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Meta-analysis of results from case control and cohort studies finds that migraine is associated with approximately twice the risk of ischaemic stroke

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Context

Several studies have linked ischaemic stroke with migraine headache. To better define this relationship, investigators performed a meta-analysis to quantitatively summarise the strength of association between migraine and ischaemic stroke risk.

Methods

A systematic search identified relevant published reports regarding ischaemic stroke risk as associated with migraine. Prespecified criteria: (1) included studies with case-control or cohort study designs with reported or extractable adjusted quantitative estimates of the risk of ischaemic stroke in migraineurs compared with non-migraineurs and (2) excluded studies of transient stroke-like syndromes, migrainous infarction, silent infarction and those that reported outcomes as associated with mixed stroke types (eg, haemorrhagic and ischaemic stroke). Of note, all but two studies from the most recent prior meta-analysis and nine additional studies were included in the present study. Included studies were required to implement standard definitions, or reasonable variations thereof, for both stroke and migraine.

OR, RR, HR and incidence rate ratios were used to estimate effect sizes. Evaluations of clinical, methodological and statistical heterogeneity of the included studies were assessed using the Cochrane Collaboration Guidelines for systematic reviews. An overall pooled effect estimate across the different effect estimate types was computed for comparison and a sensitivity analysis was performed to assess for differences in the results if only studies with a low risk of bias were included. Subgroup analyses by migraine type (with aura vs without aura) and gender were performed. To reduce potential confounding, the investigators chose to pool the adjusted rather than crude measures of effect and they also examined the degree to which excluding single studies, one by one, influenced summary results.

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Competing interests None.

Findings

The search strategy identified 21 studies that were eligible for inclusion; 13 case-control and 8 cohort studies for a total of 622 381 participants. Many of the studies included only one gender, with the average age of participants ranging between 30 and 50 years. One study was excluded on the basis of significant clinical and methodological heterogeneity as it failed to adjust for important potential confounders.

The pooled adjusted OR of ischaemic stroke comparing migraineurs with non-migraineurs using a random effects model was 2.30 (95% CI 1.91 to 2.76). The pooled adjusted effect estimates for studies that reported RRs and HRs, respectively, were 2.41 (95% CI 1.81 to 3.20) and 1.52 (95% CI 0.99 to 2.35). The overall pooled effect estimate combining all studies and effect measures was 2.04 (95% CI 1.72 to 2.43). In subgroup analyses, there was a stronger association of ischaemic stroke and migraine with aura (pooled adjusted OR for seven studies 2.51; 95% CI 1.52 to 4.14) compared with the association of ischaemic stroke and migraine without aura (pooled adjusted OR for six studies 1.29; 95% CI 0.81 to 2.06). The pooled adjusted OR for ischaemic stroke in studies of only women migraineurs versus non-migraineurs (seven studies) was 2.89 (95% CI 2.42 to 3.45). Male-only analyses could not be performed secondary to insufficient data. Results were robust to sensitivity analyses excluding lower quality studies.

Commentary

Given the high incidence and prevalence of ischaemic stroke in the global population, a better understanding of less well-established risk factors, such as migraine, is highly important. To address this issue, Spector and colleagues performed the largest meta-analysis to date evaluating the association between migraine and ischaemic stroke. Their study demonstrated that migraine is associated with a twofold increased risk of ischaemic stroke. These results expand on those of a prior smaller systematic review and meta-analysis, which reported a similar magnitude of ischaemic stroke risk in participants with migraine with aura and among women. While it is not surprising that the results of these two studies were similar given the overlap of the studies included, it is important to note that the risk estimates of the present study remained similar with the inclusion of several additional large studies.

As the investigators mention, meta-analyses share the limitations of the studies included. As such, any bias in the included studies will also influence the results of the meta-analyses. An important potential bias in all studies of migraine and stroke is the confounding of migraine aura with transient cerebral ischaemia (TIA). This can be addressed by determining whether stroke is more associated with recent onset ‘aura’, suggesting misclassification with TIA, or with the frequency and severity of auras, suggesting a true association. In the present study, the investigators have done their best to remove any studies that showed excess clinical, methodological and statistical heterogeneity. Further review of the included studies for potential publication bias demonstrated none, although this concern can never be fully alleviated. Because the included studies were comprised primarily of individuals of European descent, these results may not be generalisable to other ethnicities. Further, no

firm conclusions can be drawn about stroke risk as associated with migraine in men. Finally, the study provided no mechanistic data for the associations seen.

Consistent with prior studies, the investigators found a greater risk of ischaemic stroke in migraine with aura than migraine without aura, and also among women. These findings may highlight higher risk populations in which more aggressive standard vascular risk factor (hypertension, diabetes, etc) control may be warranted. Overall, these results indicate that migraine may be another modifiable risk factor for stroke, however additional longitudinal studies are required before this can be definitely determined.

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