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RESEARCH ARTICLE

# Association of Migraine With Incident Hypertension After Menopause

## A Longitudinal Cohort Study

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## Abstract

### Objective

Migraine has been identified as a potential risk factor for hypertension in prospective studies. In women, migraine prevalence decreases after menopause, but no studies have determined whether migraine is associated with hypertension after menopause. This study sought to determine whether history of migraine was associated with an increased risk of hypertension among menopausal women.

### Methods

We assessed associations between migraine and hypertension in a longitudinal cohort study of 56,202 menopausal women participating in the French E3N cohort, with follow-up beginning in 1993. We included women who did not have hypertension or cardiovascular disease at the time of menopause. Migraine was classified as ever or never at each questionnaire cycle. Cox proportional hazards models were used to investigate relations between migraine and hypertension, controlling for potential confounding. A secondary analysis with baseline in 2011 considered aura status, grouping participants reporting migraine as migraine with aura, migraine without aura, or unknown migraine type.

### Results

During 826,419 person-years, 12,501 cases of incident hypertension were identified, including 3,100 among women with migraine and 9,401 among women without migraine. Migraine was associated with an increased risk of hypertension in menopausal women (hazard ratio $[HR]_{migraine}$ 1.29 [95% confidence interval 1.24, 1.35]) and was consistent in post hoc sensitivity analyses, such as when controlling for common migraine medications. Associations between migraine and hypertension were similar whether or not women reported aura ($HR_{migraine\ aura}$ 1.54 [1.04, 2.30], $HR_{migraine\ no\ aura}$ 1.32 [0.87, 2.02], $p$ heterogeneity 0.60). Associations were slightly stronger among ever users of menopausal hormone therapy ($HR_{migraine}$ 1.34 [1.27, 1.41]) than among never users ($HR_{migraine}$ 1.19 [1.11, 1.28]).

### Conclusions

Migraine was associated with an increased risk of hypertension among menopausal women. In secondary analysis, we did not observe a significant difference between migraine with aura and migraine without aura.

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## Glossary

**BMI** = body mass index; **CVD** = cardiovascular disease; **E3N** = Etude Épidémiologique de Femmes de la Mutuelle Générale de l'Education; **HR** = hazard ratio; **MGEN** = Mutuelle Générale de l'Education Nationale; **MHT** = menopausal hormone therapy; **PY** = person-years; **WHI** = Women's Health Initiative.

Migraine is a common primary headache disorder characterized by recurrent headache attacks of moderate to severe intensity. Migraine more often affects women than men and is most prevalent in women in the perimenopausal period.[1,2] In some people, migraine can be preceded by certain symptoms, known as aura. Migraine is associated with the presence of cardiovascular risk factors such as high body mass index (BMI), lower levels of physical activity, smoking, family history of cardiovascular disease (CVD), and dyslipidemia.[3,4] Migraine, especially migraine with aura, has been identified as a risk factor for CVD.[5-10] Attacks of migraine are known to cause transient changes in blood pressure[11] and the presence of migraine is considered a risk factor for stroke.[12-14]

Migraine prevalence is 3–4 times higher in women than in men during the fourth decade of life,[15] which is possibly due to differences in sex hormones. Population-based studies have noted a decline in migraine prevalence after menopause,[16] possibly related to the stop in monthly hormonal changes and estrogen fluctuations.[17,18] However, sex hormones, especially estrogens, have been implicated in various protective pathways against hypertension in experimental studies in animals and humans.[19] It is less clear how history of migraine could be associated with hypertension after menopause. This prospective study aimed to investigate whether migraine was associated with the risk of hypertension in a large cohort of menopausal women.

## Methods

### E3N Cohort and Study Population

As previously described,[20] The Etude Épidémiologique de Femmes de la Mutuelle Générale de l'Education (E3N) (E3N.fr) is a French prospective cohort started in 1990 comprising 98,995 women aged 40–65 years at baseline and insured by the MGEN (Mutuelle Générale de l'Education Nationale), a health insurance plan for workers in the National Education System and their families. The objective of E3N was to study the main risk factors of cancer and chronic diseases in women. E3N is the French component of the European Prospective Investigation into Cancer and Nutrition.

