

# Headache after ischemic stroke

## A systematic review and meta-analysis

Andrea M. Harriott, MD, PhD, Fahri Karakaya, PhD, and Cenk Ayata, MD, PhD

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### Correspondence

Dr. Harriott  
aharriott@mgh.harvard.edu

## Abstract

### Objective

Headache associated with ischemic stroke is poorly understood. To gain further insight, we systematically reviewed studies examining the prevalence and characteristics of new-onset poststroke headache.

### Methods

Medline and PubMed databases were queried. A total of 1,812 articles were identified. Of these, 50 were included in this systematic review. Twenty were included in a meta-analysis and meta-regression.

### Results

Headache occurred in 6%–44% of the ischemic stroke population. Most headaches had tension-type features, were moderate to severe, and became chronic in nature. Meta-analysis using an inverse-variance heterogeneity model revealed a pooled prevalence of 0.14 (95% confidence interval [CI] 0.07–0.23) with heterogeneity among studies. Metaregression revealed a significant association between prevalence and study location, the source population's national human development index (HDI), and study quality. We found higher prevalence in European (0.22, 95% CI 0.14–0.30) and North American (0.15, 95% CI 0.05–0.26) studies compared with Middle Eastern and Asian studies (0.08, 95% CI 0.01–0.18). However, within each region, populations from countries with higher HDI ( $p = 0.03$ ) and studies with higher quality ( $p = 0.001$ ) had lower prevalence. Calculated crude odds ratios (ORs) showed that posterior circulation stroke (pooled OR 1.92, 95% CI 1.4–2.64;  $n = 7$  studies) and female sex (pooled OR 1.25, 95% CI 1.07–1.46;  $n = 11$  studies) had greater odds of headache associated with ischemic stroke.

### Conclusions

Taken together, these data suggest that headache is common at the onset of or shortly following ischemic stroke and may contribute to poststroke morbidity. Better understanding of headache associated with ischemic stroke is needed to establish treatment guidelines and inform patient management.

From the Neurovascular Research Laboratory (A.M.H., C.A.), Department of Radiology, Massachusetts General Hospital, Charlestown; Vascular Division (A.M.H., C.A.) and Headache and Neuropathic Pain Division (A.M.H.), Department of Neurology, Massachusetts General Hospital, Boston; and University of Massachusetts Dartmouth (F.K.).

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## Glossary

CI = confidence interval; HAIS = headache associated with ischemic stroke; HDI = human development index; ICHD = International Classification of Headache Disorders; OR = odds ratio; QS = quality score.

Ischemic stroke affects approximately 800,000 individuals annually in the United States alone and accounts for 1 in every 20 deaths.<sup>1</sup> Stroke is among the top 20 conditions contributing to years lived with disability. While the focus after stroke is often on recovery of neurologic function and reducing the risk of recurrence, the emergence of comorbid conditions like poststroke headache is often overlooked and undertreated.

Evidence suggests a link between stroke and headache disorders. For example, migraine with aura, a primary headache disorder, is associated with a twofold higher risk of ischemic stroke.<sup>2,3</sup> While the associations between a preexisting history of migraine and stroke are well-known, the epidemiology, predictive potential, and treatment underlying new onset poststroke headache or headache as a symptom heralding stroke remain unclear. While headache as a presenting feature of cerebrovascular conditions, such as venous sinus thrombosis, cervical artery dissection, reversible cerebral vasoconstriction syndrome, and vasculitis, has been well-described, few studies focus on new-onset and persistent headache after ischemic stroke in the absence of these conditions.

Prior studies report a wide range of prevalence of headache associated with ischemic stroke.<sup>4-6</sup> New-onset headache presenting at the time of acute ischemic stroke is a predictor of persistent headache 6 months after the stroke.<sup>7</sup> Indeed, headache after stroke has been characterized as a common form of chronic poststroke pain.<sup>8,9</sup> Given the high prevalence of stroke in the United States, poststroke headache can be a significant cause of disability. However, the dearth of epidemiologic and outcome-based studies limits our understanding and treatment of persistent poststroke headache. Therefore, we undertook a systematic literature review and meta-analysis of stroke onset and poststroke headache, its presentation, epidemiology, and clinical outcomes.

## Methods

### Systematic review strategy

Medline and PubMed electronic databases were queried using the search terms “headache after stroke” or “poststroke headache” or “onset headache and stroke” and “headache and stroke.” Abstracts of observational and clinical studies written in English and containing the search terms in the title or abstract body were reviewed. If the articles found using the search terms referenced epidemiologic or outcomes data from other primary research articles, those articles were also included. A total of 1,812 articles on stroke and headache were thus identified. To determine the epidemiology of onset and poststroke headache and its characteristics, retrospective and prospective

studies were included after abstracts were reviewed by A.M.H. and F.K. Case reports and reviews, articles without an abstract, articles on specific disease entities such as venous sinus thrombosis, arterial dissection, moyamoya disease, and primary headache disorders (i.e., migraine headache), and articles that included only intracranial hemorrhage or TIA were excluded. Of 1,812 articles, 50 primary research articles published between 1993 and 2018 were included in the systematic review (figure 1). Of the 50 primary research articles published between 1993 and 2018 included in this study, 38 were prospective cohort studies and 11 were retrospective, representing diverse populations throughout the world.

