Migraine and the risk of stroke: a systematic review and meta-analysis

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Abstract

Background and Purpose

The relationship between migraine status and stroke risk was not determined. This study aims to summarize the existing evidence from prospective cohort studies.

Methods

We searched Pubmed, Embase, and the Cochrane Library from inception to Dec 2020, and all retrieved articles were screened by two independent reviewers. We extracted and assessed data by a structured and standardized data extraction form. The effect values were calculated using a random-effects model. This review was prospectively registered with the PROSPERO database (CRD42020197137).

Results

Out of 10,705 records, 19 cohort studies including a combined total of 3,523,235 participants were finally included in the meta-analysis. At a mean of 9.31 years (range 1.4–20 years) follow-up, migraine was associated with an elevated risk of total stroke (pooled RR 1.69, 95%CI 1.36 to 2.11, $P < 0.001$, $I^2 = 86\%$), ischemic stroke (pooled RR 1.46, 95%CI 1.14 to 1.87, $P < 0.001$, $I^2 = 95.8\%$), and hemorrhagic stroke (pooled RR 1.37, 95%CI 1.04 to 1.81, $P < 0.001$, $I^2 = 85.9\%$). The prespecified subgroup analysis found that this kind of relationship existed in migraine with aura (ischemic stroke: pooled RR 1.75, 95%CI 1.35 to 2.29, $P < 0.001$, $I^2 = 81.7\%$; hemorrhagic stroke: pooled RR 1.63, 95%CI 1.26 to 2.10, $P = 0.266$, $I^2 = 23.2\%$), but not migraine without aura.

Conclusions

Our study implies that migraine, particularly migraine with aura, was associated with an increased risk for both ischemic and hemorrhagic stroke.

Introduction

According to the Global Burden of Disease Study, migraine is becoming the second cause of years lived with disability (YLDs) in the general population¹ and the most disabling disease among people under 50 years old². Among all the neurological disorders, stroke and migraine rank the top two in disability-adjusted life years (DALYs)³, causing severe health and socioeconomic burdens. Some case-control studies and cohort studies have found that people with migraine or a history of migraine will present an elevated stroke risk⁴, which implies the possibility that migraine is a modifiable risk factor for stroke.

Since the latest systematic reviews concerning migraine and stroke risk^{5,6,7,8,9}, new cohort studies have been published, especially many with prospective cohort design and large population sample. We performed an updated meta-analysis by comprehensively meta-analyzing all relevant studies published to date. As the evidence from prospective cohort studies presents a higher quality level, we only include prospective cohort studies to make a qualitative and quantitative evaluation for the longitudinal effect of migraine status on stroke risk. Since the mechanisms underlying ischemic and hemorrhagic stroke are quite different, we investigated the relationship of migraine status with different stroke subtypes (ischemic versus hemorrhagic) separately. Some studies did not specify the subtype of stroke or only calculated total stroke events, so we also investigated the relationship of migraine status with total stroke events (also called unspecified stroke events).

Methods

Search Strategy

Three databases (PubMed, EMBASE, and the Cochrane Library) were independently searched for research on the relationship of migraine status with stroke risk from earliest inception to Dec 02, 2020, by two independent investigators (S.M.J. and W.M.Y.). The following search terms were used to identify potential studies for inclusion: (migraine OR headache) and (stroke OR cerebrovascular disease OR cerebrovascular disorder OR cerebrovascular accident OR cerebrovascular event OR cerebral ischemia OR brain ischemia OR ischemic stroke OR cerebral infarction OR brain infarction OR brain hemorrhage OR hemorrhagic stroke). The Medical Subject Heading (MeSH) terms, as well as the “explode” option available in EMBASE, were applied. No search filters or restrictions were applied. Besides, we conducted a manual search in reference lists of retrieved studies and relevant review articles in this field to prevent missing any potential studies. We carefully followed the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines^{10,11}. This meta-analysis was prospectively registered with the PROSPERO database (CRD42020197137).

Eligibility Criteria

Only published and full-text available studies were taken into consideration. The final inclusion criteria include: (1) Studies should be a prospective cohort study, (2) Studies should report clear diagnostic criteria for both migraine status and stroke events, (3) Studies should have an explicit assessment for stroke outcomes, whether it was hemorrhagic, ischemic, or both, and (4) The research results should include a measure of the association of migraine on stroke risks, such as odds ratio (OR), relative risk (RR), or hazard ratio (HR) with 95% confidence interval (CI), or provide enough data to allow calculation for these effect estimates.

