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Effect of Influenza Vaccination on Risk of Stroke: A Systematic Review and Meta-Analysis

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Influenza vaccination · Influenza · Stroke

Abstract
Background: Despite the presence of a strong association between influenza infection and stroke, whether influenza vaccination reduces the risk of stroke is yet a matter of controversy. We conducted a meta-analysis to determine whether influenza vaccination protects against stroke. ***Methods:*** We searched PubMed, EMBASE, and the Cochrane Library from database inception date to November 18, 2016, without language restrictions, to identify studies investigating the effect of influenza vaccination on subsequent risk of stroke. We conducted a meta-analysis to quantify the risk of stroke in overall and subgroup analyses and calculated a pooled OR for developing stroke with a 95% CI. Publication bias was assessed by Begg's rank correlation test. ***Results:*** Eleven studies fulfilled our inclusion criteria. In a random-effects model, vaccinated individuals had a decreased risk of stroke compared with unvaccinated individuals (OR 0.82; 95% CI 0.75–0.91; $p < 0.001$). The relationship between influenza vaccination and stroke risk remained robust in subgroup analyses. The significant effect of influenza vaccination was associated with ascertainment of vaccination status and stage of prevention. ***Conclusion:*** Vaccination against influenza is associated with a lower risk of stroke. Well-designed prospective studies are needed to provide stronger evidence of the protective effect of influenza vaccination against stroke.

Introduction

Stroke is a leading cause of death worldwide and can also result in long-term disability; about 5 million stroke survivors are alive today [1]. Over the last 30 years, the age-adjusted incidence of stroke has declined, but the aging of the population suggests that absolute numbers of stroke will increase over the next decades [2]. To prevent stroke, it is important to identify and modify risk factors. Besides conventional risk factors for stroke (i.e., increasing age, hypertension, smoking, diabetes, and elevated cholesterol), current evidence has raised the possibility that other risk factors, such as infection, also play a role [3].

Cardiovascular disease (CVD) including stroke is more common in the winter and during influenza epi-

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demics, which could partially be explained by seasonal changes in metabolic risk factors or cold-induced vascular stress [4, 5]. However, a large body of evidence suggests that influenza itself could be a trigger of major CVD, further adding to the morbidity and mortality associated with this infection. A recent meta-analysis [6] shows that influenza infection is significantly associated with acute myocardial infarction, and a similar association with stroke was reported in several previous studies [7, 8]. This poses the question of whether immunizing against influenza could reduce the risk of major CVD.

Of late, there is growing interest in the use of influenza vaccines for preventing CVD, primarily coronary artery disease In mouse models, influenza vaccination protects against acute myocardial infarction, with reduced atherosclerotic plaque size, increased plaque stability, and decreased pro-inflammatory markers [9]. An increasing body of evidence suggests that influenza vaccines protect against heart disease in terms of both primary prevention and secondary prevention [6, 10]. However, associations with the risk of stroke have been investigated in limited epidemiological studies and their results have been inconsistent. Whereas some studies showed that influenza vaccination, either alone [8, 11–13] or combined with pneumococcal vaccine [14], was associated with reduced risk of stroke, other studies did not [15].

Many countries recommend annual influenza vaccination for elderly people and/or those with CVD, which are risk groups for serious influenza infection. Also, influenza vaccination is estimated to be a cost-effective method of influenza prevention among older adults without direct consideration of CVD protection [16]. If influenza vaccination has a protective effect against stroke, this could increase the rate of vaccinations, which are currently underused [17]. Thus, we conducted a meta-analysis of studies investigating the protective effect of influenza vaccination against stroke.

Methods

Search Strategy

We searched PubMed, EMBASE, and the Cochrane Library from the databases' inception to November 18, 2016, without language restrictions. Search terms were related to stroke (stroke or cerebrovascular disease or cerebrovascular accident or transient ischemic accident) and influenza vaccination (influenza vaccine or influenza vaccination or flu vaccine or flu vaccination). We also reviewed the reference lists of relevant articles to identify additional papers not captured in the database searches. Our review followed the guidelines for meta-analysis of observational studies in epidemiology [18]. Ethical approval was not required because the data included in this study were extracted from published literature.

