Cite this article as: BMJ, doi:10.1136/bmj.38302.504063.8F (published 20 December 2004)

Papers

Risk of ischaemic stroke in people with migraine: systematic review and meta-analysis of observational studies

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Abstract

Objective To explore the association between migraine and risk of ischaemic stroke.

Design Systematic review and meta-analysis.

Data sources Observational studies published between 1966 and June 2004 (identified through Medline and Embase) that examined the association between migraine and risk of ischaemic stroke.

Results 14 studies (11 case-control studies and 3 cohort studies) were identified. These studies suggest that the risk of stroke is increased in people with migraine (relative risk 2.16, 95% confidence interval 1.89 to 2.48). This increase in risk was consistent in people who had migraine with aura (relative risk 2.27, 1.61 to 3.19) and migraine without aura (relative risk 1.83, 1.06 to 3.15), as well as in those taking oral contraceptives (relative risk 8.72, 5.05 to 15.05).

Conclusions Data from observational studies suggest that migraine may be a risk factor in developing stroke. More studies are needed to explore the mechanism of this potential association. In addition, the risk of migraine among users of oral contraceptives must be further investigated.

Introduction

Migraine is the most common type of headache in young adults, with an estimated prevalence of 4% before puberty and as high as 25% in women by their mid to late 30s.[1] Some observational studies have shown an increase in the risk of stroke among people with a history of migraine,[2] but others have failed to find this association.[3] The mechanism of this potential association is believed to be in part through platelet hyperaggregability and the reduction in cerebral blood flow that usually occurs in migraine with aura.[4] A potential association between the risk of stroke and migraine is an important public health concern, especially in young women who use oral contraceptives, which by itself may be an independent risk factor for stroke.[5]

We sought to explore the association between migraine and ischaemic stroke by conducting a meta-analysis. Specifically, we set out to quantify the risk of ischaemic stroke among people with migraine (with and without aura), as well as to quantify this risk among different age groups and users of oral contraceptives.

Methods

Search strategy

We systematically searched Medline (1966-June 2004) and Embase (1974-June 2004) for both English and non-English language articles by entering "brain ischemia," "cerebrovascular accidents," "cerebrovascular disorders," "cerebral infarction," "ischemic attack," "migraine," and "oral contraceptives" as both medical subject heading (MeSH) terms and text words. We then retrieved all relevant articles as determined by consensus among the authors and searched the reference lists of retrieved articles to find other potentially relevant articles.

Data extraction

We included studies if they used clear diagnostic criteria for migraine; had clearly stated diagnostic criteria for the outcome of ischaemic stroke; had controlled for potential confounders by using risk adjustment in the analysis or matching in the study design; and provided odds ratios or relative risks and 95% confidence intervals or provided enough data to allow us to calculate these numbers. In order to quantify the risk of stroke among people with migraine who were also using oral contraceptives, the studies had to provide data for migraine patients who were exposed to oral contraceptives compared with those who were not taking these agents. We also scored the quality of the studies by using a 10 point scale adapted from a recently published quality scale for observational studies (five criteria ranked 0, 1, or 2) and stratified the studies by score (a score of 7 or above indicates high quality; a score of 6 or below indicates low quality).[6]

Data analysis

We weighted log relative risks for cohort studies or odds ratios by the inverse of their variances to obtain a pooled measure of the relative risks. We used the assumption that an odds ratio from a case-control study approximates the relative risk in a cohort study. We combined cohort studies and case-control studies in the absence of statistical heterogeneity. When results from the fixed and random effects models were different, we presented the second as it represents a more conservative approach. We tested for heterogeneity by using the DerSimonian and Laird Q statistic. We also measured heterogeneity by using the R_i statistic, which quantifies the proportion of the total variance that is due to between study variance.[7] We assessed publication bias graphically by using a funnel plot as well as quantitatively with Egger's regression.[8]