Participants returned mailed questionnaires on lifestyle information and disease occurrence. Questionnaires were completed every 2–3 years (1990, 1992, 1993, 1995, 1997, 2000, 2002, 2005, 2008, 2011, and 2014). The average response rate at each questionnaire cycle was 83%. We excluded women with insufficient data to determine menopausal status (n = 4,933), and those reporting cardiovascular disease (heart attack or stroke) or hypertension before the 1993 questionnaires (n = 33,682). Women who reported a diagnosis of hypertension before the age at menopause were also excluded (n = 4,178). The final study population included 56,202 menopausal women free of hypertension.

### Standard Protocol Approvals, Registrations, and Patient Consents

The cohort received ethical approval from the French National Commission for Computerized Data and Individual Freedom (Commission Nationale Informatique et Libertés) and all participants in the study signed an informed consent. The protocol is registered at clinicaltrials.gov as NCT03285230.

### Data Availability

Anonymized data can be shared following a reasonable request from qualified researchers.

### Assessment of Migraine

Starting from the 1993 questionnaire, and at each follow-up questionnaire, participants were asked to report if they had had migraine since the last questionnaire. We classed those reporting migraine at any questionnaire as ever migraine, and updated migraine status at each questionnaire.

The 2011 questionnaire asked participants to report whether their migraine included aura or not, allowing us to assess the associations between migraine with aura and incident hypertension in a secondary analysis, considering the 2011 questionnaire as baseline. If a participant did not complete this question, but had previously reported migraine, they were considered as "unknown migraine type." Otherwise they were classified as "never migraine," "migraine without aura," or "migraine with aura."

In a sensitivity analysis, we controlled for drugs commonly prescribed for migraine. Using the MGEN reimbursement database, we identified reimbursements for drugs commonly prescribed as treatment for people with migraine (WHO Anatomical Therapeutic Chemical codes M01A [nonsteroidal anti-inflammatory drugs and antirheumatic products], N02B [other analgesics and antipyretics], N02C [antimigraine preparations], N03A [antiepileptics], N06A [antidepressants], N07C [antivertigo preparations], C07 [β-blocking agents], and C08 [calcium channel blocking agents]). Exposures to both antimigraine preparations and other drugs potentially used to treat migraine were updated continuously between 2004 and 2014; prior to 2004, they were considered unknown. At least 2 reimbursements in the year prior to or after a questionnaire were required to classify a participant as a user of a given medication.

## Assessment of Hypertension

Incident hypertension cases in this study were based on self-report. Participants were asked to report whether they had hypertension in each follow-up questionnaire, the date of diagnosis, and the use of antihypertensive treatments. If the date of hypertension diagnosis was not reported by the participant, they were imputed, using June as the month of diagnosis, in the case of missing month (14% of cases), and to 12 months before they reported hypertension in a questionnaire in the case of missing year (17% of cases).

In 2004, a drug reimbursement database became available for 97.6% of participants. If a participant declared hypertension, but did not declare the date of diagnosis, we used the first date of drug reimbursement for antihypertensive medications (Anatomical Therapeutic Chemical Classification System codes C02, C03, C07, C08, and C09) as the date of diagnosis for cases identified after 2004.

To assess the accuracy of the self-reported data, we used reimbursements for blood pressure–lowering medications from the MGEN health insurance plan drug claim database. In a validation,[21] we compared self-reported hypertension to antihypertensive drug reimbursement (any of the above specified codes). Of those reporting hypertension, 82% were reimbursed for hypertensive medications.

## Assessment of Menopause

The use of menopausal hormone therapy (MHT) was assessed at baseline and all follow-up questionnaires, using a booklet containing photographs of all types of estrogens and progestogens as previously described.[22]

Age at menopause was determined based on a combination of variables as previously reported.[22] Briefly, age at menopause was defined as (in decreasing order of priority) age at last menstrual period, age at bilateral oophorectomy, self-reported age at menopause, age at start of MHT, or the age at the start of menopausal symptoms. If unavailable (n = 5,712), the median age at menopause for the cohort (51 years for natural menopause, 47 years for surgical menopause) was imputed.