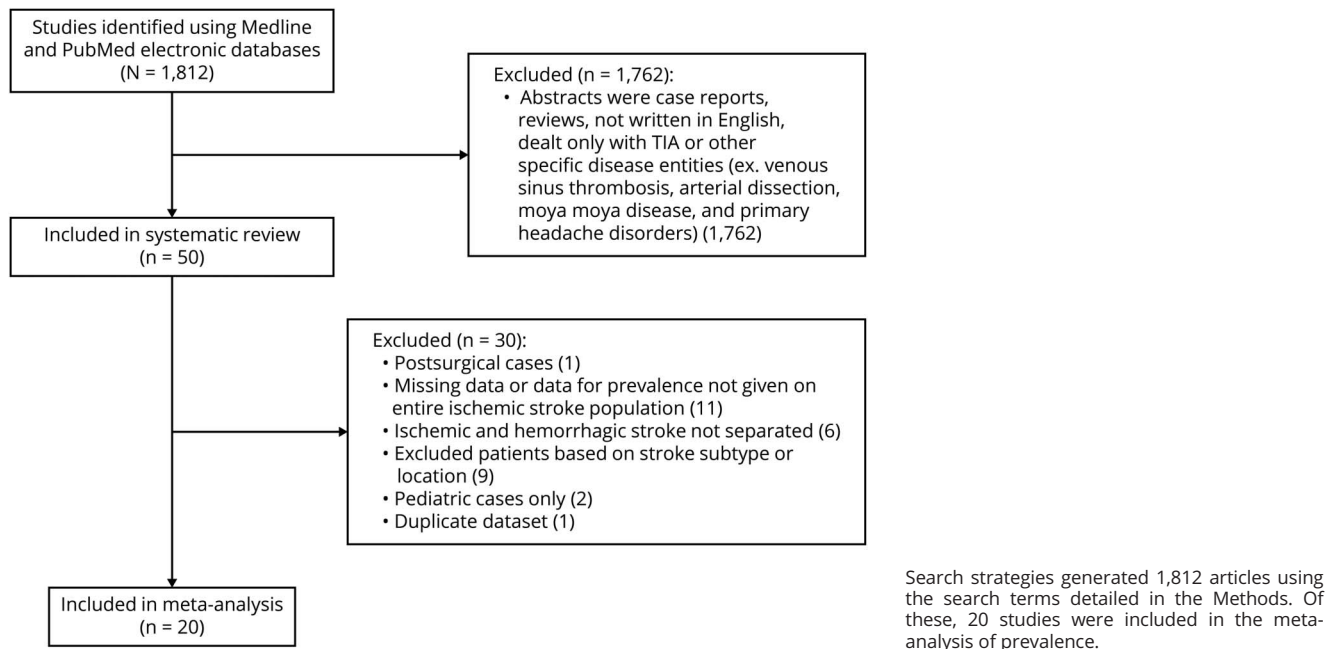
Ischemic stroke was defined based on either clinical or radiologic criteria. Headache associated with ischemic stroke (HAIS) was variably defined among the studies. Some defined it as a presenting symptom during an ischemic stroke, onset simultaneous with or in close temporal relationship to stroke onset. Some described it as a concomitant symptom or accompaniment, present at admission to the hospital, and others used specific time windows with onset ranging from 24 to 72 hours before or after stroke onset.

### Meta-analysis

Of the 50 primary research articles in the systematic review, studies were included in the meta-analysis if they met the following criteria: enrolled adult participants (age >18 years) with ischemic stroke and presented prevalence data for the entire ischemic stroke population enrolled in the study. Articles were excluded if they only enrolled patients with a specific stroke subtype or location, if they only enrolled patients with stroke and headache, if there was no distinction between hemorrhagic and ischemic stroke in headache prevalence estimates, if the study only enrolled pediatric patients (age < 18 years), if prevalence could not be calculated from the data given, or if it was a duplicate population. In the case of duplicate population data, the article with the highest enrollment was included in the meta-analysis. Twenty studies were included in the meta-analysis (table 1 and figure 1).

We extracted data on study location, dates of enrollment, year of publication, study design, population (hospital or community-based), age, sex, headache prevalence, use of headache classification criteria, subgroup analysis including prevalence values by stroke location and sex, and data for quality assessment from these studies. We generated pooled prevalence estimates using an inverse variance heterogeneity model where the weights assigned to each study vary inversely with the square of the standard error.<sup>10</sup> This model has an advantage over the random effects model that may yield faulty

**Figure 1** Flow diagram of study inclusion/exclusion



pooled estimates when there is high heterogeneity among studies. As heterogeneity or differences between studies increases, the random effects model tends towards an unweighted pooled estimate. The result of high heterogeneity on the random effects model is decreased coverage of the confidence interval (CI) and an overconfident estimate because of underestimation of the error. To overcome this shortcoming and allow for a pooled estimate in studies suffering from heterogeneity, we used an inverse variance heterogeneity model to determine the pooled estimate.<sup>10,11</sup> Nevertheless, the results of the random effects model are also provided.

### Meta-regression of heterogeneity

Heterogeneity among the studies was assessed using the  $I^2$  statistic and Cochran  $Q$ . To help understand the sources of heterogeneity, meta-regression analysis was performed using study characteristics as moderator variables, including year of publication, population source (community-based, single-center, or multicenter), and geographic region (North American, European, and Other, including the Middle East and Asia). Because the reporting of headache after stroke may vary depending on health literacy and awareness of the source population, we included the United Nations national human development index (HDI), which incorporates life expectancy, education, and gross national income per capita, for each study's source population as a variable in the meta-regression. For studies that included patients from multiple countries, the average HDI of these countries was used. For one study from Taiwan,<sup>4</sup> HDI for mainland China was used as there was no HDI published for Taiwan. Finally, we also included study quality as an independent variable in the form of a score derived in part from the STROBE checklist for

observational study reporting<sup>12</sup> (study design, location, date and period of recruitment, eligibility criteria, diagnostic criteria, assessment of bias, description of statistical methods and confounding variables, reporting of demographic data and subgroup analysis, discussion of study limitations, generalizability of study results to the population, and assessment of missing data for subgroup analyses). We added 2 other criteria relevant to stroke and headache epidemiology (use of International Classification of Headache Disorders [ICHD] or International Headache Society criteria for diagnosis of headache, use of CT or MRI for diagnosis of stroke). Each criterion was assigned 0 if not present and 1 if present. The quality score (QS) for each study was expressed as a fraction by dividing the total points by the highest possible score (12).

### Patient characteristics as risk factors for headache after stroke

To determine the effect of stroke location (posterior vs anterior circulation) and sex on ischemic stroke headache, data from studies that reported headache prevalence in these subgroups were used to calculate a crude odds ratio (OR) using  $2 \times 2$  tables for each study and combined using a fixed effects heterogeneity model to generate a pooled estimate.

### Publication bias

Publication bias was graphically represented with funnel and doi plots.<sup>13</sup>

### Statistical analysis

Meta-regression data were generated using Meta-XL software (Epigear; epigear.com/index\_files/metaxl.html) and analyzed using Stata Statistical Software.

