Migraine and risk of cardiovascular disease in women: prospective cohort study

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ABSTRACT

OBJECTIVE
To evaluate the association between migraine and incident cardiovascular disease and cardiovascular mortality in women.

DESIGN
Prospective cohort study among Nurses' Health Study II participants, with follow-up from 1989 and through June 2011.

SETTING
Cohort of female nurses in United States.

PARTICIPANTS
115 541 women aged 25-42 years at baseline and free of angina and cardiovascular disease. Cumulative follow-up rates were more than 90%.

MAIN OUTCOME MEASURES
The primary outcome of the study was major cardiovascular disease, a combined endpoint of myocardial infarction, stroke, or fatal cardiovascular disease. Secondary outcome measures included individual endpoints of myocardial infarction, stroke, angina/coronary revascularization procedures, and cardiovascular mortality.

RESULTS
17 531 (15.2%) women reported a physician's diagnosis of migraine. Over 20 years of follow-up, 1329 major cardiovascular disease events occurred and 223 women died from cardiovascular disease. After adjustment for potential confounding factors, migraine was associated with an increased risk for major cardiovascular disease (hazard ratio 1.50, 95% confidence interval 1.33 to 1.69), myocardial infarction (1.39, 1.18 to 1.64), stroke (1.62, 1.37 to 1.92), and angina/coronary revascularization procedures (1.73, 1.29 to 2.32), compared with women without migraine. Furthermore, migraine was associated with a significantly increased risk for cardiovascular disease mortality (hazard ratio 1.37, 1.02 to 1.83). Associations were similar across subgroups of women, including by age (<50/≥50), smoking status (current/past/never), hypertension (yes/no), postmenopausal hormone therapy (current/not current), and oral contraceptive use (current/not current).

CONCLUSIONS
Results of this large, prospective cohort study in women with more than 20 years of follow-up indicate a consistent link between migraine and cardiovascular disease events, including cardiovascular mortality. Women with migraine should be evaluated for their vascular risk. Future targeted research is warranted to identify preventive strategies to reduce the risk of future cardiovascular disease among patients with migraine.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Migraine has been consistently linked with increased risk of ischemic stroke

Few studies have shown an association of migraine with coronary events and cardiovascular mortality

WHAT THIS STUDY ADDS

Analysis of data from a large prospective cohort study in women show that migraine is associated with any cardiovascular disease, including coronary events and cardiovascular mortality

These results further add to the evidence that migraine should be considered an important risk marker for cardiovascular disease, at least in women

Introduction

Migraine is a primary headache disorder that affects approximately one fifth of the general US population for at least part of their lives, and women are affected three to four times more often than men.[1-3] Migraine, specifically migraine with aura, has been consistently associated with increased risk of stroke, including both ischemic and hemorrhagic subtypes.[4 5] Although the pathophysiology of migraine has close links to the vascular system, the mechanisms by which migraine increases risk of stroke remain unclear.[6 7] Potential mechanisms for an association between migraine and stroke include endovascular dysfunction,[8 9] increased thrombogenic susceptibility,[10] increased prevalence of vascular risk factors,[11] shared genetic markers,[12 13] cortical spreading depolarization,[14 15] and inflammation.[16 17]

As most of these mechanisms also increase the risk of other cardiovascular disease events, migraine may be viewed as a marker of increased risk for any vascular disease event. However, as the one year prevalence of migraine peaks in midlife whereas the incidence of cardiovascular events increases exponentially with age, links between migraine and any cardiovascular disease are not easily identifiable. Long follow-up, particularly of younger populations, is needed to study this association. Few prospective studies have reported an association between migraine and any cardiovascular disease events,[18-21] including ischemic heart disease and cardiovascular death.[18 20 21]

Because of the high prevalence of migraine, any association between migraine and cardiovascular disease would have a substantial effect on public health. We thus aimed to evaluate the association of migraine with total and specific cardiovascular disease events as well as cardiovascular disease specific mortality in the Nurses' Health Study II, one of the largest prospective cohort studies on health in younger women, aged 25 to 42 at baseline.