## Assessment of Covariates

Height and weight were self-reported in each questionnaire and were used to calculate BMI, defined as weight (kg) divided by squared height ($m^2$) (continuous variable). In the cohort, self-reported anthropometry has proven reliable in a validation study.[23]

Total physical activity was assessed at every second questionnaire, and included questions on weekly hours spent walking, cycling, and performing light and heavy household chores/cleaning, or recreational activities and sports (e.g., swimming and tennis), and considering the winter and the summer seasons. It included questions on the time spent walking (to work, shopping, and leisure time), cycling (to work, shopping, and leisure time), housework, and sports activities (such as racket sports, swimming, or running), as previously described.[24] Each activity was assigned a metabolic equivalent value (continuous variable) based on values from the Compendium of Physical Activities.[25]

Family history of cardiovascular disease (i.e., stroke or coronary heart disease, yes/no), type 2 diabetes (yes/no), education (no high school diploma, high school diploma, or university diploma), and smoking (former smoker, current smoker, or never smoker) were based on self-reports during follow-up.

## Statistical Methods

In order to determine hazard ratios (HRs) for self-reported hypertension, migraine status was included in Cox proportional hazards models. Migraine status and the values of time-dependent covariates were updated at each questionnaire cycle, with participants adding person-years (PY) to the models for each interquestionnaire period. Women contributed PY starting from the age at their menopause, and the end of follow-up was reported diagnosis of hypertension, death, loss to follow-up, or the end of the study period, whichever happened first.

Models were adjusted on age (model 1), and then on family history of cardiovascular disease, education level, smoking (time dependent), diabetes (time dependent), use of menopausal hormone therapy (time dependent), BMI (time dependent), and total physical activity (time dependent) (model 2) to calculate HRs and their corresponding 95% confidence intervals.

A number of post hoc sensitivity analyses were conducted. We excluded cases occurring within 5 years and within 7 years to assess potential reverse causation. As blood pressure altering agents such as β-blockers can be prescribed for migraine,[26] a second sensitivity analysis controlled for medications commonly prescribed for migraine, using data from the MGEN database as previously described. Third, we considered specific migraine treatments (N02C class drugs) as a proxy for migraine severity. We cross-referenced self-reported migraine with reimbursements for specific migraine treating medications (N02C). A 3-level variable was created, grouping participants into "N02C treated," "other migraine," and "no migraine" as the exposure. In order to assess the effect of imputing dates on the self-reported data, we excluded all cases where the MGEN drug reimbursement database was used to impute the date of hypertension diagnosis, and then excluded all cases for which the year of diagnosis was not provided. Finally, we controlled for alcohol intake in a subset of women (n = 43,295, cases = 9,915) who completed a diet history questionnaire in 1993.

Effect modification from MHT use (yes/no), age at menopause (over or below 45 years), and the type of menopause (natural or surgical) was assessed by including a cross-multiplied term in the adjusted Cox model. Models were then

stratified on these variables if the *p* value of the cross-term was statistically significant.

As a secondary analysis, we further investigated migraine aura status (migraine with aura and migraine without aura as reported in the 2011 questionnaire with date the 2011 questionnaire was returned as baseline) with the risk of incident hypertension. Person-time was recalculated accordingly, and models were adjusted as previously described. The exposure was classified as no migraine, migraine with aura, migraine without aura, and unknown migraine type. A *p* value for heterogeneity between migraine with aura and migraine without aura was estimated by changing the reference category in this model to migraine with aura, and taking the *p* value for migraine without aura.

For all adjustment variables at baseline, missing values (occurring for less than 5% of participants) were imputed using the mean or median value. For smoking and BMI, missing data during follow-up were imputed from the last reported value provided by the study participants; for example, if BMI at questionnaire 7 was not reported, BMI from questionnaire 6 was used and so on.

All statistical analyses used R version 3.5.1 (r-project.org) and the survival package (github.com/therneau/survival), with an $\alpha$ of statistical significance equal to 0.05.

## Results

At the start of follow-up, 9,543 women reported having ever had migraine, increasing to 11,030 in 2005. Age and BMI at the start of follow-up were similar between women with and without migraine, and those with migraine reported slightly higher physical activity (table 1). Those reporting migraine more often reported familial cardiovascular disease and dyslipidemia, were less likely to smoke, and were more likely to have used MHT (table 1). Among women without hypertension reporting migraine at 2005, 37.4% were reimbursed for antimigraine medications (N02C), and 8.4% were reimbursed for β-blockers (C07) (table 2), both of which were higher proportions than those not reporting migraine (N02C: 1.8%, C07: 5.5%).

