

## Migraine and Risk of Stroke: Review of Current Evidence

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**Context:** Migraine is a kind of primary headache that affects 10% to 20% of people worldwide. Recent studies have shown that migraines can be involved in strokes incidences, especially ischemic strokes. Hence, the current study aimed to review evidence in relation to migraine and risk of stroke.

**Evidence Acquisition:** A literature search was done for related articles dated between 1993 and 2013 on PubMed, Science Direct, Embase, Web of Science and Scopus for both English and non-English language articles by entering “migraine”, “migraine with aura”, “headache” and “ischemic and hemorrhagic stroke” as keywords.

**Results:** In most evaluated studies, there was a positive association between migraine with aura (MA) and strokes incidences, especially ischemic strokes. Moreover, patients with high frequency of migraine attacks had greater odds of having a stroke compared with those who had low frequency of migraine attacks. Also, the association between migraine and stroke was more significant in subjects under 45 years old. Some migraine symptoms such as vomiting and nausea had a protective role in the development of ischemic strokes.

**Conclusions:** Migraine, especially MA, is a risk factor for incidences of strokes, especially ischemic strokes. However, due to conflicting results on the association between different types of migraine and stroke, more studies are needed in this field.

**Keywords:** Migraine Disorders; Headache; Stroke

### 1. Context

Migraine is a common chronic, disabling, debilitating and progressive intermittent neurovascular headache disorder that affects 80% of people worldwide (1-3). Recent data indicate that one in every four American adults has frequent or severe headaches including migraines (4). Most patients experience their first migraine attack before the age of 40, and women are approximately three times more likely to get migraine disease as compared with men (3, 5). Specifically, migraine is characterized by severe, pulsating and one-sided headache attacks, which typically last 4-72 hours (1, 2, 6). In some patients, usually prior to headache onset, a migraine with aura (MA) occurs, characterized by transient neurological symptoms, most often affecting the visual field (1). Other related symptoms include nausea, sometimes vomiting (1, 6), muscle tension (1), excruciating pain (6), photophobia and phonophobia (1, 3, 7). In addition, migraine in adults are associated with seasonal allergies, asthma, epilepsy, continuous nightmares, atopic disorders, cardiovascular disorders, sleep problems, motion sickness, epistaxis and among women of reproductive age are related to preeclampsia and uterine bleeding (4). Furthermore, migraine is considered as an important risk factor for strokes.

Several recent studies have shown that patients with migraines are at increased risk of stroke, however results in this regard are conflicting (1, 3, 8-20). Based on the literature, the increased risk of stroke associated with migraine isn't uniform across all migraine or stroke subgroups. Some authors have claimed that only migraine with aura may be related to strokes (1, 8-20), however others have shown no relationship between the two conditions (10, 21, 22). Thus, the potential association between risk of stroke and migraine is an important public health concern, and due to conflicting results on relationship between these two conditions, we aimed to review the current evidence in this regard.

### 2. Evidence Acquisition

In this review article, we performed an electronic search on articles published during 1993-2013 on PubMed, Science Direct, Embase, Web of Science and Scopus, for both English and non-English language articles, using the following key words: “migraine”, “migraine with aura”, “headache” and “ischemic and hemorrhagic stroke” as medical subject heading (MeSH). The references of retrieved items were also searched to identify additional