Methods

Study population

Established in 1989, the Nurses' Health Study II is an ongoing prospective cohort study of 116 430 female registered nurses in the United States who were 25-42 years old at baseline. Information on reproductive factors, lifestyle factors, and medical history was collected through a self administered questionnaire at baseline and has been updated every two years through follow-up questionnaires. The cumulative response rate based on person time is more than 90%. For the purpose of this analysis, we included follow-up from baseline through June 2011. We excluded 889 women who reported cardiovascular disease at baseline (angina, a coronary revascularization procedure, myocardial infarction, or stroke) from our analyses, leaving 115 541 women free of angina or any symptomatic cardiovascular disease for our analyses.

Patient involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for recruitment, design, or implementation of the study. No patients were asked to advise on interpretation or writing up of results. Results of the study will be disseminated to patients' organizations and via the webpage of the Nurses' Health Study (http://www.nurseshealthstudy.org).

Assessment of migraine

On the baseline (1989) and two follow-up questionnaires (1993 and 1995), women were asked to indicate whether a physician had diagnosed them as having migraine. Person time status for having a migraine started whenever migraine was first reported. Agreement between self reported migraine and 2004 International Headache Society criteria was high in another comparable cohort of female health professionals.[22] Information on migraine aura, migraine frequency, or migraine specific drugs was not available.

Ascertainment of cardiovascular disease events

Every two years, women reported any incident cardiovascular disease event on the follow-up questionnaires and then completed a supplemental questionnaire confirming the event. Self reported information on cardiovascular disease was confirmed through review of medical record or supporting information by a physician who was blinded to the exposure status and the specific research question under study. Deaths were identified by reports from next of kin, from postal authorities, or by searching the National Death Index. At least 98% of deaths among the Nurses' Health Study II participants were identified using these approaches.[23] Causes of death were confirmed by review of autopsy reports, medical records, and death certificates.

The occurrence of non-fatal myocardial infarction was confirmed if symptoms met World Health Organization criteria, which require typical symptoms plus either diagnostic electrocardiographic findings or elevated cardiac enzyme concentrations.[24] If medical records were unavailable, we considered myocardial infarctions probable when additional confirmatory information was provided by the participant. Information on angina and coronary revascularization procedures (percutaneous transluminal coronary angioplasty or coronary artery bypass grafting surgery) was self reported, and we included only events that occurred before a manifest cardiovascular disease event.

A non-fatal stroke diagnosis was confirmed, according to National Survey of Stroke criteria, if the participant had a new focal neurologic deficit with sudden or rapid onset that persisted for more than 24 hours.[25] We excluded cerebrovascular pathology due to infection, trauma, or malignancy, as well as "silent" strokes discovered only by radiologic imaging. Radiology reports of brain imaging (computed tomography or magnetic resonance imaging) were available in 89% of those with medical records. We classified strokes as ischemic stroke (thrombotic or embolic occlusion of a cerebral artery), hemorrhagic stroke (subarachnoid and intraparenchymal hemorrhage), or stroke of probable/unknown subtype (a stroke was documented but the subtype could not be ascertained owing to medical records being unobtainable).

Fatal cardiovascular disease was defined as fatal coronary heart disease, fatal stroke, or fatal cardiovascular disease. Fatal coronary heart disease was defined as ICD-9 (international classification of diseases, ninth revision) codes 410-412 and was considered confirmed if fatal coronary heart disease was confirmed via medical records or autopsy reports or if coronary heart disease was listed as the cause of death on the death certificate and there was prior evidence of coronary heart disease in the medical records. We designated as probable those cases in which coronary heart disease was the underlying cause on the death certificates but no prior knowledge of coronary heart disease was indicated and medical records concerning the death were unavailable. Similarly, we used ICD-9 codes 430-434 to define fatal stroke and followed the same procedures to classify cases of confirmed or probable fatal stroke. Lastly, fatal cardiovascular disease was defined by ICD-9 codes 390-458.