We excluded the retrospective cohort studies, cross-sectional studies, or case-control studies, etc. Subjects included in cohort studies should be grouped by migraine, not any other type of headache. We also excluded studies which not focused on the incidence of specific or total stroke, but the death of stroke, hospital readmission of stroke, etc. Finally, we excluded studies that did not report essential data. However, if essential data can be obtained from provided data by mathematical calculation, the study should be included. If more than one selected articles drew its conclusion from a single study cohort, we chose to include the study with the latest follow-up time or the longest follow-up period, or with the most detailed information. However, if one reported the relationship of migraine status with ischemic stroke and the other one reported that with hemorrhagic stroke, they were regarded as completely different results and both studies should be included in our analysis.

Data Extraction

Two independent investigators(S.M.J. and W.M.Y.) completed the data extraction procedure respectively. A structured and standardized data extraction form was employed to extract the following information: last name of the first author, publication year, country, the population characteristics (the mean age at baseline, sex, the study size of cohort sample, the number of events), the subtypes of stroke (total, ischemic, or hemorrhagic), and duration of follow-up time, fully adjusted effect estimate values, and the adjusted confounders in the final analysis. Any discrepancy was resolved by group discussion including all authors.

Quality assessment

The Newcastle-Ottawa quality assessment scale¹² was used to assess the research quality of all included studies. If the score of one study achieved 7 out of 9 points, this study was considered high quality. A prespecified sensitivity analysis including studies ranked high-quality by the Newcastle-Ottawa Scale was performed. The publication bias was evaluated through the visual inspection of funnel plots and Egger's test¹³.

Statistical Analysis

For prospective cohort studies, the effect estimates should be represented by RR or HR with 95% confidence intervals (CIs) and RR or HR can be pooled together without distinction¹⁴. In this meta-analysis, two included publications chose odds ratios (ORs) with their 95% CIs as estimate effect size^{15,16}. Considering the extremely low incidence of stroke events in the general population, OR can be equally regarded as RR/HR without distinction¹⁴. Besides the calculation of the overall pooled effect estimates, we also computed results separately for different effect estimates for comparison.

The random-effects meta-analysis model by the method of Der-Simonian and Laird was adopted for all analyses to calculate the pooled estimates and 95 % CIs¹⁷. The estimate of heterogeneity across individual studies was quantified by the Cochrane Q test with a significance level at $p < 0.10$ and Higgins I^2 index¹⁸. An I^2 value of $>50\%$ was regarded as high heterogeneity. In observational studies, the adjustment of possible confounding factors will certainly affect the validity and the reliability of effect sizes. Therefore, the effect values from adjusted models rather than that from the crude ones were chosen. When there are more than one available adjusted models, the model adjusted for maximum number of confounding variables, also called the most adjusted model, was chosen.

The analysis showed results separately for different stroke subtypes, including total stroke (also called unspecified stroke), ischemic stroke, and hemorrhagic stroke. As aura was considered to be a potential effect modifier in prior meta-analyses, subgroup analyses stratifying for different migraine subtypes (i.e. migraine without aura versus migraine with aura) were planned. We also performed subgroup analyses stratifying for different subgroups of age and sex when the corresponding data applicable. To further explore sources of heterogeneity, we performed random-effects model meta-regression analyses, which included the evaluation of the age at baseline, the midpoint of the recruitment time, and length of the follow-up period.

All statistical analyses were performed using the STATA statistical software (version 16.0, 2019; Stata Corp, College Station, Texas, United States). All statistical tests were two-sided and $p < 0.05$ was considered statistically significant, except where otherwise specified.

Results

Literature search

The process of literature identification and inclusion was shown in Figure 1. Initially, 15,087 articles were identified with the search terms previously described, of which 10,705 non-repeated articles remained after duplicates articles were removed. We excluded 10,624 reports according to the title and abstract as the contents of these articles did not correspond with our research topic. Among the remaining 81 articles, 62 were further excluded for various reasons: 28 were comments, reviews, meta-analysis, conference abstract/summary, erratum, and note, etc.; 14 were the case-control, retrospective cohort, or cross-sectional design; 2 evaluated other types of headache, but not migraine; 6 reported hospitalization rate or stroke-related mortality rate, but not the incidence of stroke; 8 did not report required extractable data on the variables of interest; 4 studies reported earlier results and overcome by larger ones(supplementary table 2). Eventually, 19 studies published between 1995 and 2019 were eligible for our final review and meta-analysis.

