Neurol Sci 1988;15:310-313.

31. Righini CA, Bing F, Bessou P, et al. An acute ischemic stroke secondary to sphenoid sinusitis. Ear Nose Throat J 2009;88:E23-E28.

32. Buysschaert I, Van Dorpe J, Dujardin K. Hypertensive crisis and end-organ damage induced by over-the-counter nasal decongestant abuse. Eur Heart J 2011;32:3114.

33. Salerno SM, Jackson JL, Berbano EP. Effect of oral pseudoephedrine on blood pressure and heart rate: a meta-analysis. Arch Intern Med 2005;165:1686-1694.

34. Da Saliva JA. Safety of glucocorticoids—clinical trials. Clin Exp Rheumatol 2011;29:S99-S103.

35. Christensen DN, Franks ZG, McCrary HC, et al. A systematic review of the association between cigarette smoke exposure and chronic rhinosinusitis. Otolaryngol Head Neck Surg 2018;158:801-816.

36. Bhat VM, Cole JW, Sorkin JD, et al. Dose-response relationship between cigarette smoking and risk of ischemic stroke in young women. Stroke 2008;39:2439-2443.