**Table 1** Prevalence of headache after ischemic stroke (IS) and characteristics of studies included in the meta-analysis

First author	Year	Population source	Geographic region	Sample size (IS)	Female, %	Age, y, median or average	Headache cases	Prevalence	95% CI	HDI <sup>a</sup>	Fractional QS
Puustjarvi et al. <sup>40</sup>	2015	Single-center	Europe	1,196	42.1	—	77	0.06	0.05–0.08	0.920	0.8
Chen et al. <sup>4</sup>	2013	Multicenter	Other (East Asia)	11,523	37.1	—	848	0.07	0.07–0.08	0.752	0.9
Lutski et al. <sup>31</sup>	2017	Multicenter	Other (Middle East)	3,579	42.9	—	316	0.09	0.08–0.10	0.903	0.8
Libman <sup>e54</sup>	2001	Multicenter	North America	1,219	39.5	—	117	0.10	0.08–0.11	0.924	0.8
Lisabeth et al. <sup>18</sup>	2009	Single-center	North America	461	48.6	67.0	59	0.13	0.10–0.16	0.924	0.8
Abadie et al. <sup>19</sup>	2014	Community	Europe	1,185	53.9	—	160	0.14	0.12–0.16	0.901	0.9
Kumral <sup>e58</sup>	1995	Single-center	Europe	2,255	44.7	54.2	365	0.16	0.15–0.18	0.944	0.7
Maino et al. <sup>6</sup>	2013	Multicenter	Europe	2,473	35.0	—	420	0.17	0.16–0.19	0.931	0.8
Ahmadi Aghangar et al. <sup>15</sup>	2015	Multicenter	Other (Middle East)	263	47.1	76.4	49	0.19	0.14–0.24	0.798	0.6
Rathore et al. <sup>27</sup>	2002	Community	North America	402	47.3	62.5	90	0.22	0.18–0.27	0.924	0.8
Vestergaard et al. <sup>30</sup>	1993	Multicenter	Europe	214	52.9	69.0	56	0.26	0.21–0.32	0.929	0.8
Tentschert et al. <sup>26</sup>	2005	Multicenter	Europe	2,196	44.6	66.0	588	0.27	0.25–0.29	0.908	0.8
Leira <sup>e52</sup>	2002	Single-center	Europe	241	31.9	—	73	0.30	0.25–0.36	0.696	0.7
Kropp et al. <sup>43</sup>	2013	Multicenter	Europe	4,431	40.6	44.7	1,395	0.32	0.30–0.33	0.891	0.8
Mitsias et al. <sup>25</sup>	2006	Single-center	North America	375	43.7	—	118	0.32	0.27–0.36	0.924	0.7
Arboix et al. <sup>29</sup>	1994	Single-center	Europe	195	35.8	65.0	62	0.32	0.25–0.39	0.891	0.7
El Tallawy et al. <sup>16</sup>	2015	Community	Other (Middle East)	477	41.9	62.2	133	0.33	0.28–0.37	0.891	0.6
Ferro <sup>e57</sup>	1995	Single-center	Europe	182	39.0	—	62	0.34	0.27–0.41	0.847	0.9
van Os et al. <sup>20</sup>	2016	Multicenter	Europe	284	38.4	68.0	109	0.38	0.33–0.44	0.931	0.9
Siddique <sup>e60</sup>	2009	Single-center	Other (South Asia)	80	42.5	—	35	0.44	0.33–0.55	0.608	0.6

Abbreviations: CI = confidence interval; HDI = human development index; QS = quality score.

— Indicates total population mean or median age not provided.

Data available from Dryad (Additional References, References e52–e60); doi.org/10.5061/dryad.b53cc6s

<sup>a</sup> HDI from the United Nations Development Program, 2018 Statistical Update. For Chen et al.,<sup>4</sup> HDI for Taiwan was not provided. Taiwan was therefore assigned the HDI of China (0.752), which was slightly higher than that of the regional HDI for East Asia and the Pacific (0.733). The study by Kropp et al.<sup>43</sup> was a multicenter study enrolling patients from 14 different European countries. The HDIs varied from 0.780 (Georgia) to 0.938 (Ireland). The average HDI was used (0.891, SD 0.045). QS: study quality was assessed using a 12-point score that included STROBE checklist criteria, radiographic stroke diagnosis, and International Classification of Headache Disorders or International Headache Society headache diagnosis.

$p \leq 0.05$  was considered significant. The pooled estimates and 95% CIs are given. The effect of posterior circulation stroke or female sex was considered significant if the CI of the pooled estimate did not contain the null value of 1.

## Data availability

Data will be provided to other investigators upon request made to the corresponding author, A.M.H., in accordance with International Committee of Medical Journal Editors requirements.

## Results

### Meta-analysis

#### Prevalence of HAIS

We performed a meta-analysis of 20 prospective studies (8 single-center, 9 multicenter, and 3 community-based) to estimate the prevalence of HAIS (table 1). Studies included 11 European, 4 North American, and 5 Asian or Middle Eastern populations. Enrollment ranged between 80 and 11,523 participants. The ratio of women ranged between 32% and 54%, whereas the average or median age ranged between 44.7 and 76.4 years, when reported. The prevalence of HAIS was between 0.06 and 0.44. An inverse variance heterogeneity model showed a pooled prevalence rate of 0.14 (95% CI 0.07–0.23; figure 2); this model was chosen over a random effects model to better account for the high degree of heterogeneity in the prevalence estimates among the studies ( $I^2$  99%, Cochran Q statistic 2,229). The random effects model yielded a higher pooled prevalence of 0.22 (95% CI 0.17–0.27; figure 2). Publication bias may have influenced the pooled prevalence estimate given the wide distribution of studies on the funnel plot and the asymmetric doi plot (figure 3).

#### Sources of heterogeneity

To better understand the contribution of study characteristics to the heterogeneity, we performed a meta-regression using the variables publication year, population source, geographic region, HDI, and QS. The initial model showed a significant association with the double arcsine-transformed prevalence ( $R^2 = 0.831$ ,  $p < 0.001$ ), suggesting that one or more of the variables included in the model could predict the prevalence (table 2). To determine which study characteristics likely contribute to the heterogeneity, we examined the relationship between the individual moderator variables and the prevalence. There was no significant effect of publication year or population source on the prevalence. However, geographic region was significantly associated with prevalence. Studies performed in Europe ( $p < 0.001$ ) or North America ( $p = 0.044$ ) had a higher HAIS prevalence as compared to those performed in other regions (i.e., Asia and the Middle East) when Other was taken as the referent level. When North America was used as the referent level, there was no significant difference in prevalence between European and North American studies (table 2). The pooled prevalence rate of HAIS for studies performed in Europe was 0.22 (95% CI 0.14–0.30), North America was 0.15 (95% CI 0.05–0.26), and Other (Middle East and Asia) was 0.08 (95% CI 0.01–0.18; figure 4). The pooled prevalence of the Other category is heavily influenced by a single Taiwanese study<sup>4</sup> because of the large sample size and narrow CI.