Characteristics of the included studies

The basic characteristics of the 19 selected studies were represented in Table 1. The 19 studies included for the analysis were published from 1995 to 2019 and came from six different countries. The follow-up period varied from 17 months up to around 20 years. The cohort size ranged from 917 to 1,411,306 and enrolled a total of 3,523,235 participants. These studies included 661,057 migraineurs and 2,755,670 non-migraineurs, and reported 32,379 stroke events in total.

Out of the 19 studies, 6 studies reported the outcome of total stroke only^{15,19,20,21,22,23}, 3 study reported the outcome of ischemic stroke only^{24,25,26}, and 2 study reported the outcome of hemorrhagic stroke only^{27,28}. 2 studies reported the outcome of both ischemic and hemorrhagic stroke^{29,30}, 1 study reported the outcome of both total and ischemic stroke¹⁶, 5 studies reported the outcome of total stroke, ischemic and hemorrhagic stroke^{31,32,33,34,35}. Notably, the study cohort of the Women's Health Study updated the outcome of hemorrhagic stroke in 2010 separately after the initial report of all stroke outcome in 2005^{27,33}. Similarly, the outcome of the Physician's Health Study reported all outcomes in one publication except the subsequent renewal of ischemic stroke^{24,31}.

Out of all the studies, 2 studies included only male participates^{24,31}, 4 studies included only female participates^{22,23,27,33}, and the leaving 13 studies included both male and female participates. The information on the method of migraine assessment and the definition of stroke by each study was available in supplementary table 3.

Quality assessment

The quality of 19 included studies were evaluated by the Newcastle-Ottawa Quality Assessment Scale, the results of which were summarized in Table 2. Sixteen studies scored more than 7 points and ranked high quality, while the other three studies were rated as moderate quality with a score of fewer than 7 points^{15,23,34}. Eighteen out of the 19 studies made adjustments for at least three variables for statistical analysis except for only one study³⁴. Some commonly adjusted variables included age (18 studies), sex (11 studies), body mass index (BMI) (12 studies), history of smoking (12 studies), hypertension (16 studies), diabetes mellitus (16 studies), hyperlipidemia (15 studies), and aspirin medication (8 studies) (supplementary table 4).

Association between migraine and stroke risk

Figure 2A shows the relationship of migraine status with the risk of total stroke events. Among all the 12 studies, 8 studies found a positive correlation, while the other 4 studies attained no statistical significance. The pooled adjusted effect size for the outcome of total stroke events was 1.69 with 95% CI from 1.36 to 2.11 and substantial heterogeneity ($I^2 = 86.0\%$, Q-statistic P-value <0.001). Figure 2B demonstrates the correlation of migraine status with the ischemic stroke risk. Out of the 11 studies, six studies reported a positive correlation, and the other 5 studies found no statistical significance. The pooled RR was 1.46 with 95% CI from 1.14 to 1.87 ($I^2 = 95.8\%$, $p < 0.001$). Figure 2C shows the correlation of migraine status with hemorrhagic stroke risk. Among all the 8 studies, 2 showed a positive association and the other 6 studies had no statistical significance. The pooled RR was 1.37 with 95%CI ranging from 1.04 to 1.81 ($I^2 = 85.9\%$, $p < 0.001$). Overall, our results founded that migraine was associated with an elevated risk of total, ischemic, and hemorrhagic stroke.

Subgroup and sensitivity analyses

Results separately for different effect estimates did not illustrate any statistically significant differences (supplementary figure 1). Similarly, the sensitivity analysis limited to high-quality studies did not alter the pooled effect sizes substantially (supplementary figure 2). Besides, there existed no significant differences in the direction of effect size when any one study was excluded from the analysis (supplementary figure 3). Although some studies declared that only with enough long follow-up time, there existed a significant relationship between migraine and hemorrhagic stroke²⁷, the results from our meta-regression analyses indicated that the age at baseline, the midpoint of the recruitment time, and length of follow-up period accounted for no significant statistical heterogeneity.