Our primary outcome measure was major cardiovascular disease, a combined endpoint of myocardial infarction, stroke, or fatal cardiovascular disease (fatal stroke, fatal myocardial infarction, and fatal coronary heart disease). We chose this composite outcome as it has been used as outcome in previous studies,[18 26] and it follows guidelines on prevention of all cardiovascular disease to capture the full impact of risk factors and cardiovascular health.[27] We further assessed the following secondary outcome measures: total myocardial infarction, which was defined as fatal or non-fatal myocardial infarction; total stroke, which included all fatal and non-fatal stroke cases (ischemic, hemorrhagic, and undetermined subtypes); angina/coronary revascularization procedure; and cardiovascular disease mortality.

Statistical analyses

We calculated person time from the return date of the 1989 questionnaire until the date of diagnosis of

cardiovascular disease, date of death, or end of follow-up (June 2011), whichever occurred first. We used Cox proportional hazards models with age and two year follow-up cycle as timescale to evaluate the association between migraine and the various outcomes. We calculated age adjusted and multivariable adjusted hazard ratios and corresponding 95% confidence intervals. The multivariable adjusted models controlled for age (continuous), elevated cholesterol (yes/no), diabetes (yes/no), hypertension (yes/no), body mass index (<25, 25-<30, ≥30), smoking status (never, past, current), alcohol consumption (0, 0-14.9, ≥15 g/day), physical activity (metabolic equivalent of tasks (METs) in fifths) (continuous), postmenopausal hormone use (never, past, current), menopausal status (premenopausal, postmenopausal, dubious), ever used oral contraceptive (never, past, current), aspirin use (<2 days/week, ≥2 days/week), acetaminophen (paracetamol) use (<2 days/week, ≥2 days/week), non-steroidal anti-inflammatory drug use (<2 days/week, ≥2 days/week), and family history of myocardial infarction before the age of 60 (yes/no). We adjusted for all the covariates in the models in a time varying fashion on the basis of information available on each of the biennial questionnaires (1991 to 2009).

We evaluated effect modification by age (<50/≥50), smoking status (current/past/never), hypertension (yes/no), postmenopausal hormone therapy (current/not current), and oral contraceptive use (current/not current). We tested effect modification by including an interaction term for migraine and the potential effect modifier in the outcome models.

We tested the proportional hazards assumption by including an interaction term for migraine status and the logarithm of follow-up time for the primary outcomes in age adjusted models. We found no statistically significant violation. In sensitivity analyses, we repeated the analyses on the basis of migraine information provided at baseline only.

We had 3.1% missing information on all covariates and used a missing variable indicator to account for this lack of information in our multivariable models. In sensitivity analyses, we used multiple imputation (proc mi) to account for missing information and also ran a model excluding all missing information.

We used SAS 9.3 for all analyses. All P values were two sided, and we considered a P value of less than 0.05 to be statistically significant.

Results

Of the 115 541 women in this study, 17 531 (15.2%) reported a physician's diagnosis of migraine at baseline in 1989. An additional 6389 women newly reported a physician's diagnosis on subsequent questionnaires and were classified having migraine during follow-up. Women with migraine were more likely to have an unfavorable cardiovascular risk factor profile, including hypertension, hypercholesterolemia, family history of myocardial infarction, body mass index of 30 or above, and current smoking status. They were also more likely to use aspirin, acetaminophen, and non-steroidal anti-inflammatory drugs (table 1).

Table 2 summarizes the associations between migraine and various cardiovascular outcomes. During follow-up, 1329 major cardiovascular disease events (678 total myocardial infarctions, 651 total strokes, and 203 angina/coronary revascularization procedures) occurred. A total of 223 deaths due to cardiovascular disease occurred. Compared with women without migraine, those with a self reported physician's diagnosis of migraine had a multivariable adjusted hazard ratio of 1.50 (95% confidence interval 1.33 to 1.69) for developing major cardiovascular disease. Findings were significant for all evaluated individual outcomes, and the highest estimates were seen for stroke (hazard ratio 1.62, 1.37 to 1.92) and angina/coronary revascularizations (1.73, 1.29 to 2.32).