During 826,419 PY, 12,501 cases of incident hypertension were identified, with a rate of 15.1 cases/1000 PY. The median age at diagnosis was 64.2 (6.8) years in the entire cohort, 63.1 (6.5) years among women with migraine, and 64.6 (6.9) years among women without migraine.

Migraine was associated with an increased risk of incident hypertension ($HR_{migraine}$ = 1.29 [1.24, 1.35], table 3). The incident rate of hypertension was 14.3/1,000 PY in women without migraine compared to 19.2/1000 PY among women with migraine.

Results were stable under all sensitivity analyses conducted. Associations remained stable when excluding cases occurring within the first 5 or 7 years after baseline (5 years: $HR_{migraine}$ = 1.29 [1.24, 1.35], cases = 11,617; 7 years: $HR_{migraine}$ = 1.29 [1.26, 1.35], cases = 10,694). When excluding hypertension cases that used a date imputed by the MGEN database, results were consistent ($HR_{migraine}$ = 1.24 [1.19, 1.30], cases = 11,095), and were consistent when excluding all cases with an imputed date ($HR_{migraine}$ = 1.23 [1.17, 1.29], remaining cases = 9,326). When controlling for medications commonly prescribed for migraine, results were consistent ($HR_{migraine}$ = 1.35 [1.29, 1.40]), and when controlling for alcohol consumption ($HR_{migraine}$ = 1.29 [1.23, 1.35], cases = 9,915). When considering separately migraine with or without specific medications, using data from 2004 onwards, results were consistent ($HR_{N02C\ treated}$ = 1.42 [1.23, 1.65], $HR_{other\ migraine}$ = 1.27 [1.18, 1.36], *p* heterogeneity = 0.28), with 184 cases occurring among those with treated migraine, 1,053 cases among those with other/untreated migraine, and 3,594 cases occurring among those not reporting migraine.

Age at menopause did not modify associations (*p* interaction = 0.78), nor did the type of menopause (*p* interaction = 0.19). Effect modification was likely for the use of MHT (*p* interaction = 0.02). Associations between hypertension and migraine were stronger among users of MHT ($HR_{migraine}$ = 1.34 [1.27, 1.41], cases = 7,122) compared to never users of MHT ($HR_{migraine}$ = 1.19 [1.11, 1.28], cases = 5,377).

In secondary analysis, we considered migraine with and without aura, which was provided by 13% of women with migraine. From 2011, 1,458 cases of incident hypertension were identified during 124,770 PY of follow-up. The mean age at 2011 was 70.0 ± 6.2 years (table 4). Overall migraine was associated with an increased risk of hypertension ($HR_{migraine}$ = 1.35 [1.20, 1.52]). The presence of an aura in women with migraine was associated with a higher risk of incident hypertension ($HR_{aura}$ = 1.54 [1.04, 2.29], table 3), while associations for migraine without aura were similar to those of overall migraine ($HR_{no\ aura}$ = 1.32 [0.87, 2.02], table 5). There was no evidence that the estimates for migraine with aura or without aura significantly differed (*p* heterogeneity = 0.60). The incidence rate of hypertension among women with no migraine was 10.9/1000 PY compared to 16.8/1000 PY among women with migraine with aura and 14.4/1000 PY among women with migraine without aura.

## Discussion

In this longitudinal cohort study, we confirmed previous observations that migraine is associated with an increased risk of incident hypertension in menopausal women. In secondary analysis, migraine with aura was associated with the risk of incident hypertension, and no significant difference was observed between migraine with or without aura.