Of the 19 studies included in the analysis, 7 reported the effect size representing the association between different migraine subtypes and ischemic stroke^{16,25,26,29,30,33,35}, and 5 reported that value for hemorrhagic stroke^{27,28,29,30,35}. The prespecified subgroup analysis showed that migraine with aura was related to an elevated risk of ischemic stroke (the pooled RR 1.75, 95%CI 1.35 to 2.29, $P < 0.001$, $I^2 = 81.7\%$), while we found no significant relationship between migraine without aura and ischemic stroke risk (the pooled RR 1.17, 95%CI 0.94 to 1.46, $P < 0.001$, $I^2 = 86.7\%$) (figure 3A). This was also true for hemorrhagic stroke: there was evidence of the association between migraine with aura and an elevated risk of hemorrhagic stroke (the pooled RR 1.63, 95%CI 1.26 to 2.10, $P = 0.266$, $I^2 = 23.2\%$), while no positive relation was found between migraine without aura and hemorrhagic stroke (the pooled RR 1.32, 95%CI 0.99 to 1.74, $P = 0.012$, $I^2 = 69.1\%$) (figure 3B). The statistical heterogeneity concerning the outcome of hemorrhagic stroke was improved when the subgroup analysis stratifying for the aura status was performed.

Due to the lack of data, subgroup analysis stratifying for different age subgroups could not be performed. Subgroup analysis stratifying for sex did not show any difference for ischemic stroke. Both female and male migraineurs showed an elevated risk of ischemic stroke (For female: the pooled effect size 1.29, 95%CI 1.13 to 1.47, $P = 0.748$, $I^2 = 0.0\%$; For male: the pooled effect size 1.24, 95%CI 1.01 to 1.52, $P = 0.224$, $I^2 = 33.1\%$) (figure 4A). Some interesting statistics results were found for subgroup analysis for hemorrhagic stroke. The results from the pooled analysis showed that female migraineurs were not at a higher risk of hemorrhagic stroke (the pooled RR 1.44, 95%CI 0.74 to 2.81, $P = 0.034$, $I^2 = 77.8\%$), while the prevalence of hemorrhagic stroke in male migraineurs increased significantly (the pooled effect size 2.31, 95%CI 1.68 to 3.17, $P = 0.388$, $I^2 = 0.0\%$) (figure 4B).

Evaluation of publication bias

For total, ischemic, and hemorrhagic stroke groups, the visual inspection of the funnel plot (supplementary figure 4) or the Egger's test ($P = 0.366$ for total stroke, $P = 0.631$ for ischemic stroke, $P = 0.672$ for hemorrhagic stroke, respectively) both indicated no publication bias.

Discussion

Compared with the latest meta-analysis of prospective cohort studies on migraine and stroke risk⁵, the present systematic review included 6 recently published studies^{23,25,26,29,30,35} and an older eligible study that had previously gone undetected²⁸. Our meta-analysis involving 3,523,235 participants from 19

prospective cohort studies showed that migraine, or more specifically migraine with aura, was associated with an elevated risk of ischemic and hemorrhagic stroke.

Our results were in line with former studies which found a positive relationship between migraine and the risk of ischemic stroke^{5,7,8,9}. However, previous studies provided controversial or uncertain evidence concerning the relationship between hemorrhagic stroke risk and migraine^{5,6,8}. The discrepancies in results might result from differences in the quantity and quality of the included studies. Previous meta-analyses defined less-rigorous criteria for inclusion of studies: cross-sectional studies, retrospective cohort studies, prospective cohort studies, and case-control studies, were all included^{6,8}. However, we included only prospective cohort studies, which had a higher level of evidence than case-control studies and reduced biases than retrospective cohort design. Moreover, the new research data from the large prospective cohorts published in 2018 and 2019 developed and strengthened the evidence of the relationship of migraine with hemorrhagic stroke^{29,30} as the number of participants and outcome events in previous studies had insufficient power and limited the conclusiveness of the results⁵.

The underlying mechanisms of migraine and stroke remain inconclusive, but some hypotheses have been proposed by researchers. The pathogenic mechanisms explaining how migraine influences ischemic stroke risk include cortical spreading depression (CSD) theory^{36,37,38}, endovascular dysfunction theory^{39,40,41}, the theory of cerebrovascular hypoperfusion induced by vasospasm⁴², hypercoagulability theory^{43,44}, neurogenic inflammation theory⁴⁵, companion theory of increased prevalence of vascular risk factors^{46,47,48}, and theory of shared genetic defects^{49,50}, etc. The pathogenic mechanism illustrating the relationship between migraine and elevated hemorrhagic stroke risk was limited. This relationship was often regarded as a secondary outcome of the linking between migraine and cardiovascular diseases. Taking the endovascular dysfunction theory, for example, decreased and inactivated endothelial progenitor cells in migraineurs can facilitate hemorrhagic stroke by alterations of the cerebral vessel wall^{51,52}. Moreover, the increased prevalence of vascular risk factors of migraineurs, such as platelet dysfunction and arterial hypertension, can also serve as mediating factors^{46,53}. Since both migraine and stroke are highly biologically heterogeneous, all these theories might contribute in part to the underlying mechanisms. Of course, these hypotheses are not mutually exclusive.