After controlling for the geographic region, increasing HDI was associated with lower HAIS prevalence ( $p = 0.030$ ; table 2). The United Nations HDI was not available for Taiwan. Therefore, the HDI for mainland China (0.752) was used for the Taiwanese study in the meta-regression.<sup>4</sup> Since this study is heavily weighted,

we examined if changing the HDI for this study influenced the association between prevalence and HDI in our meta-regression. If the HDI for Taiwan is changed from 0.75 to 0.7, 0.8, or 0.85, the association between the HDI and prevalence remains significant ( $p = 0.029$ ,  $p = 0.027$ , and  $p = 0.020$ , respectively).

After controlling for the other variables, higher manuscript quality score was associated with lower HAIS prevalence ( $p = 0.001$ ). Studies with the lowest quality score of 0.58 had a pooled prevalence of 0.29, whereas those with the highest quality score of 0.92 had a prevalence of 0.09 (figure 4).

#### Risk factors

A higher rate of HAIS has been reported with posterior circulation strokes and in women. Therefore, we compared the pooled prevalence and crude ORs of HAIS in anterior vs posterior circulation strokes. In the meta-analysis, a majority of studies that specified stroke location reported an almost 2-fold higher prevalence of HAIS in posterior circulation strokes (pooled OR 1.92, 95% CI 1.4–2.64; figure 5). A majority of studies that specified sex showed a modestly higher odds of HAIS in women (pooled OR 1.25, 95% CI 1.07–1.46; figure 5). Age was not reported as a dichotomous or stratified variable in most studies, and therefore, was not included in the meta-analysis.

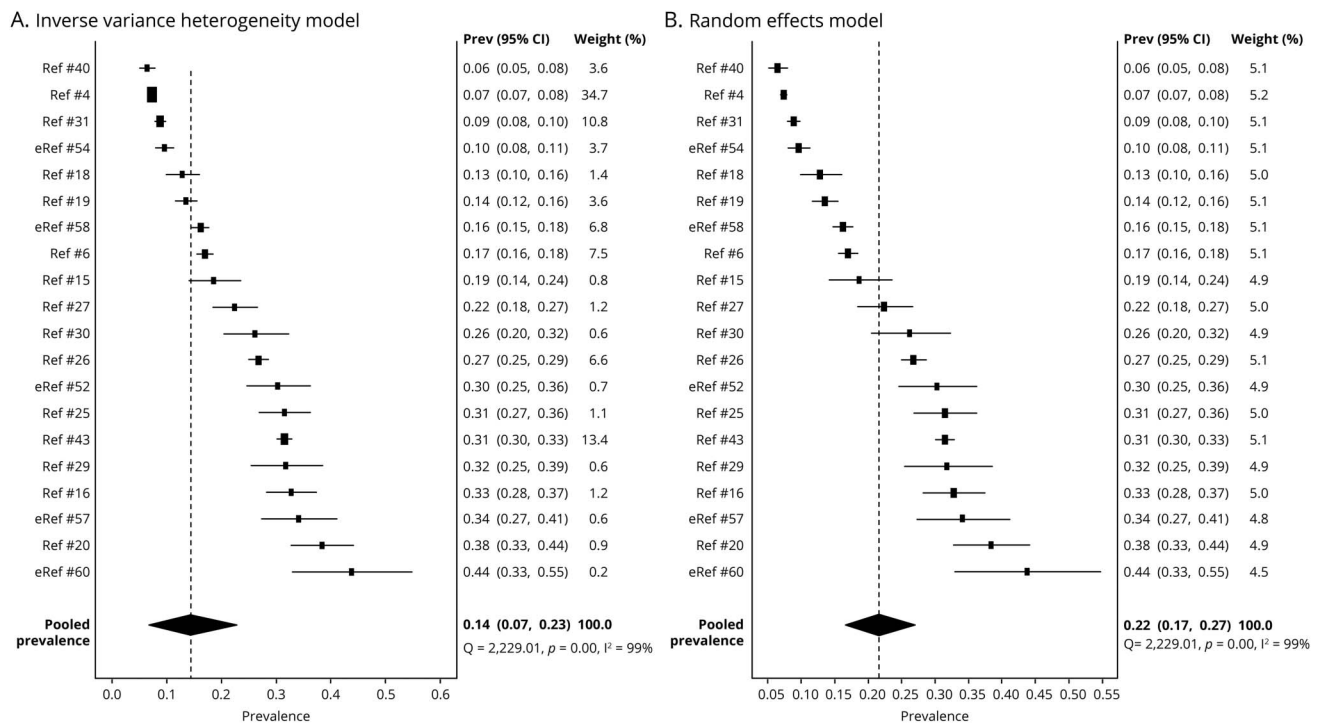
#### Systematic review

We further conducted a systematic review of the literature on HAIS of 50 articles, including the 20 used for the meta-analysis, to gain insight on timing, duration, characteristics, and outcome of HAIS, and the effect of age and stroke subtype.<sup>4,6,7,14–50,e51–e60</sup>

#### Prevalence, time of onset, and duration of headache in relation to stroke symptom onset

The prevalence of headache in the larger systematic review was within the range found in the meta-analysis.<sup>4,6,14–30</sup> ICHD-3 defines HAIS as either acute or persistent and if “headache has developed in very close temporal relation to other symptoms and/or clinical signs of ischemic stroke, or has led to the diagnosis of ischemic stroke.”<sup>e61</sup> Of the 16 studies that described the timing of headache assessment, 12 studies evaluated headache within 3–4 days of stroke symptoms,<sup>6,15,20,22–25,30,35,49,e55,e57</sup> and the remaining 4 within 8–14 days.<sup>14,34,37,48</sup> The headache onset occurred prior to, simultaneous with, or after stroke symptom onset. In one study, 86% of patients reported headache onset on the day of stroke symptoms; the remainder had headache onset 2–5 days after.<sup>48</sup> In another study exclusively of lacunar infarction, 93% reported headache occurring simultaneously with stroke symptoms and only 7% occurring prior.<sup>24</sup> In a third study, 31% had headache prior to, 11% simultaneous with, and 45% after the onset of stroke symptoms (1% within seconds, 10% within minutes, and 34% within hours). The timing was unknown in the remaining 13%.<sup>20</sup> Altogether, these data suggest that most patients experience headache symptoms on the day of stroke presentation.