Study Selection and Inclusion Criteria

We included original studies of the association between influenza vaccination and stroke risk in humans. Eligibility criteria were the reporting of the risk of stroke (i.e., not only stroke-related mortality) and measures of association (e.g., hazard ratio, incidence ratio, OR) and precision (e.g., CI) irrespective of study design. We collected the fully adjusted measures of association. In the case of multiple publications based on the same study sample, the most relevant publication was included in the analysis. As an individual's risk of CVD and likelihood of receiving a vaccine is known to increase over an observation period [19], we considered stroke data only from the year that the vaccination was received [13, 20].

Data Extraction

All potentially relevant articles were independently evaluated by 2 investigators, and disagreements were resolved by consensus or consultation with a third author. The following data were extracted from each study: first author, year of publication, country, study population and setting, study design, stroke subtype, method of ascertainment of vaccination status, stage of prevention, measures of association with corresponding 95% CIs, and core-adjusted variables. Some estimates had to be recalculated (e.g., pooling the estimates of 2 cohorts [12] and those for various time periods after vaccination [8]). We used the Newcastle-Ottawa Scale (NOS) to assess the methodological quality of studies (online suppl. Table 1, see www.karger.com/doi/10.1159/000478017). Low quality was defined as an NOS score ≤7 and high quality as an NOS score ≥8 (maximum score, 9). Further, we stratified articles by their risk of selection bias based on core-adjusted variables into low, moderate, or high risk.

Statistical Analysis

We investigated the effect of influenza vaccination on subsequent risk of stroke. Subgroup analyses were performed depending on the methodological quality (low or high), the risk of selection bias (low risk or moderate to high risk), method of ascertainment of vaccination status (computerized database or recall), stage of prevention (first stroke, recurrent stroke, or any stroke), and stroke subtype (all types or ischemic stroke). We calculated a pooled OR with a 95% CI from those reported in the individual studies. We assumed that the other relative measures were close to the OR because the stroke incidence was sufficiently low for the rare disease assumption to apply [21]. To calculate the variance of log OR from each study, we converted the 95% CI to its natural logarithm by taking the width of the CI and dividing it by 3.92. To test for heterogeneity, we used Higgins I^2, which indicates the percentage of variation across studies (0–100%). When substantial heterogeneity (I^2 >50%) was observed, we used the DerSimonian and Laird random-effects model, which is the generally preferred approach. Publication bias was assessed using the Begg's rank correlation test. All statistical analyses were performed with Stata version 12.1 (StataCorp, College Station, TX, USA).