Table 1 | Age standardized baseline characteristics (1989) according to migraine status in Nurses' Health Study II (n=115 541). Values are percentages unless stated otherwise

Characteristics	No migraine (n=98 010)	Migraine (n=17 531)
Mean (SD) age*, years	34.2 (4.7)	35.1 (4.5)
Body mass index†:		
<25	70.1	65.5
25 to <30	18.3	19.9
≥30	10.9	13.9
History of hypertension	4.9	8.6
History of hypercholesterolemia	9.7	14.7
History of diabetes	0.8	1.00
Smoking status:		
Never	65.5	62.6
Past	21.2	22.3
Current	13.2	15.0
Alcohol consumption, g/day:		
0	37.1	39.4
>0 to 14.9	58.8	57.6
≥15	3.1	2.3
Mean (SD) physical activity, METs/week	24.9 (36.8)	24.9 (36.7)
Menopausal status:		
Premenopausal	97.4	95.3
Postmenopausal	2.0	4.00
Dubious/unknown	0.4	0.5
Postmenopausal hormone use:		
Never	89.2	83.3
Past	6.9	9.9
Current	3.3	6.1
Oral contraceptive use:		
Never	17.1	13.4
Past	69.6	74.8
Current	13.2	11.7
Family history of myocardial infarction	14.3	17.5
Aspirin use:		
<2 days/week	89.9	83.2
≥2 days/week	10.1	16.8
Acetaminophen (paracetamol) use:		
<2 days/week	80.0	66.9
≥2 days/week	20.0	33.1
Non-steroidal anti-inflammatory drug use:		
<2 days/week	82.6	69.7
≥2days/week	17.4	30.3

Percentages may not add to a 100% because of rounding or missing values.
MET=metabolic equivalent.
*Value is not age adjusted.
†Calculated as weight in kilograms divided by height in meters squared.

Table 2 | Age adjusted and multivariable adjusted hazard ratios for cardiovascular disease outcomes according to migraine status in Nurses' Health Study II (n=115 541)

Outcome	Hazard ratio (95% CI)		
	No migraine (n=98 010)	Any migraine (n=17 531)	P value
Major cardiovascular disease event (n=1329):			
Age adjusted	1.00	1.84 (1.64 to 2.06)	<0.01
Multivariable adjusted	1.00	1.50 (1.33 to 1.69)	<0.01
Myocardial infarction (n=678):			
Age adjusted	1.00	1.79 (1.52 to 2.10)	<0.01
Multivariable adjusted	1.00	1.39 (1.18 to 1.64)	<0.01
Stroke (n=651):			
Age adjusted	1.00	1.89 (1.60 to 2.22)	<0.01
Multivariable adjusted	1.00	1.62 (1.37 to 1.92)	<0.01
Angina/coronary revascularization (n=203):			
Age adjusted	1.00	2.35 (1.77 to 3.12)	<0.01
Multivariable adjusted	1.00	1.73 (1.29 to 2.32)	<0.01
Cardiovascular mortality (n=223):			
Age adjusted	1.00	1.66 (1.25 to 2.21)	<0.01
Multivariable adjusted	1.00	1.37 (1.02 to 1.83)	0.04

Multivariable models were adjusted for age (continuous), elevated cholesterol (yes/no), diabetes (yes/no), hypertension (yes/no), body mass index (<25, 25-29.9, ≥30), smoking status (never, past, current), alcohol consumption (0, >0-14.9, ≥15g/day), physical activity (METs in fifths), postmenopausal hormone use (never, past, current), menopausal status (premenopausal, postmenopausal, dubious), ever used oral contraceptive (never, past, current), aspirin use (<2, ≥2 days/week), acetaminophen (paracetamol) use (<2, ≥2 days/week), non-steroidal anti-inflammatory drug use (<2, ≥2 days/week), and family history of myocardial infarction before age of 60 (yes/no).