In stratified analysis by aura status, our results further identified the significant relationship of migraine with aura with an elevated risk of ischemic stroke and hemorrhagic stroke, whereas there existed no reliable relationship of migraine without aura with any stroke events. Neurophysiological studies have demonstrated that as a focal transient cerebral disturbance, migraine aura was originated in the development of CSD and associated with concurrent cerebral vascular hypoperfusion^{54,55}. Therefore, peripheral vascular dysfunction in migraine, which was characterized by arterial stiffness and endothelial dysfunction, was regarded as an important mediator between migraine and cerebrovascular disease⁵⁶. Our finding of no noticeable difference in ischemic stroke risk stratifying for sex is inconsistent with the previous results of elevated ischemic stroke risk in female migraineurs⁸. We found elevated hemorrhagic stroke risk in male migraineurs, but no significant result was found in female migraineurs. However, our analyses stratifying for sex were based on too few studies to allow reliable ascertainment, and these findings should not be taken as conclusive.

There are several strengths to our study. First, this is the largest meta-analysis to date concerning the relationship of migraine with prospective follow-up of stroke outcomes. Our large sample size, the higher level of evidence, and the low risk of publication bias of included studies make our results reliable and robust. Second, the selection of the most adjusted model in the calculation for estimates effect values helps minimize the risk of confounding variables. Third, we conduct multiple analyses: sensitivity analyses for high-quality studies and step by step; subgroup analysis stratified by type of effect estimate, migraine type, and sex status; meta-regression analyses evaluating the age at baseline, the midpoint of the recruitment time, and length of the follow-up period. These analyses allow careful assessments for sources of statistical heterogeneity.

Some limitations matter in our meta-analysis. First, the included studies vary differently in terms of baseline age ranges, sex ratio, method of migraine assessment, the definition of stroke, and adjusted confounders. Different studies chose to adjust for different possible confounders making them hard to compare. Notably, one study only adjusted for age and sex and the other one made no adjustments^{15,34}. These different confounders should contribute as a source of clinical and methodological heterogeneity. Moreover, the methods used in the adjustment models and the unknown confounders in the selected studies suggest potential sources of bias. Second, the included studies were conducted mainly in the United States and Europe, with 12 of them in the United State, 2 in the United Kingdom, 1 in Denmark, 1 in Sweden, 2 in China (Taiwan), and 1 in The Republic of Korea. Therefore, a potential source of clinical and methodological heterogeneity was the sources of the study cohort. Given that the disease burden of both migraine and stroke can vary significantly according to geographic and ethnic backgrounds, these findings should be taken with caution and more relevant studies in other countries, such as East Asia, Southeast Asia, and West Asia, were warranted in further studies. Third, we did not perform subgroup analysis stratifying for different age groups as the number of studies with the outcome of stratified analysis by age group was limited, and studies with the stratified outcome by age group defined different age ranges. Due to the lack of data, we could not perform further analyses, such as subgroup analyses stratified by race or ethnicity.

In summary, our meta-analysis revealed that migraine, or more specifically migraine with aura, is a possible risk factor for future ischemic and hemorrhagic stroke. Future research should determine whether it is a real etiological association or just an epiphenomenon coming into existence.

Declarations

Ethics approval and consent to participate

Not required

Consent for publication

Not applicable

Availability of data and materials

All data generated or analysed during this study are included in this published article and its supplementary information files.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

S.M.J. participated in the design of the study. S.M.J. and W.M.Y. carried out the data collection and analysis. All authors wrote the manuscript, read and approved the final manuscript.

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Tables

Table 1. Basic characteristic of studies included in the analysis.