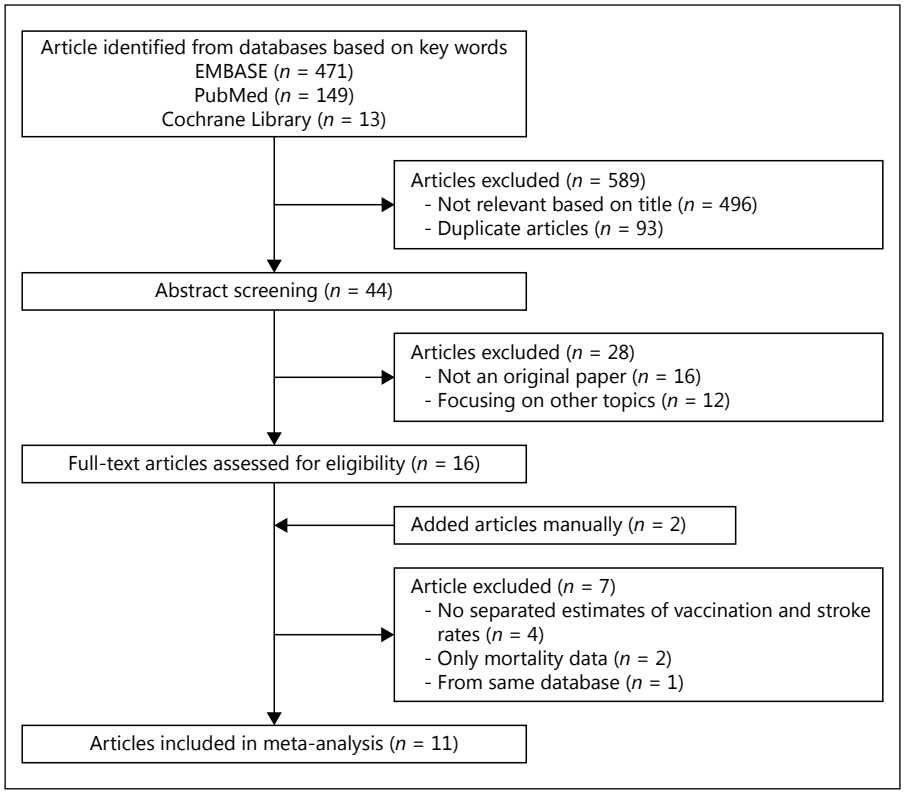

Fig. 1. Flow diagram for identifying relevant articles.

Results

Figure 1 shows a flow diagram for the identification of relevant studies. Of the 633 articles retrieved, 44 underwent abstract review, and 16 of these met our eligibility criteria. After reviewing the full text of these 16 articles, we excluded 7 articles for the following reasons: no separate estimate of influenza vaccination or on stroke ($n = 4$), only mortality data presented ($n = 2$), or the data were from a sample described by another study included in our analysis ($n = 1$). After adding 2 studies identified through manual searches, a total of 11 studies were included in the final analysis. Of 3 studies sampled from the United Kingdom General Practice Research Database, 2 studies included overlapping groups of participants [22, 23]; we used data from each study in overall and subgroup analyses as appropriate.

Characteristics of the included studies are summarized in Table 1. Most were conducted in western countries ($n = 9$). Two studies [14, 24] were prospective intervention designs. Half of the studies were limited to elderly people ($n = 5$), and half of the studies reliably ascertained vaccination status ($n = 6$). Information on stroke subtype (i.e., all strokes, ischemic stroke, and hemorrhagic stroke) varied across studies. The risk of selection bias was assessed based on core-adjusted variables, and 7 studies [8, 11, 13, 14, 23–25] were deemed to have a low risk of bias.

Overall, vaccinated individuals had a decreased risk of stroke (OR 0.82; 95% CI 0.75–0.91; $p < 0.001$; Fig. 2). No single study had an unduly large influence on the results. The association between influenza vaccination and stroke risk remained robust in most subgroup analyses; some did not reach significance (Table 2). Funnel plot asymmetry among studies was not observed among the studies ($p = 0.299$; Fig. 3).

Discussion

Given that influenza infection is a trigger of stroke, a logical and appealing inference is that influenza vaccination could prevent stroke. Influenza vaccination has been approved as a simple protective strategy for reducing influenza-related complications [26]. In this meta-analysis, we found that vaccinated people have a decreased risk of developing stroke, which has considerable clinical and health policy implications given the profound underuse of vaccinations. This finding also suggests that influenza itself and/or its associated morbidity could be an underrecognized residual CVD risk factor.

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Table 1. Characteristics of studies on the effect of influenza vaccination on stroke risk within the same year