**Figure 2** Pooled prevalence of ischemic stroke headache



(A) Inverse variance heterogeneity model: forest plot shows prevalence by individual study and the % weight, which is inversely proportional to the squared value of the standard error. The pooled prevalence of ischemic stroke–related headache is 14%. (B) Random effects model: pooled prevalence of ischemic stroke headache using the random effects model yields a higher pooled estimate (22%). Because of the high degree of heterogeneity, the random effects model tends to unweight the studies, as demonstrated by the % weight values falling between a narrow range of 4.5–5.2. CI = confidence interval.

The initial headache duration varied from 1 to 4 days in the 3 studies in which it was reported.<sup>20,24,48</sup> Similarly, few studies examined headache persistence during follow-up (on average >3 months) as defined by ICHD-3, with a wide prevalence of persistent headache ranging from 1% to 23%.<sup>14,17,23,45</sup> In one cohort, only 1%–2% had persistent headache at 48–175 days after stroke.<sup>14</sup> In another cohort, 12% had persistent headache at 3 years follow-up, 81.2% of whom had 2–14 headache days per month, and 18.8% reported daily headache.<sup>17</sup> In a study of 299 participants, headache persisted in 23% of the cohort at both 3 and 6 months.<sup>23</sup> In a small study of 21 patients with severe strokes that required hemicraniectomy, 42.9% continued to have headache an average of 3 years after stroke, although it is unclear if this was related to the severity of the stroke or persistent postoperative pain.<sup>32</sup> Altogether, these data suggest that HAIS can persist for months, and in some, even years.

### Headache characteristics

In most studies, HAIS had tension-type features (50%–80% of headaches) though the quality of the pain appeared to be severe and intractable.<sup>7,24,26,50,e51</sup> In one cohort, 66% described pressure, aching, or soreness, while only 17% had throbbing pain.<sup>20</sup> Migraine-like symptoms were less common: photophobia occurred in 13%, phonophobia in 8%, nausea in 17%, and vomiting in 16% of patients with headache. Similarly, in a different cohort, 80% of patients had bilateral and

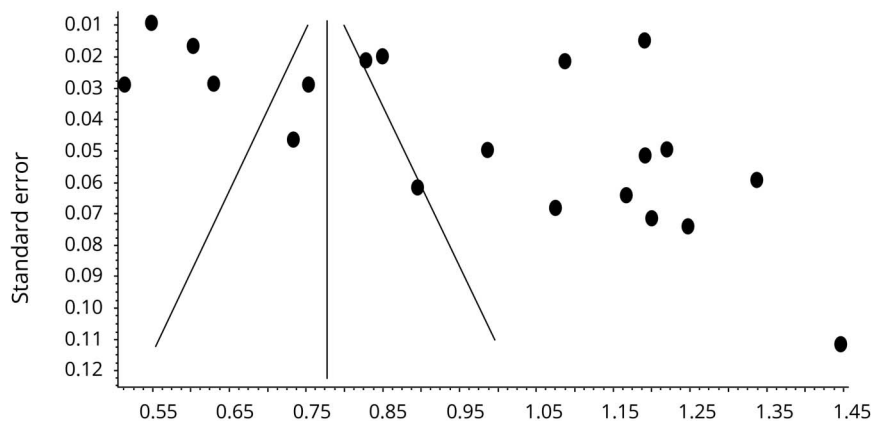
pressure-like headache, whereas only 16% had throbbing and 10% had stabbing pain.<sup>37</sup> In this study, 30% had photophobia, 24% phonophobia, and 28% nausea or vomiting. In a third cohort, 50% of patients with HAIS had tension-type features while 31% had migrainous features.<sup>17</sup> Despite the paucity of migraine-like symptoms, more than 50% reported moderate to severe pain intensity. Few studies attempted to employ ICHD criteria to better categorize the poststroke headache quality. In one study examining 124 patients using ICHD criteria, the headache was described as tension-type, with predominantly bilateral (59%–75%) and anterior or frontal location (42%–69%).<sup>48</sup> Over the first week after stroke onset, 53%–67% of patients reported pressure, 11%–24% reported throbbing, and 0%–9% reported stabbing pain. Taken together, these data suggest that while HAIS is more often associated with tension-type features (i.e., less often migraine-like), the headache intensity tends to be more severe.

### Influence of age on HAIS

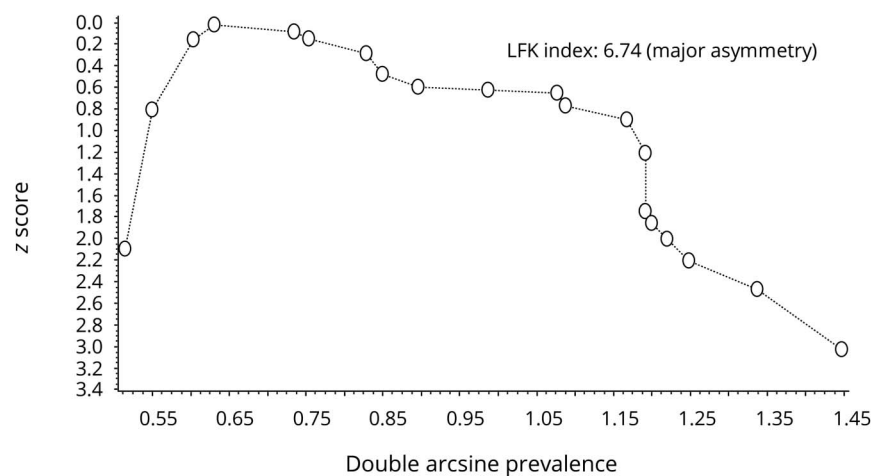
Most studies found an association between younger age and headache at stroke onset.<sup>4,22–24,26,39,43,47</sup> In a prospective study of first ever ischemic stroke, 12.2% of those younger than 50 developed HAIS, compared with 8.5% of those older than 50 ( $p < 0.002$ ).<sup>31</sup> In another population, 45.8% of younger patients (average age 42) developed HAIS vs 20.2% of older patients (average age 75,  $p < 0.05$ ).<sup>21</sup> Contradicting these reports, 2 studies found no association.<sup>18,20</sup> Taken

**Figure 3** Assessment of publication bias

**A.** Funnel plot



**B.** Doi plot



Given broad scatter of the funnel plot (A) and asymmetry of the doi plot (B), the prevalence estimate is likely affected by publication bias.

together, these data suggest that younger adult stroke patients (<50 years) are more prone to develop HAIS. There are very few studies dedicated to examining onset headache in the pediatric stroke population. In pediatric stroke studies, 24%–55% of the population had onset headache.<sup>35,42</sup>