**Table 1.** Synthesis of Cross-Sectional Studies Exploring the Association Between Migraine and Stroke

	Study Subjects	Migraine and Stroke Diagnosis	Objectives	Stroke Risk in Migraine Cases	Outcomes
<b>Tzourio et al. 1993 (8)</b>	212 patients with ischemic stroke aged 18-80 years; 212 controls matched for sex, age, hypertension	Direct interview by neurologist; IHS criteria	To determine whether migraine is a risk factor for ischemic stroke	OR = 4.3 (1.2, 6.3) for women aged $\leq$ 45 years	Prevalence of migraine was not different between patients with stroke and matched controls except among women aged $\leq$ 45 years
<b>Tzourio et al. 1995 (9)</b>	72 women hospitalized for ischemic stroke aged 18-44 years; 173 controls matched for age	Direct interview by neurologist; IHS criteria	To determine whether migraine is a risk factor for ischemic stroke in young women	OR = 3.0 (1.5, 5.8) for migraine without aura, OR = 6.2 (2.1, 18.0) for migraine with aura	Ischemic stroke was strongly associated with both migraine without aura and migraine with aura
<b>Chang et al. 1999 (10)</b>	291 women with ischemic, hemorrhagic, or unclassified arterial stroke aged 20-44 years; 736 controls matched for age	Direct interview by neurologist; IHS criteria	To assess the association between migraine and ischemic, hemorrhagic, or unclassified arterial stroke in young women	OR 2.97 (0.66-13.5) for migraine without aura, OR 3.81 (1.26-11.5) for MA	Migraine, especially with aura, significantly increased the risk of ischemic but not hemorrhagic stroke
<b>Donaghy et al. 2002 (11)</b>	86 cases of ischemic stroke aged 20-44 years; 214 controls women matched for age	Direct interview by neurologist; IHS criteria	To investigate the effect of duration, frequency, time and type of migraine on the risk of ischemic stroke	OR = 8.37 (2.33-30.1) for migraine with aura, OR = 2.21 (0.49, 10.1) for migraine without aura	A relation was seen between ischemic stroke and migraine with aura
<b>Mosek et al. 2001 (23)</b>	100 patients with ischemic stroke aged $\geq$ 60 years; 100 patients with no vascular disease matched for age and sex	Direct interview by neurologist; IHS criteria	To assess migraine in elderly patients hospitalized with ischemic stroke compared with vascular and nonvascular control groups	prevalence of migraine was 8% in patients with ischemic stroke and 8% in the nonvascular control (x2 test, P > 1) with no differences in sex and age	Elderly patients with migraines were not at increased risk of developing a ischemic stroke
<b>Schwaag et al. 2003 (12)</b>	160 with first ischemic stroke or transient ischemic attack aged $\leq$ 46 years; 160 controls matched for age and sex	Direct interview by neurologist; IHS criteria	To investigate the association between migraine and juvenile stroke	OR = 2.11 (95% CI = 1.16-3.82) for juvenile stroke; OR = 2.68 (95%, CI = 1.25-5.75) in the female subgroup; OR = 3.26 (95%, CI = 1.33-7.98) in the subgroup under the age of 35	There was a significant association between migraine and juvenile stroke in women and patients under the age of 35
<b>MacClellan et al. 2007 (13)</b>	386 women ages 15 to 49 years with first ischemic stroke; 614 controls matched for ethnicity	Direct interview by neurologist; IHS criteria	To investigate the association of probable migraine with and without visual aura with ischemic stroke	OR = 1.5 (95% CI = 1.11-2.0)	Migraine with visual aura was associated with an increased risk of stroke, particularly stroke of undetermined origin

items about this topic. Only articles that had used standardized criteria for diagnosing migraine and stroke and had reported original data about the association between migraine and stroke were finally included in this review. In total, we found 89 items after elimination of duplicates among the three different biomedical platforms. Careful reading of title, abstract and full text (when available), allowed exclusion of 77 items due to lack of patient history (13 articles), lack of discrimination between chronic pains and pulsating headache (16 articles), uncertain diagnosis of migraine and stroke (27 articles), lack of matching for potential confounders in case and control groups (19 articles) and being a review article (2 articles). Therefore, 12 studies (7 cross sectional and 5 cohort) were finally included in this study.