Source	Country	Participant age	Setting	Design	Vaccination from	Prevention for	Stroke risk (95% CI)	Core adjusted variables	Selection bias
Vamos et al. [22], 2016	UK	≥18 years old[a]	114,198 vaccinated/ 59,882 unvaccinated	Nested case-control	Database	Any stroke	All: 0.70 (0.53–0.91)	Lifestyle factors Non-season data	Moderate
Siriwardena et al. [23], 2014	UK	≥18 years old	26,784 stroke patients/ 26,784 matched controls	Nested case-control	Database	First stroke	All: 0.81 (0.77–0.85)	Lifestyle factors GP consultation rate	Low
Lavallee et al. [24], 2014	International	≥18 years old[b]	17,363 vaccinated/ 5,747 unvaccinated	Prospective cohort	Questionnaire	Recurrent stroke	IS: 1.01 (0.88–1.17)	Propensity score matching Lifestyle factors	Low
Lin et al. [20], 2014	Taiwan	≥65 years old	520 stroke patients/2,600 matched controls	Nested case-control	Database	First stroke	All: 0.80 (0.64–0.98) IS: 0.76 (0.60–0.97) HS: 0.89 (0.56–1.42)	None	High
Hung et al. [14], 2010	Hong Kong	≥65 years old	2,076 vaccinated/ 25,393 unvaccinated	Prospective cohort	Intervention	Any stroke	IS: 0.85 (0.61–1.17)	SES smoking	Low
Pinol-Ripoll et al. [15], 2008	Spain	NR	393 stroke patients/393 matched controls	Case-control	Interview	Any stroke	IS: 1.02 (0.77–1.36)	Lifestyle factors	Moderate
Puig-Barbera et al. [25], 2007	Spain	≥65 years old	134 stroke patients/ 246 matched controls	Case-control	Database	Any stroke	All: 0.07 (0.01–0.48)	Lifestyle factors Use of healthcare Functionality Propensity score Non-season data	Low
Grau et al. [11], 2005	German	NR	370 stroke patients/ 370 matched controls	Case-control	Interview	Any stroke Recurrent stroke	All: 0.46 (0.28–0.77) IS: 0.37 (0.22–0.60) HS: 0.31 (0.08–1.21) All: 0.46 (0.30–0.68)[c]	Lifestyle factors SES Non-season data	Low
Smeeth et al. [8], 2004	UK	≥18 years old	19,063 stroke patients 4,125 stroke patients	Nested case-control	Database	First stroke Recurrent stoke	All: 0.86 (0.76–0.97)[c] All: 0.75 (0.70–0.82)[c]	Case-series method	Low
Nichol et al. [12], 2003	USA	≥65 years old	165,095 vaccinated/ 121,288 unvaccinated	Nested case-control	Database	Any stroke	All: 0.80 (0.72–0.90)[c]	Use of healthcare	Moderate
Lavallee et al. [13], 2002	France	≥60 years old	90 stroke patients/ 180 matched controls 149 stroke patients/ 270 matched controls	Case-control	Interview	First stroke Any stroke	IS: 0.37 (0.15–0.87) IS: 0.50 (0.26–0.94)	Lifestyle factors SES Use of healthcare	Low

UK, United Kingdom; NR, not reported; IS, ischemic stroke; HS, hemorrhagic stroke; GP, general practitioner; SES, socioeconomic status.
[a] All participants had type 2 diabetes.
[b] Pooled from 2 prospective cohort studies and one randomized trial, all of which included patients with recent ischemic stroke or transient ischemic accident.
[c] Recalculation.

Table 2. Stroke risk among individuals who received influenza vaccination

	Number of studies	Summary OR (95% CI)	Heterogeneity, I^2, %	Model
Overall [8, 11–15, 20, 23–25]	10	0.82 (0.75–0.91)	63.5	Random-effect
Study quality[a]				
Low [11–13, 15, 20, 22, 24, 25]	8	0.78 (0.65–0.93)	72.2	Random-effect
High [8, 14, 23]	3	0.81 (0.77–0.85)	0	Fixed-effect
Risk of selection bias				
Low [8, 11, 13, 14, 23–25]	7	0.79 (0.68–0.92)	72.9	Random-effect
Moderate to high [12, 15, 20, 22]	4	0.81 (0.74–0.88)	18.9	Fixed-effect
Vaccination status				
Confirmed [8, 12, 14, 20, 23, 25]	6	0.81 (0.77–0.84)	20.6	Fixed-effect
By recall [11, 13, 15, 24]	4	0.77 (0.55–1.09)	76.3	Random-effect
Prevention for				
First stroke [8, 13, 20, 23]	4	0.81 (0.78–0.85)	23.8	Fixed-effects
Any stroke [11–15, 22, 25]	7	0.73 (0.59–0.90)	63.5	Random-effects
Recurrent stroke [8, 11, 24]	3	0.75 (0.70–1.01)	89.9	Random-effects
Stroke subtype				
All strokes [8, 11, 12, 20, 23, 25]	6	0.79 (0.71–0.86)	54.1	Random-effect
Ischemic stroke [11, 13–15, 20, 24]	6	0.77 (0.60–0.98)	75.6	Random-effect

[a] Assessed using the NOS score (≤7 vs. ≥8).