Hypertension and migraine are both common disorders in women, but relatively few longitudinal cohort studies have

**Table 1** Characteristics of the Cohort Depending on Migraine Status at Age at Menopause

| Baseline characteristics | Study sample (n = 56,202) | No migraine (n = 46,659) | Migraine (n = 9,543) |
|---|---|---|---|
| Incident hypertension cases, n | 12,501 | 9,401 | 3,100 |
| Age at menopause, y | 50.4 ± 3.9 | 50.3 ± 4.0 | 50.8 ± 3.7 |
| BMI, kg/m$^2$ | 22.8 ± 3.1 | 22.8 ± 3.1 | 22.8 ± 3.2 |
| Physical activity, METs/wk | 55.1 ± 32.7 | 54.7 ± 32.6 | 57.1 ± 33.1 |
| Ever use of menopausal hormone therapy | 43.2 | 41.0 | 53.9 |
| Surgical menopause | 9.8 | 9.9 | 9.2 |
| Type 2 diabetes | 0.8 | 0.8 | 0.8 |
| Dyslipidemia | 8.9 | 8.5 | 10.8 |
| Family history of CVD | 30.3 | 30.0 | 33.9 |
| No high school | 8.1 | 8.4 | 6.6 |
| High school | 54.6 | 54.6 | 54.7 |
| University | 37.3 | 37.0 | 38.7 |
| Never smoker | 52.9 | 53.4 | 50.0 |
| Past smoker | 32.1 | 31.3 | 36.4 |
| Current smoker | 15.0 | 15.3 | 13.6 |

Abbreviations: BMI = body mass index; CVD = cardiovascular disease; MET = metabolic equivalent.
Values are mean ± SD or % unless indicated otherwise.

**Table 2** Percentage of Participants With at Least 2 Reimbursements for Medications Associated With Migraine in the Year 2004/2005, According to Ever Migraine Status in 2005, Excluding Hypertension Cases and Death Occurring Prior to 2005

| Medication type | Study sample (n = 48,825) | Migraine (n = 11,030) | No migraine (n = 37,795) |
|---|---|---|---|
| M01A (nonsteroidal anti-inflammatory drugs and antirheumatic products) | 69.4 | 78.3 | 68.1 |
| C07 (β-blocking agents) | 5.9 | 8.4 | 5.5 |
| C08 (calcium channel blocking agents) | 2.0 | 1.4 | 2.0 |
| N02B (nonopioid analgesics and antipyretics) | 64.5 | 72.1 | 63.3 |
| N02C (antimigraines) | 5.0 | 37.4 | 1.8 |
| N03A (antiepileptics) | 6.6 | 9.4 | 6.1 |
| N06A (selective serotonin reuptake inhibitors) | 20.0 | 26.2 | 18.8 |
| N07C (antivertigo preparations) | 6.3 | 10.7 | 5.9 |

been conducted to understand this relationship, and none in only menopausal women. In agreement with our results, 2 previous prospective studies have identified that migraine was associated with an increased risk of hypertension.[27,28] Rist et al.[27] observed an increased risk of hypertension in participants with history of migraine, but the highest risk was observed in participants with migraine without aura. Entonen et al.[28] also identified positive associations between history of migraine and hypertension, but did not include information on aura. Regarding aura, our results are also in agreement with the cross-sectional Genetic Epidemiology of Migraine study[3] and the Northern Manhattan Study,[29] which both identified migraine with aura as having positive associations with hypertension. Our secondary analysis showed that the associations between hypertension and migraine with aura or migraine without aura were not significantly different.

There are multiple routes in which migraine may be linked to hypertension. People with migraine have been shown to have early signs of arterial stiffness and increased blood pressure,[30,31] and as treatment, patients with migraine can be prescribed vasoconstrictors,[32] which reduce the diameter of blood vessels. Stiffer, smaller vessels are unable to accommodate the systolic blood flow by dilating, resulting in pressure increases. People with migraine with aura have also been shown to have higher levels of circulating endothelial particles,[33] which is a biomarker for endothelial dysfunction. Endothelial dysfunction results in reduced availability of vasodilating agents and reduced dilatory capability of the artery.[34] Endothelial dysfunction and hypertension are highly associated, although the direction of this association is not fully understood. It is possible that endothelial dysfunction occurs prior to hypertension. It is also possible that associations between hypertension and migraine could be due to common genetic traits. A meta-analysis has identified that migraine and arterial function share certain genetic markers,[35] which could also explain the higher prevalence of family history of CVD in women with migraine in the E3N cohort. Because migraine increases the likelihood of cardiovascular events, identification of additional risk factors such as the higher likelihood of hypertension among people with migraine could aid in individualized treatment or prevention, and to determine how much of the association with CVD is mediated by increases in blood pressure.