In order to assess publication bias further we also did a sensitivity analysis, in which we assessed the potential effect of publication bias on our pooled relative risks by using three assumptions: published studies included in our meta-analysis represent only half of the studies ever conducted; the remaining unpublished studies have found null associations (that is, relative risk = 1); the unpublished studies included as many cases and controls as the average of the published studies. This approach has been used in previously published meta-analysis.[9] We used HEpiMA version 2.13 for all analyses.[10]

Table 1 Relative risks of ischaemic stroke according to type of migraine

First author, year	Relative risk (95% CI) of migraine			Adjustment for covariates and confounders	Cases:controls or cohort size	Cases:controls with migraine
	Any	With aura	Without aura			
Case-control studies						
Collaborative group, 1975[11]	2.0 (1.2 to 3.3)	NS	NS	Age, contraceptives, smoking	430:429	105:256
Henrich, 1989[12]	1.8 (0.9 to 3.6)	2.6 (1.1 to 6.6)	1.3 (0.5 to 3.6)	Not specified	89:178	17:20
Marini, 1993[13]	1.91 (1.05 to 3.5)	14.85 (1.8 to 124)	1.6 (0.9 to 3.0)	Diet, obesity, alcohol, smoking, contraceptives, hypertension, diabetes	308:308	46: 25
Tzourio, 1993[14]	1.3 (0.8 to 2.3)	1.3 (0.5 to 3.8)	0.8 (0.4 to 1.5)	Age, sex, hypertension, smoking, diabetes, contraceptives	212:212	28:30
Tzourio, 1995[2]	3.5 (1.8 to 6.4)	6.2 (2.1 to 18)	3.0 (1.5 to 5.8)	Age, sex, hypertension, smoking, diabetes, contraceptives	72:173	43:52
Lidegaard, 1995[15]	2.8 (2.00 to 4.25)	NS	NS	Pregnancy, diabetes, hypertension, earlier thrombotic disease, other disease	497:1370	64:66
Carolei, 1996[3]	1.9 (1.1 to 3.1)	1.0 (0.5 to 2.0)	8.6 (1.0 to 75)	Hypertension, smoking, cholesterol, diabetes, obesity, contraceptives, alcohol	308:591	46:54
Haapaniemi, 1997[16]	2.12 (1.05 to 2.95)	NS	NS	Hypertension, cardiac disease, current smoking, diabetes, alcohol	506:345	86:42
Chang, 1999[17]	3.54 (1.30 to 9.61)	2.97 (0.66 to 13.5)	2.97 (0.66 to 13.5)	Contraceptives, hypertension, smoking	291:736	71:88
Donaghy, 2002[18]	2.98 (1.24 to 7.19)	NS	NS	Age, smoking, hypertension, heart condition, education level, social class	86:214	NS
Schwaag, 2003[19]	2.16 (1.16 to 3.82)	NS	NS	Not specified	160:160	37:20
Cohort studies						
Buring, 1995[20]	2.00 (1.10 to 3.64)	NS	NS	Age, smoking, hypertension, cholesterol, diabetes, heart condition, exercise frequency	1479:20 481	19:194
Merikangas, 1997[21]	2.1 (1.5 to 2.9)	NS	NS	Age, sex, hypertension, diabetes, heart condition, alcohol, smoking	423:11 777	NS
Nightingale, 2004*[22]	2.33 (1.04 to 5.21)	NS	NS	Age, hypertension, physician	190:1129	16:44
Cross sectional study						
Kruit, 2004[23]	7.1 (0.9 to 55)	13.7 (1.7 to 112)	2.3 (0.2 to 23)	Age, sex, smoking, hypertension, cholesterol, alcohol	161:140	NS

NS=not specified.
*Nested case-control study within a well defined cohort.