The associations between migraine and cardiovascular disease outcomes (major cardiovascular disease, total myocardial infarction, and total stroke) were not modified by age (<50/≥50) (P for interaction all ≥0.34), current postmenopausal hormone use (P for interaction all ≥0.57), current oral contraceptive use (P for interaction all ≥0.84), current smoking status (P for interaction all ≥0.26), or hypertension (P for interaction all ≥0.37). In sensitivity analyses, we restricted analysis to women with a report of migraine at baseline. The multivariable adjusted hazard ratios were 1.57 (1.38 to 1.77) for major cardiovascular disease, 1.77 (1.49 to 2.11) for total stroke, and 1.39 (1.17 to 1.66) for total myocardial infarction. The results of the association between migraine and major cardiovascular disease were very similar when we used multiple imputation (hazard ratio 1.50, 1.33 to 1.71) or when we excluded missing information (1.53, 1.35 to 1.74).

Discussion

In this large, prospective cohort study of female nurses aged 25 to 42 at inclusion who were free of cardiovascular disease at the start of follow-up and with more than 20 years of follow-up, we found consistent associations between migraine and cardiovascular disease events. We found an approximately 50% increased risk for major cardiovascular disease. This association persisted after adjustment for traditional vascular risk factor and was apparent for myocardial infarction, stroke, and coronary artery procedures as well as for angina. We also found an increased risk of cardiovascular disease mortality.

Comparison with other studies

Most studies evaluating the association between migraine and vascular events have been limited to ischemic stroke.[4][28] Some studies have reported an association between migraine and cardiovascular disease.[18-21] Results of our study are in line with findings from the Women's Health Study,[18] another large prospective cohort study among female health professionals aged 45 or older at inclusion. In the Women's Health Study, migraine was associated with an increased risk of major cardiovascular disease events (hazard ratio 1.42, 95% confidence interval 1.16 to 1.074), including cardiovascular disease mortality (1.63, 1.07 to 2.50). In the Women's Health Study, the increased risk was apparent only for women who reported migraine with aura. In our study, information on aura was not available.

In a matched cohort study of 11 541 patients with migraine who were aged 18 to 45 years and an equal number of controls from the Taiwan National Health Insurance database, Wang and colleagues reported an increased risk of ischemic heart disease for people with migraine (hazard ratio 2.50, 1.78 to 3.52).[20] The Reykjavik Study, which included 18 725 men and women, showed very similar results for the association between overall migraine and cardiovascular disease mortality.[21] After adjustment for potential confounders, participants with any indication of migraine had a 16% increased risk of dying from any cause (hazard ratio 1.16, 1.04 to 1.29). This risk was stronger for people with migraine with aura (hazard ratio 1.21, 1.12 to 1.30) and was higher for mortality from cardiovascular disease (1.27, 1.13 to 1.43) compared with people without headache. Results from the American Migraine Prevalence and Prevention study also indicate an increased risk of cardiovascular disease events. In this population based case-control study of 6102 patients with migraine and 5243 controls, migraine overall was associated with a relative risk for myocardial infarction of 2.16 (1.70 to 2.76) and for total stroke of 1.54 (1.16 to 2.05).[19]

Two studies have found an association between migraine with aura and angina but not myocardial infarction.[29][30] The lack of association with myocardial infarction may be related to shorter follow-up time. In our data, women with migraine had an increased risk for myocardial infarction, as well as for angina and coronary revascularization procedures.