### 3. Results

Whether migraine is a risk factor for stroke has been addressed in 7 case-control studies (Table 1) and 5 cohort

studies (Table 2). In regards to the 7 case-control studies, 5 studies showed a statistically significant relationship between migraine and stroke (9-13). The two other studies that were conducted by Tzourio et al. (8) and Mosek et al. (23) did not show a significant difference between patients with stroke and matched controls. However, all cohort studies showed increased risks of stroke in patients with migraine (1, 14-17). Regarding migraine subtypes, most studies (1, 8, 11-17) found this relationship in migraine with aura, and only two cross-sectional studies (9, 10) reported an association between stroke and migraine without aura. Pertaining to stroke subtypes, one case control study (10) and one cohort study (15) investigated the relationship between migraine and hemorrhagic stroke and others dealt with ischemic stroke. A study conducted by Chang et al. didn't show increased risk of hemorrhagic stroke among both migraines with and without aura, whereas another study performed by Kurth et al. indicated an association between migraine with aura and hemorrhagic stroke.

**Table 2.** Synthesis of Cohort Studies Exploring the Association Between Migraine and Stroke

	Study Subjects	Migraine and Stroke Diagnosis	Objectives	Stroke Risk in Migraine Cases	Outcome
<b>Buring et al. 1995 (14)</b>	22071 US male physicians aged 40 to 84 years	Self-report of the subjects; IHS criteria	To evaluate, whether migraine is an independent risk factor for subsequent stroke	OR = 1.84 (95% CI = 1.06-3.20) for total stroke, OR = 2.01 (95% CI = 1.10-3.64) for ischemic stroke	There were significantly increased risks of subsequent total stroke and ischemic stroke in patients with migraines
<b>Kurth et al. 2005 (15)</b>	39754 US health professionals age ≥ 45 years	Direct interview by neurologist; IHS criteria	To investigate the association between specific headache forms, migraine and stroke	OR = 1.53 (95% CI = 1.02-2.31) for total stroke, OR = 1.71 (95% CI = 1.11-2.66) for ischemic stroke	There were increased risks of total and ischemic stroke in patients with migraine with aura
<b>Kurth et al. 2009 (16)</b>	27798 US women aged ≥ 45 years	Direct interview by neurologist and cardiologist; IHS criteria for stroke; World Health Organization criteria for CVDs	To investigate the association between migraine frequency and CVDs	OR = 4.25 (95% CI = 1.36-13.29) for women with active migraine with aura	Ischemic stroke was associated with a high-attack frequency of patients with migraine with aura
<b>Kurth et al. 2010 (17)</b>	27860 US female health professionals aged ≥ 45 years	Direct interview by vascular neurologist; self-reported by participants; IHS criteria	To examine the association between migraine and risk of hemorrhagic stroke	OR = 0.98 (95% CI = 0.56, 1.71, P = 0.93) for migraine without aura, OR = 2.25 (95% CI = 1.11-4.54, P = 0.024) for migraine with aura	Hemorrhagic stroke was associated with migraine with aura, but migraine without aura had no increased risk of hemorrhagic stroke
<b>Schurks et al. 2010 (1)</b>	27840 US female health professionals aged ≥ 45 years	Self-reported by participants; World Health Organization criteria for CVDs	To investigate the association between migraine and cardiovascular disease	OR = 1.79 (95% CI = 1.15-2.78; P = 0.01) for ischemic stroke in migraine with aura	Migraine with aura doubled the risk for CVD, ischemic stroke, and myocardial infarction

All studies except one case-control (23) and two cohort (14, 15) studies found a significantly higher risk of strokes in women than men and among younger (under the age of 45 years) than older individuals especially for the subgroup of patients with migraine with aura. In four studies (11, 13, 16, 17), patients with high frequency of migraine attacks had greater odds of having a stroke compared with those who had a low frequency of migraine attacks. Furthermore, three studies (9, 10, 13) reported that association between migraine and stroke elevated among women who smoked or used oral contraceptives (OCs). Also, one study showed that some migraine symptoms such as vomiting and nausea have a protective role in the development of ischemic stroke (1).