**Influence of stroke location and etiology on HAIS**

Consistent with the findings of the meta-analysis, other studies also reported an association between posterior circulation stroke and HAIS.<sup>22,28,36,43,e59,e62</sup> In a small cohort study of 57 posterior circulation strokes, a large majority (79%) had accompanying headache.<sup>36</sup> In a larger multicenter study, headache was associated with strokes involving the vertebrobasilar circulation (OR 2.07, 95% CI 1.48–2.9;  $p < 0.001$ ) but not posterior cerebral artery territory (OR 1.17, 95% CI 0.85–1.63), suggesting higher risk with posterior fossa strokes.<sup>43</sup>

Ischemic lesions involving putative brain regions responsible for pain processing may also contribute to HAIS. In a study enrolling 100 patients with ischemic stroke, headache was

associated with infarcts involving insular and somatosensory cortical brain regions.<sup>37</sup> In another small prospective study, headache intensity was associated with strokes involving the posterior insula and operculum, while cranial autonomic symptoms accompanying headache were found in strokes affecting the parietal lobe, somatosensory cortex, and middle temporal cortex.<sup>34</sup>

HAIS may be associated with cortical as opposed to subcortical or deep strokes. In one study, headache accompanying minor ischemic strokes was positively associated with cortical infarcts (OR 1.78, 95% CI 1.31–2.41;  $p = 0.0001$ ) and negatively associated with small, deep, or subcortical infarcts (OR 0.58, 95% CI 0.44–0.76;  $p = 0.00006$ ). The prevalence of headache was 12% in those with small deep infarcts vs 29% in those with cortical infarcts.<sup>e62</sup> These data are consistent with other studies examining cortical vs deep or subcortical infarct location.<sup>6,e57</sup>

The stroke subtype may also be associated with HAIS. Most studies report a greater association between HAIS and

**Table 2** Meta-regression analysis of heterogeneity introduced by study characteristics

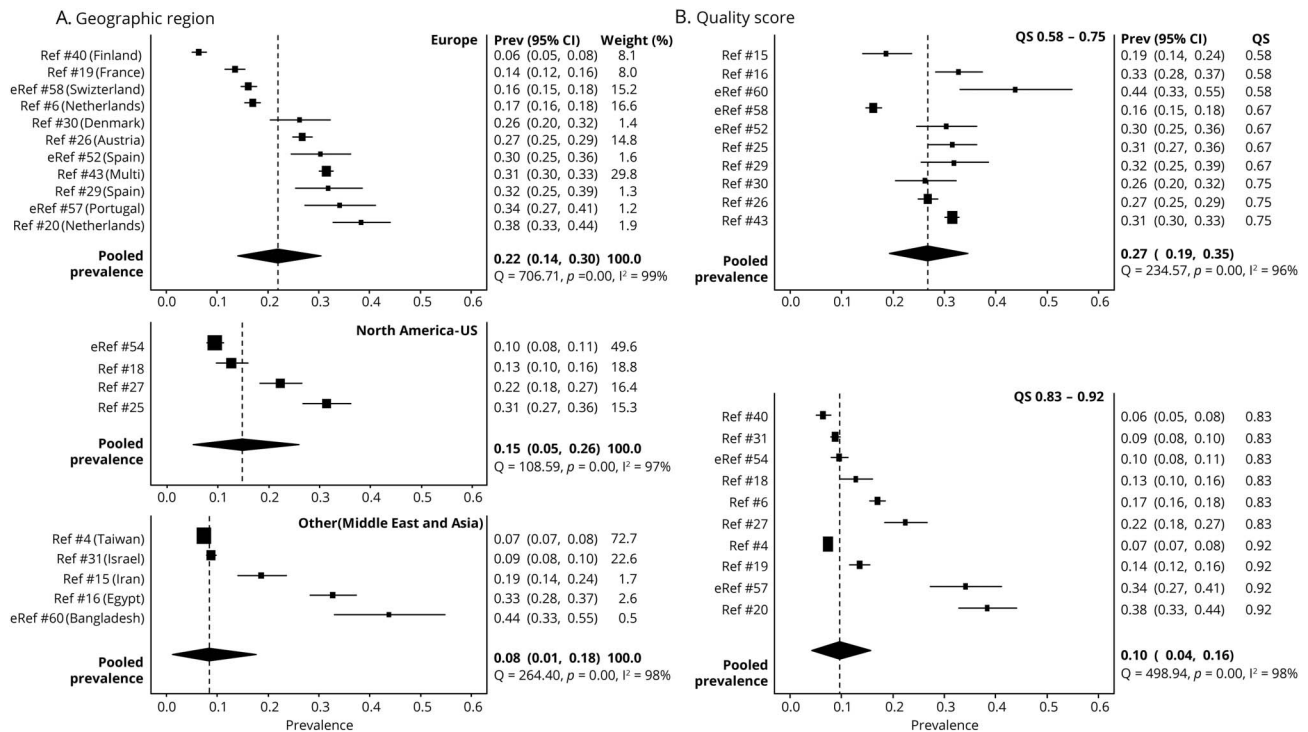
Transformed prevalence	Coefficient	SE	t	p >  t	95% CI
<b>Year</b>	0.01	0.006	0.97	0.353	-0.01 to 0.02
<b>Population source</b>					
<b>Multicenter (vs community)</b>	0.03	0.097	0.33	0.747	-0.18 to 0.24
<b>Multicenter (vs single-center)</b>	0.18	0.114	1.55	0.147	-0.07 to 0.42
<b>Single-center (vs community)</b>	-0.14	0.154	-0.94	0.367	-0.48 to 0.19
<b>Geographical region</b>					
<b>Europe (vs other)</b>	0.46	0.096	4.77	<0.001	0.25 to 0.67
<b>Europe (vs North America)</b>	0.16	0.121	1.29	0.222	-0.11 to 0.42
<b>North America (vs other)</b>	0.30	0.135	2.25	0.044	0.01 to 0.60
<b>HDI (2018)</b>	-1.13	0.461	-2.46	0.030	-2.14 to -0.13
<b>Fractional QS</b>	-1.69	0.386	-4.37	0.001	-2.53 to -0.85

Abbreviations: CI = confidence interval; HDI = human development index; QS = quality score. There is a significant association between geographical region, HDI, and manuscript quality and prevalence.  $F_{7,12} = 22.62$ ; Prob > F < 0.001;  $R^2$  0.831; root mean square error 0.137.