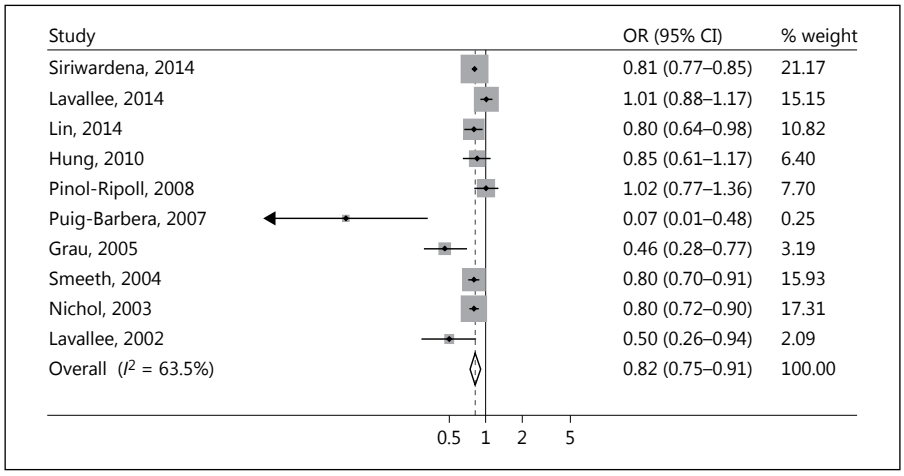

Fig. 2. Forest plot showing the effect of influenza vaccination on risk of stroke. OR, odds ratio; CI, confidence interval.

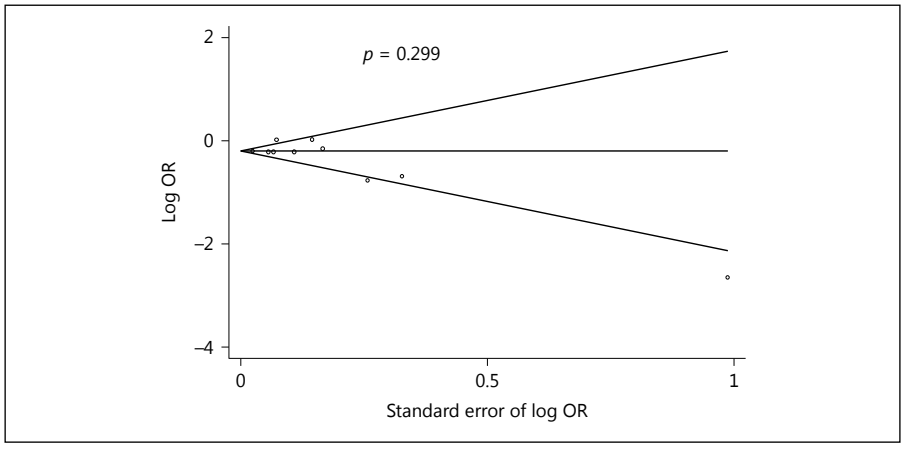

Fig. 3. Begg's funnel plot with 95% confidence limits for incident stroke among the included studies. OR, odds ratio.

The question of whether influenza vaccination has a preventive effect against stroke can be definitively answered only with a trial design. Although a small randomized controlled trial sought this question, stroke events were too rare to analyze [27]. Instead, most previous studies have employed an observational design, which is susceptible to many potential biases. A crucial but inevitable flaw in observational studies is the presence of systematic differences between vaccine recipients and nonrecipients [28]. Attitudes toward health issues, especially for primary prevention such as vaccination, are tightly associated with health consciousness and socioeconomic factors, and healthier people at lower risk of stroke are more likely to be vaccinated [29]. To minimize this "healthy vaccine" bias, researchers have adjusted for other preventive (e.g., a blood cholesterol assay) and lifestyle factors in their analyses. Indeed, our sub-analysis of studies stratified by their risk of selection bias indicates that this bias may amplify the protective effect of influenza vaccination. The converse bias that people who are frailer are less likely to be vaccinated and more likely to suffer stroke (referred to as "frailty bias") is also potentially important [30], but few studies have adjusted for relevant confounding factors (e.g., general practitioner consultation rate).