Results

Our search resulted in 11 case-control studies,[2–3 11–19] three cohort studies,[20–22] and one cross sectional study[23] (table 1). We excluded the cross sectional study from the analysis, as the timing of diagnosis of migraine with respect to development of ischaemic stroke was difficult to infer in this study. In total, we included 14 studies in the meta-analysis.[2–3 11–22] Six studies provided data on the risk of ischaemic stroke and migraine with and without aura.[2 3 12–14 17] The age of the participants in the included studies ranged from 15 to 84 years. The incidence of stroke among people with migraine in the three cohort studies ranged from 3.56 to 350 cases per 100 000 person years.[20–22]

The pooled relative risk for ischaemic stroke among patients with any type of migraine headache was 2.16 (95% confidence interval 1.89 to 2.48) (table 2, fig 1). The relative risks for people with migraine with and without aura were 2.27 (1.61 to 3.19) and 1.83 (1.06 to 3.15). This risk did not differ when we stratified our analysis by age (table 2). Users of oral contraceptives had an approximately eightfold increase in the risk of stroke compared with those not using these agents.

We did not find evidence of publication bias either graphically from the funnel plot (fig 2) or quantitatively ($P = 0.685$ for Egger's test of asymmetry). The pooled relative risk for the sensitivity analysis still showed a significant increase in the risk of stroke (relative risk 1.43, 1.21 to 1.68).

Discussion

The results of our study strongly suggest that migraine may be an independent risk factor for stroke. The magnitude of this risk remained the same across all studies (case-control and cohort) as well as in those that provided data on migraine with aura, migraine without aura, and oral contraceptive users. The risk of stroke among oral contraceptive users is very high, although these data come from only three studies. Other studies in women who were users of oral contraceptives have shown that those with a history of migraine have twice the likelihood of developing an ischaemic stroke compared with those without migraine (relative risk 2.15, 95% confidence interval 0.85 to 5.45).[24] Given that use of oral contraceptives is prevalent among young women, the potential risk of stroke among women with migraine who are also users of oral contraceptives must be further investigated. Possible mechanisms for this association include irregularities in blood flow,[25] cardiac abnormalities,[26] and abnormal production of prostaglandins as well as noradrenergic or cholinergic transmitters and receptors.[27]

Table 2 Pooled relative risks of ischaemic stroke stratified by migraine type, oral contraceptive use, and age

	No of studies	Relative risk (95% CI)	Ri*	P value†
Migraine (any)				
All studies	14	2.16 (1.89 to 2.48)	0.00	0.77
Case-control studies	11	2.18 (1.86 to 2.56)	0.00	0.51
Cohort studies	3	2.10 (1.61 to 2.75)	0.00	0.96
Migraine with aura				
Case-control studies	7	2.27 (1.61 to 3.19)	0.49	0.08
Migraine without aura				
Case-control studies	6	1.83 (1.06 to 3.15)	0.60	0.04
Migraine among oral contraceptive users				
Case-control studies	3	8.72 (5.05 to 15.05)	0.26	0.28
Migraine among men and women <45 years				
Case-control studies	9	2.36 (1.92 to 2.90)	0.07	0.38
Migraine among women <45 years				
Case-control studies	7	2.76 (2.17 to 3.52)	0.00	0.82

*Proportion of the total variance due to between study variance. Large values (>0.75) indicate large heterogeneity between studies; small values (<0.4) indicate lack of heterogeneity.[7]
†DerSimonian and Laird Q statistic.

Limitations

Our meta-analysis is subject to several limitations. Firstly, most of the studies in the meta-analysis were case-control studies, which are subject to recall bias. Cases may have been more likely to classify their headache as a migraine headache (as opposed to a tension headache). Secondly, although almost all the studies controlled for appropriate confounders in either the design or the analysis, some important confounders may not have been controlled for. For example, use of antihypertensive drugs may be a potential confounder, as these drugs may be used to prevent migraine attacks as well as future strokes. However, use of these drugs among people with migraine would probably have produced a decrease in the risk of stroke, which was not seen in our study. Antiphospholipid antibodies have been thought to be linked to stroke and possibly to migraine.[28] None of the studies included in the meta-analysis provided information on this potential confounder. People who have migraine attacks might be less likely to be diagnosed as having a stroke, as the symptoms of migraine may be confused with those of stroke. Although this remains a possibility, many of the studies included in the meta-analysis used strict criteria to define ischaemic stroke, including duration of symptoms of at least 24 hours, as well as confirmation of diagnosis by brain imaging or autopsy. Finally, we could not infer from the studies a temporal relation between the onset of migraine and the diagnosis of stroke.