Many studies have focused on the evaluation of potential modifying factors and on the identification of a subgroup of patients with migraine who are at high risk for developing a subsequent stroke. Studies have consistently found that the association between migraine and stroke was observable only among younger people and was stronger among women.[28] Among women, several studies have focused on the role of smoking and oral contraceptive use.[28][31][32] In particular, the combination of smoking and oral contraceptive use among young women with migraine with aura markedly increased the risk of ischemic stroke, reaching a 10-fold increase for current cigarette smokers and oral contraceptives users.[33] However, for overall vascular risk status, several studies indicate that the association between migraine and ischemic stroke is apparent only among those with a low cardiovascular risk profile.[33][34]

Studies on modifying effects of other cardiovascular disease events are sparse. Findings of the Women's Health Study indicate that migraine with aura and an increased vascular risk profile resulted in a higher risk of incident myocardial infarction.[34] However, the event rate among women with migraine with aura was still too small to robustly evaluate the role of individual vascular risk factors, including postmenopausal hormone use.

Potential biological mechanisms

Several mechanisms that have been implied for migraine have also been linked with increased risk of cardiovascular disease, such as increased thrombogenic susceptibility,[10] shared genetic markers,[12 13] and inflammation processes.[16 17] Our findings confirm results of other studies that women with migraine have a higher prevalence of vascular risk factors, such as hypertension, higher body mass index, and hypercholesterolemia.[11 19] However, as all studies evaluating the association between migraine and cardiovascular disease have controlled for these factors, the association between migraine and cardiovascular disease is unlikely to be explained by this. Evidence suggests that the pathophysiology of migraine can also be viewed in part as a systemic disorder affecting the endovascular system.[9 35-39]

Strengths and limitations of study

Our study has several strengths, including the prospective design, large number of participants and outcome events, long follow-up, high participation rate, standardized evaluation of migraine and cardiovascular disease risk factors, confirmation of outcomes by physician's review, and the homogeneous nature of the cohort (all were nurses), which may reduce confounding by factors such as access to medical care.

Several limitations should be considered when interpreting our results. Firstly, physician diagnosed migraine status was self reported, leading to potential misclassification. In addition, people with mild migraines may not have reported symptoms to a clinician and thus not received a diagnosis. Because of the prospective design, however, such misclassification would probably result in underestimation of relative risks and would be unlikely to explain the observed association pattern. Furthermore, a previous report in a comparable study of female health professionals showed that self reported migraine had good agreement with the second edition of the International Classification of Headache Disorders,[22] and our prevalence of migraine is close to that reported in other population based studies.[18 40 41] Secondly, we had no information on the presence or absence of migraine aura, and migraine with aura has been suggested to be the subgroup carrying most of the risk of cardiovascular disease.[4 18] Furthermore, no information on frequency of migraine or migraine specific information was available. Thirdly, residual confounding—for example, by markers of inflammation or genetic factors[10 12 13]—remains a potential alternative explanation, as our data

are observational. Finally, participants in this study were all nurses aged 25 to 42 at baseline and mostly white, so generalizability to other populations might be limited. However, we have no reason to believe that that the biological mechanisms by which migraine might be associated with vascular events and mortality would be different in other populations of women.

Implications of findings

The results of our study support the findings of other population based studies linking migraine with increased risk of cardiovascular disease.[18-20] Although most studies link migraine with aura with increased risk of ischemic stroke,[4 28] emerging evidence indicates that this risk extends to other cardiovascular disease as well. Our data support consideration of a history of migraine as a marker for increased risk of any cardiovascular disease event.

To date, no clear mechanisms have been identified that could explain the increased risk of cardiovascular disease and mortality among patients with migraine, and no data exist on whether prevention of migraine attacks reduces these risks. Data from the National Health and Nutrition Examination Survey and results of a randomized clinical trial provide initial evidence that the combination of a statin and vitamin D may reduce the burden of migraine,[42 43] which may be explained by the anti-inflammatory effects of these drugs. Future targeted research, such as on whether statins and vitamin D reduce the burden of migraine and cardiovascular disease, is urgently warranted to provide answers to patients and their treating physicians.

Conclusions

Results of this large, prospective cohort study among women support the hypothesis that migraine is a marker for increased risk of any cardiovascular events. Given the high prevalence of migraine in the general population, an urgent need exists to understand the biological processes involved and to provide preventive solutions for patients.

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