cardioembolic<sup>4,23,e53</sup> and large vessel stroke<sup>4,23</sup> as compared to small vessel/lacunar stroke.<sup>22,24,e57</sup> In one study, small vessel occlusion was associated with a lower prevalence of headache (prevalence ratio [PR] 0.72, 95% CI 0.64–0.81;  $p < 0.001$ ) as

compared to those caused by large vessel atherosclerosis (PR 1.28, 95% CI 1.14–1.44;  $p < 0.001$ ) or cardioembolism (PR 1.27, 95% CI 1.0–1.61;  $p < 0.05$ ).<sup>4</sup> Similar to this and other studies,<sup>e57</sup> one study found that headache was more common

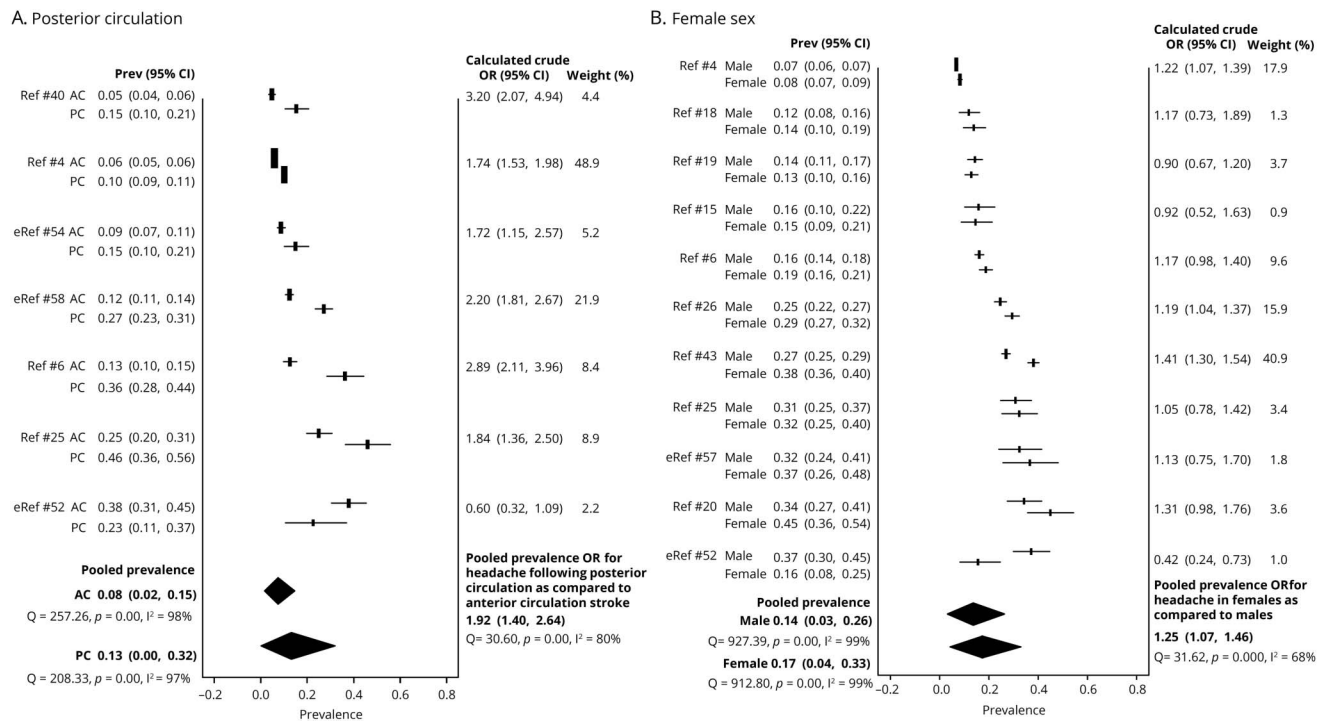
**Figure 4** Study characteristics: geographic region and quality score (QS)



(A) Headache prevalence varies depending on regional location. European studies had higher prevalence values as compared to studies from other regions (Middle East and Asia). Likewise, studies whose source population was from the United States had higher prevalence values than those from Middle East and Asia. (B) Studies with a lower QS report a higher headache prevalence as compared to studies with higher QS (QS – fractional QS). CI = confidence interval.



**Figure 5** Patient characteristics: posterior circulation (PC) stroke and female sex are associated with greater odds of ischemic stroke headache



(A) Headache prevalence for PC and anterior circulation (AC) stroke is reported for each study. The pooled headache prevalence for PC stroke is higher than that for AC stroke. The odds of having headache is 2-fold higher with PC stroke as compared with AC stroke. (B) Headache prevalence for female and male participants is reported for each study. There is a modestly higher prevalence of stroke-related headache in women as compared to men with a pooled odds ratio (OR) of 1.25. CI = confidence interval.

in those with nonlacunar stroke (9.9%) as compared to those with lacunar stroke (6.3%) ( $p = 0.03$ ).<sup>22</sup> In another study that separated patients into cardioembolic and noncardioembolic subgroups, cardioembolic stroke was associated with a higher prevalence of HAIS (36.8% vs 28.8%;  $p < 0.05$ ).<sup>e53</sup> Conflicting data have also been reported.<sup>26</sup> The rates of HAIS for cardioembolic, small vessel, large vessel, and undetermined stroke causes vary considerably among the 4 studies that reported these prevalence values (cardioembolic 4.4%–38.9%, large vessel 4.9%–40.8%, small vessel 5.5%–24.9%, and undetermined etiology 0%–35%). Given the wide and overlapping rates, the presence of headache at stroke onset does not provide further insight into stroke mechanism.<sup>4,22,26,29</sup>

Altogether, these studies suggest that HAIS is associated with posterior circulation and cortical strokes and that HAIS characteristics (quality, intensity, and accompanying symptoms) may be associated with stroke involving brain regions implicated in neural networks responsible for pain processing. HAIS prevalence may be higher in strokes of cardioembolic or large vessel origin.