Conclusion

Data from observational studies suggest that migraine may be a risk factor in developing stroke. More studies are needed to explore the mechanism of this potential association. The risk of migraine among users of oral contraceptives must be further investigated.

Contributors: ME, BT, and FCI initiated the project. ME, BT, FCI, and AS screened and extracted the data. BT analysed the data. All authors participated in discussing the results and writing the paper. ME is the guarantor.

Funding: No specific funding. ME is funded by a Canadian Institutes of Health Research postdoctoral fellowship award. AS is supported by the National Institutes of Health and the Department of Veterans Affairs through the Parkinson Disease Research Education and Clinical Center grant.

Competing interests: None declared.

Ethical approval: Not needed.

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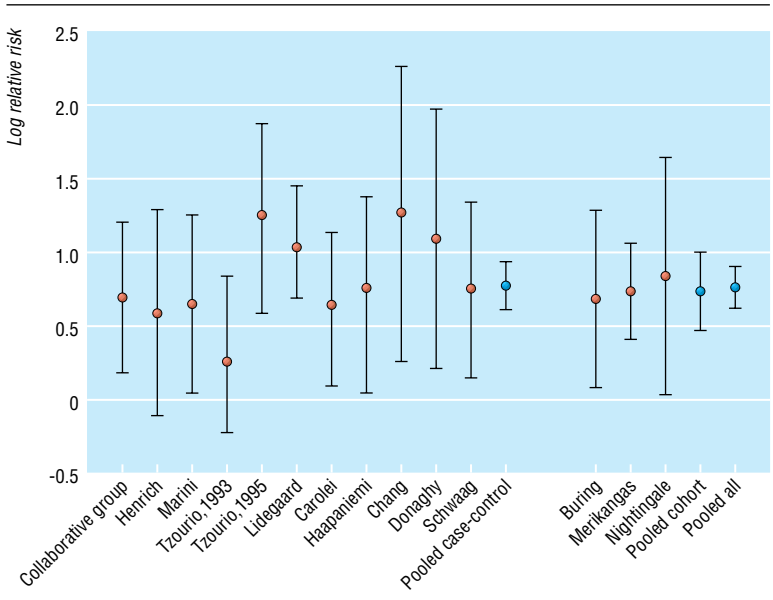

Fig 1 Forest plot of the studies of migraine and ischaemic stroke

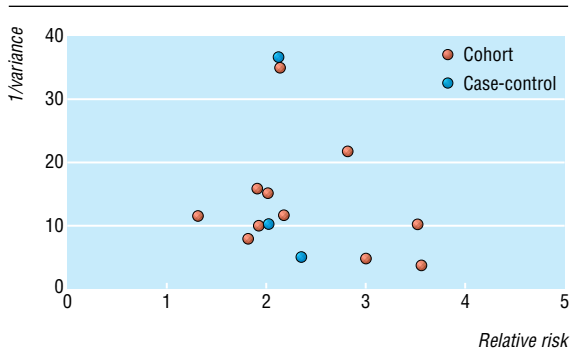

Fig 2 Funnel plot of the studies of migraine and ischaemic stroke

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What is already known on this topic

Studies have suggested that migraine may be a risk factor for stroke, but results from these studies have been inconsistent

What this study adds

Migraine both with and without aura may be an independent risk factor for ischaemic stroke

This risk is higher among oral contraceptive users and younger adults (<45 years)

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(Accepted 9 November 2004)

doi 10.1136/bmj.38302.504063.8F

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Amendment

This is Version 3 of the paper. In this version, Mahyar Etminan's first name is spelt correctly [in the previous version it was spelt Mayhar] and the University of Washington is correctly located in Seattle, WA [rather than in Washington DC].