Study	publication year	Country	Size of cohort	No. of stroke cases	Sex	Female, %	Age at baseline, mean (range), y	Follow-up, mean, months.unless specified	Enrolment period	Study type
Buring et al	1995	United States	21,960	213	Male	0	53(40–84)	60.2	1982	Population-based
Merikangas et al	1997	United States	12,090	421	Both	60	25–74	120	1971–1975	Population-based
Hall et al	2004	United Kingdom	140,814	618	Both	74	Any	35 Migraine: 35.6 No migraine: 33.3	1992-1999	Population-based
Velentgas et al	2004	United States	260,822	314	Both	76	38 Migraine: 38 No migraine: 38	17	1995-1999	Population-based
Kurth et al (WHS)	2005	United States	39,754	385	Female	100	≥45 Migraine: 53 No migraine: 55	108	1992–1995	Population-based
Stang et al.	2005	United States	12,750	382	Both	56	60 (45-64)	72	1993-1995	Population-based
Kurth et al (PHS)	2007	United States	20,084	750	Male	0	40–84 Migraine: 57 No migraine: 58	188	1993	Population-based
Becker et al	2007	United Kingdom	103,376	200	Both	72	N/A (<79)	84	1994-2001	Population-based
Kurth et al (WHS)	2010	United States	27,860	85	Female	100	≥45	163	1993	Population-based
Kuo et al	2013	Taiwan	125,550	368	Both	69.7	≥18	24	2001	Population-based
Monteith et al	2015	United States	1,292	114	Both	63	68	132	1998	Population-based
Gelfand et al	2015	United States	1,566,952	88	Both	N/A Migraine:66 No migraine:47	2–17 Migraine:9.2 No migraine: 7.5	N/A Migraine: 6.4 year No migraine: 4.7 year	1997-2007	Population-based
Kurth et al (NHS)	2016	United States	115,541	651	Female	100	25–42	240	1989	Population-based
Androulakis et al	2016	United States	12,758	746	Both	56	59	240	1987–1989	Population-based
Peng et al	2017	Taiwan	238034	1361	Both	72	41	43.2	2005-2009	Population-based
Rambarat et al	2017	United States	917	42	Female	100	58 Migraine: 54 No migraine: 59	78	1996–1999	Population-based
Lantz et al	2017	Sweden	53,404	1297	Both	54.3	45.3 Migraine with aura:42.5 Migraine without aura:44.9 non-migraine:45.6	142.8	1998-2002, 2005-2006	Population-based
Adelborg et al	2018	Denmark	561,352	N/A	Both	71	35 Migraine: 35 No migraine: 35	228	1995-2013	Population-based
Lee et al	2019	Korea	207,925	NA	Both	74.8 Migraine: 74.8 No migraine: 74.8	≥20	80.9 Migraine: 80.9 No migraine: 80.9	2002-2013	Population-based

Table 2. Newcastle Ottawa Quality Assessment Scale for Cohorts of included studies.

Study		Selection				Comparability	Outcome			Total score
		Representativeness of the exposed cohort	Selection of the non exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	
Buring et al	1995	*	*		*	*	*	*	*	7
Merikangas et al	1997	*	*			*		*	*	5
Hall et al	2004	*	*	*	*	*	*	*	*	8
Velentgas et al	2004	*	*	*	*	**	*		*	8
Kurth et al (WHS)	2005	*	*	*		**	*	*	*	8
Stang et al.	2005	*	*	*	*	*	*	*		7
Kurth et al (PHS)	2007	*	*	*	*	*	*	*	*	8
Becker et al	2007	*	*	*	*	**	*	*	*	9
Kurth et al (NHS)	2010	*	*	*	*	**	*	*	*	9
Kuo et al	2013	*	*	*	*	**	*		*	8
Monteith et al	2015	*	*	*	*	*	*	*	*	8
Gelfand et al	2015	*	*	*		*	*	*		6
Kurth et al (NHS)	2016	*	*	*	*	**	*	*	*	9
Androulakis et al	2016	*	*	*	*	*	*	*		7
Peng et al	2017	*	*	*	*	**	*	*	*	9
Rambarat et al	2017	*	*			**	*	*		6
Lantz et al	2017	*	*		*	**	*	*	*	8
Adelborg et al	2018	*	*		*	**	*	*	*	8
Lee et al	2019	*	*		*	**	*	*		7
WHS: Women's Health Study, PHS: Physician's Health Study, NHS: Nurses' Health Study										

Figures

Figure 1

PRISMA flowchart of study selection.

Figure 2

Association between migraine and the risk of stroke. A. Association between migraine and the risk of total stroke. B. Association between migraine and the risk of ischemic stroke. C. Association between migraine and the risk of hemorrhagic stroke.

Figure 3

Subgroup analyses of stroke according to the aura status. A. Subgroup analyses of ischemic stroke according to the aura status. B. Subgroup analyses of hemorrhagic stroke according to the aura status.

Figure 4

Subgroup analyses of stroke stratifying for sex. A. Subgroup analyses of ischemic stroke stratifying for sex. B. Subgroup analyses of hemorrhagic stroke stratifying for sex.

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