### Stroke outcomes

HAIS was associated with stroke misdiagnosis in several studies.<sup>38,41,44</sup> In one retrospective study, HAIS was 3 times more common in cases with a missed diagnosis (OR 2.99,

95% CI 1.74–5.14),<sup>38</sup> whereas another showed that HAIS was present in 55% of the patients with a probable missed diagnosis of stroke.<sup>41</sup> One study linked HAIS to early signs of stroke on CT and higher levels of CSF glutamate, interleukin-6, and nitric oxide metabolites, raising the possibility that headache could signify more severe neuroinflammation or early stroke progression.<sup>e52</sup> Despite this, HAIS did not appear to be associated with worse stroke outcomes. In one cohort, initial stroke severity and 3-month functional outcomes did not differ between patients with and without HAIS.<sup>20</sup> In a larger study, patients with HAIS showed a greater improvement in deficits at discharge and a better functional outcome at 1 month.<sup>4</sup> HAIS also did not appear to affect the risk of any recurrent stroke in a 14-year follow-up study (OR 0.97, 95% CI 0.76–1.24).<sup>6</sup>

## Discussion

To our knowledge, this is the first meta-analysis of HAIS prevalence and risk factors. Our meta-analysis and systematic review show that new onset headache is common in the ischemic stroke population. The overall prevalence suggests that approximately 14% of adult patients with ischemic stroke have headache at the time of or shortly following their stroke diagnosis. That the headache often persists for months to years, can be continuous or daily, and can be moderate to

severe in intensity implicate significant disability associated with HAIS and punctuate the need for evidence-based treatment approaches. The meta-analysis and systematic review also highlight the predominant patient-related phenotypes associated with HAIS including younger age, female sex, nonlacunar cortical stroke syndromes, and involvement of the posterior fossa.

The data presented in this study add to the previously published systematic reviews by integrating prior studies and using statistical methods to provide a more precise estimate of headache prevalence in the stroke population. The reproducible association between headache and ischemic stroke, and the close temporal relationship between the headache and stroke symptom onset, strongly argue against the headache being a random occurrence. Indeed, the pooled point prevalence of HAIS assessed at the time of stroke in studies included in the meta-analysis was at least as high as the point prevalence of all headache disorders, which ranges from 5.7%<sup>e63</sup> to 16.4%.<sup>e64</sup>

There are several putative explanations for the association between posterior circulation stroke and HAIS. One possible explanation is a difference in trigeminal and autonomic innervation of the posterior cerebral vessels.<sup>e65</sup> Indeed, differences in the innervation pattern of the meninges overlying the posterior cerebral cortices and cerebellum<sup>e66</sup> raise the possibility that strokes involving these areas may have a greater ability to stimulate pain-sensing trigeminal and cervical dorsal root ganglion afferent fibers innervating the coverings overlying these regions. The posterior circulation may have differential cerebral autoregulation<sup>e67</sup> and become more susceptible to fluctuations in vasomotor tone and permeability. There may be increases in posterior fossa compartmental pressures following ischemic stroke as compared to anterior strokes. Finally, this association may also be related to migraine as a confounding variable. In migraineurs with aura, there is an increased risk of ischemic stroke, particularly involving the posterior circulation.

Migraine was not systematically assessed in many of the studies included in these meta-analyses.

Therefore, it is also possible that the increased prevalence of headache is related to a higher proportion of migraineurs in the subpopulation of patients with posterior circulation strokes as compared to anterior circulation strokes. Similarly, the modest association between female sex and HAIS could be related to a sex or hormonal influence on the development of trigeminal pain, and reflect a confounding effect of a preexisting migraine in this population. Nevertheless, the predominantly tension-type features could distinguish HAIS from a migraine attack. In fact, the difference in headache quality indicates that even in migraine patients with ischemic stroke, HAIS is probably a new secondary headache diagnosis.

The mechanisms underlying HAIS remain unclear. While an overlap with migraine pathogenesis (i.e., activation of trigeminovascular afferents or meningeal inflammation) has been postulated, that HAIS is qualitatively different from migraine suggests otherwise. It is unknown if and to what extent traction and mechanical forces, electrical events like spreading depolarization, platelet-derived factors, serotonergic mechanisms, or peptide-containing nociceptors contribute to HAIS.

There are several study-related limitations. For example, most studies did not state whether ICHD criteria were used, potentially leading to differences in when and how HAIS was defined. Most studies did not assess for preexisting diagnoses of primary headache disorders, potentially leading to misclassification bias. Recall bias was less likely because we included only prospective studies in the meta-analysis. While studies from multiple institutions and regions included in the meta-analysis increase the likelihood of generalizability of the pooled estimate, a single study with a lower headache prevalence of 8% contributed the largest weight to the pooled prevalence, raising the possibility for underestimation. Most studies excluded patients with severe stroke syndromes and aphasia, creating selection bias possibly contributing to underestimation. Finally, while the inverse variance heterogeneity model provides better coverage of the CI as compared to the random effects model in situations of high heterogeneity,<sup>10</sup> well-defined cohort studies with clear inclusion/exclusion criteria and implementation of standard diagnostic criteria for HAIS would more appropriately address this problem.

HAIS is a common disorder that contributes to the global health burden of stroke. However, because of study limitations and methodologic heterogeneity between studies, the results presented herein underscore the need for future prospective studies to better estimate the true HAIS incidence and prevalence. In particular, we recommend that future cohort studies (1) report clear inclusion and exclusion criteria; (2) use ICHD criteria to define HAIS; (3) use ICHD criteria to define a preexisting history of migraine or other primary headache disorder; (4) report descriptive characteristics of HAIS, including demographic information and headache quality, severity, timing, and accompanying symptoms; and (5) report HAIS rates by ischemic stroke etiology and location. The overall disability and reduced quality of life associated with this diagnosis remain poorly understood. Therefore, cohort studies assessing the effect of HAIS on poststroke disability and quality of life are also needed. Finally, no clinical trials on poststroke headache treatments were found in this review of the literature. While tricyclic antidepressants and anticonvulsants have been suggested for central poststroke pain syndrome,<sup>e68</sup> there is a regrettable lack of evidence supporting the use of daily medications aimed at reducing poststroke headache frequency. Future research should therefore be directed towards clinical trials of the efficacy of established headache preventive medications for the treatment of HAIS and secondary prevention approaches.

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## Appendix Authors

Name	Location	Role	Contribution
<b>Andrea M. Harriott, MD, PhD</b>	Massachusetts General Hospital	Author	Designed and conceptualized study, analyzed the data, drafted the manuscript for intellectual content
<b>Fahri Karakaya, PhD</b>	University of Massachusetts Dartmouth	Author	Designed and conceptualized study, analyzed the data, drafted the manuscript for intellectual content
<b>Cenk Ayata, MD, PhD</b>	Massachusetts General Hospital	Author	Designed and conceptualized study, analyzed the data, drafted the manuscript for intellectual content

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