Although self-reported vaccination history is reported to be highly accurate [31], our analysis indicates that problems in recall could inflate the observed protective effect of vaccination, as stroke patients might not accurately remember their vaccination status. Also relying on one's memory of the date of their influenza vaccination could result in immortal time bias. Therefore, agreement between self-reports and computerized databases is needed to confirm vaccination status in future studies. Furthermore, interview-based studies are also prone to selection bias because severe stroke patients (i.e., with aphasia or reduced consciousness) are ineligible.

Several mechanisms could explain the association between influenza vaccination and stroke risk. Compelling evidence suggests that nearly all types of infectious agents increase the incidence of stroke, and the risk of stroke might be associated with an aggregate viral burden rather than an individual pathogen, not excepting influenza [32]. The influenza-induced systemic inflammatory response precipitates vulnerable plaque rupture via altered concentrations of reactant proteins and cytokines, accelerates endothelial injury by impairing vasodilatation via metabolic derangements, and enhances thrombotic tendencies through altered clotting factors and platelet dysfunction [33]. In a study with apoE knockout mice, influenza vaccination resulted in atherosclerotic regions with lower lipid content and higher concentrations of smooth muscle cells and collagen [9].

The immune response to vaccination itself may be another mechanism by which vaccination confers a reduced risk of CVD. Vaccine-induced antibodies activate the bradykinin-2 receptor that induces nitric oxide production and vasodilatation, which may eventually result in atherosclerotic plaque stabilization [34]. However, this observation was made in animals with intact immune responses. Moreover, clinical studies exploring the effect of other vaccines could not support this hypothesis. In particular, a large case-series study showed that tetanus vaccination did not produce a detectable change in the risk of major CVDs [8], and Grau et al. [11] reported that other combined vaccinations were not associated with reduced risk of stroke.

Overall, ischemic strokes make up 80–90% of all stroke cases. Most pathogenic mechanisms of infection are more closely linked to ischemic strokes than hemorrhagic strokes, as inflammatory cascades promote atherosclerosis, plaque rupture, and thrombosis, leading to ischemic stroke [3]. Influenza vaccination may also protect against ischemic strokes such as cardiac embolism by reducing heart disease, which may prevent thromboembolic complications in the brain. By contrast, few published studies have assessed the association between infection and hemorrhagic strokes, although infection can contribute to aneurysmal rupture through endothelial instability via procoagulant mechanisms, fever, dehydration, and proteolytic lesions to the vessel wall [3]. One case-control study [35] identified a borderline association between subarachnoid hemorrhage and recent respiratory infection, and a larger prospective study [36] failed to detect an association with intracranial hemorrhage. To our knowledge, preventive effect of influenza vaccination against hemorrhagic stroke has been explored only in 2 studies, but neither reached significance [11, 20].

Given the seriousness of CVD morbidity, the effect size for influenza vaccination would be lower for a first stroke than for other stages of prevention. Well-designed studies show that vaccines are less effective in healthy people [37]. A recent meta-analysis also shows that the largest effect of influenza vaccination is seen among patients with the highest CVD risk [10]. A major caveat is that this finding was the result of "indication bias," in that individuals with higher CVD risk are more likely to be offered vaccination. However, our finding suggests that influenza vaccination could confer additional health benefits in terms of stroke prevention even in low-risk populations.

This meta-analysis has several limitations. First, most studies were conducted in Western societies, whereas Asian and Western cultures differ notably with regard to stroke incidence and stroke-prone behaviors [38]. The pattern of vaccination uptake may also vary across countries, whereas studies included in our analysis were performed only in high-income countries with established influenza vaccination recommendations. Second, there were large variations across years in influenza activity, pathogenicity of circulating strains, and degree of vaccine-virus antigenic match. The effectiveness of annual influenza vaccines on CVD risk may vary depending on the vaccine match to circulating strains, although incompletely matched influenza vaccines still provide protection [39]. The timing of vaccination is also important, as the protective effect of influenza vaccination against stroke wanes over time following vaccination [40].

This meta-analysis of observational studies shows that influenza vaccination is associated with a lower risk of stroke events. Influenza vaccination is a readily available, inexpensive, and safe intervention that may reduce the risk of stroke. Our results underline current recommendations for annual influenza vaccination with the additional benefit of stroke prevention. Future randomized controlled trials are needed to confirm the protective effect of influenza vaccination on the risk of stroke.

Disclosure Statement

None declared.

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