#### 4. Conclusions

In most reviewed articles (1, 8, 11-17), there was a positive association between migraine, particularly with aura, and incidence of stroke. However, in some studies (9, 10) a significant relationship was seen between migraine without aura and stroke. Most studies showed a relationship between migraine and ischemic stroke (1, 8-14, 16, 17) and sparse studies (15) indicated a positive relationship between migraine and hemorrhagic strokes, which may be due to the low incidence of hemorrhagic strokes. The different risks associated with migraine and stroke types reported in reviewed studies may reflect variations in the criteria used to define migraine and stroke, different sample size as well as other confounders such as sex and age. Based on the available evidence, an association between migraine and stroke was seen in women more than men,

especially those less than 45 years and this may be due to oral contraceptive use among women less than 45 years, which is considered as a risk factor for stroke (24).

Although the pathophysiological mechanism underlying this relationship remains unknown, there are some possible mechanisms for this association (25). Firstly, one link might involve dysfunction or pathology of the vessel wall, which is supported by studies reporting smooth muscle cell dysfunction (26) and endothelial dysfunction in migraine (27-29). Also, pathological vascular resistance, already apparent in young people with migraine (28) could increase the risk of intra cerebral hemorrhage (ICH) as well as the risk of lacunar infarcts (30). Secondly, recent investigations have shown that the close relationship between migraine and stroke may be due to mutations (31). Studies have shown that migraine has a relationship with methylene tetra hydro folate reductase (MTHFR) genotype that accounts for cardiovascular diseases, stroke and myocardial infarction (32, 33). This genotype decreases MTHFR enzyme function and leads to a decline in homocysteine metabolism, and consequently augments plasma homocysteine concentrations, which is associated with various pathological conditions in humans, including stroke and cardiovascular disorders (34-37). Moreover, some studies found a link between migraine and cerebral autosomal dominant arteriopathy with subcortical infarct and leukoencephalopathy (CADASIL), which is one of the most common cause of hereditary stroke. The CADASIL is a small-artery disease of the brain affecting smooth muscle cells due to Notch 3 mutations characterized by progressive white matter degeneration and smooth muscle cell abnormalities, which

involves 30% of MA (often as the initial symptom) (38, 39).

Despite the existing hypotheses regarding the biological mechanisms linking migraine with stroke, it remains unclear why the association appears more in migraine with aura. This relationship may be due to increased prevalence (40, 41) and frequency (42) of patent foramen ovale (PFO) in patients with MA, which is considered as a risk factor for young onset of stroke. Based on studies, up to 50% of patients who have migraine with aura have PFO between the cardiac atria, which may allow shunting of vasoactive substances, such as serotonin and emboli from the venous circulation, and thus cause stroke (43). Also, some studies have shown that migraine, particularly with aura, is associated with increasing concentrations of vasoactive factors and blood coagulants such as: prothrombin factor 1.2, factor V leiden (FVL) and serotonin, which are known as significant risk factors for ischemic stroke (44-46). Furthermore, use of pain medication that inhibits platelet aggregation, such as aspirin and NSAIDs, can increase the risk of hemorrhagic stroke among patients who suffer from migraine with aura (1). Moreover, this association may be due to some stroke risk factors such as hypertension, hyperlipidemia, diabetes, use of oral contraceptives (8-10, 24, 47-49) and obesity (30, 49-51), which are more common among patients with migraine, especially with aura.

In conclusion, data from studies suggest that migraine, especially with aura, may be a risk factor for developing stroke, particularly ischemic stroke. Thus the results from these studies have been inconsistent; more studies are needed to explore the potential association as well as related mechanisms. Some limitations should be considered for this study. In most evaluated studies, the associations between characteristics of migraine attacks including severity, frequency and duration of migraine attacks with incidence of stroke were not assessed. Moreover, some confounding variables such as physical activity, dietary patterns and psychological difficulties were not adjusted in the assessment of the association between migraine and strokes. In addition, some studies had a low sample size. Hence, it is suggested that researchers should pay more attention to these limitations in future studies and conduct more studies with greater sample size and also evaluate the confounding variables.

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## Authors' Contributions

Sadeghi O, Askari GH, Maghsoudi Z, Nasiri M, Khorvash F contributed equally to this work and performed the literature search and wrote first draft; Khorvash F and Askari GH provided expert opinion and reviewed the paper.

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