The cohort under consideration consisted entirely of menopausal women. Among women with migraine, a higher prevalence of MHT use was observed, and adjusted on. We observed that use of MHT slightly modified the associations between migraine and hypertension, with associations being slightly stronger for women using MHT. Associations between MHT and migraine are poorly understood.[1] Migraine has been noted

**Table 3** Associations Between Ever History of Migraine and Hypertension

| | No migraine (cases = 9,401) | Ever migraine (cases = 3,100) |
|---|---|---|
| **Model 1** | Ref | 1.32 (1.27, 1.37) |
| **Model 2** | Ref | 1.29 (1.24, 1.35) |

Reported as hazard ratio (95% confidence interval). Adjusted on age (model 1) and on family history of cardiovascular disease, smoking, dyslipidemia, diabetes, education level, ever use of menopausal hormone therapy, body mass index, and total physical activity (model 2).

as a factor that can increase the likelihood of menopausal symptoms,[36] and MHT has been suggested as a possible approach to prevent migraine during menopause,[37] which could explain the higher rates of MHT among women with migraine in this study. However, other studies have shown that the use of MHT is associated with a higher risk of migraine,[38,39] but these observations are not consistent.[40] Clinical trials indicate that MHT can increase blood pressure slightly in older women, but not in younger women, or when a lower dose is used. Results from the Women's Health Initiative (WHI), which included women aged 50–79 years, revealed an increase of 1 mm Hg in blood pressure attributable to MHT.[41] During the intervention phase of the WHI, participants using conjugated equine estrogens were 18% more likely to develop hypertension, which reduced after cessation of MHT.[42] Similar results were observed from the HERS trial.[43] The KEEPs trial[44] among women aged 42–58 years observed no effect from MHT on blood pressure from either oral or transdermal MHT, but used a lower dose than in the WHI. Regarding the results of this study, it is possible that the higher risk of hypertension among users of MHT could be due to an additive interaction effect from MHT and migraine. It is also possible that women with migraine may be diagnosed with menopausal symptoms more frequently than those without migraine, or that women using MHT are more likely to seek help for migraines, both resulting in more frequent visits to clinicians. This may also have the effect of increasing rates of hypertension diagnosis, biasing the associations between migraine, MHT, and hypertension.

The main strengths of this analysis are the longitudinal nature of the study, the size of the cohort, the length of follow-up, and the large number of women with incident hypertension. We were able to control for a large number of potential confounding factors, such as BMI, physical activity levels, family history of CVD, MHT usage, and diabetes. We used time-updated covariates and migraine exposure, allowing us to account for changes in factors such as BMI, physical activity, and smoking. A further strength is the sensitivity analysis considering medications commonly prescribed for migraine and consistent results in numerous sensitivity analyses.

The main limitation in this study is that migraine was self-reported and could be subject to classification error,

**Table 4** Characteristics of the Cohort According to Migraine Status in 2010

| | No migraine (n = 37,144) | Migraine with aura (n = 498) | Migraine without aura (n = 561) | Unknown type of migraine (n = 7,197) |
|---|---|---|---|---|
| **Incident hypertension cases, n** | 1,097 | 25 | 22 | 314 |
| **Age at start of follow-up, y** | 70.3 ± 6.4 | 68.7 ± 5.6 | 67.7 ± 5.1 | 68.5 ± 5.4 |
| **BMI, kg/m$^2$** | 23.2 ± 3.6 | 23.0 ± 3.3 | 22.8 ± 3.3 | 23.1 ± 3.5 |
| **Physical activity, METs/wk** | 60.7 ± 37.5 | 65.9 ± 39.8 | 59.5 ± 36.0 | 63.2 ± 37.0 |
| **Ever use of menopausal hormone therapy** | 50.0 | 70.0 | 71.3 | 67.9 |
| **Surgical menopause** | 9.2 | 9.4 | 8.2 | 8.7 |
| **Type 2 diabetes** | 2.1 | 1.8 | 1.1 | 1.5 |
| **Dyslipidaemia** | 25.5 | 24.3 | 24.2 | 24.7 |
| **Family history CVD** | 27.1 | 34.5 | 35.7 | 35.6 |
| **No high school** | 8.0 | 4.4 | 5.4 | 6.9 |
| **High school** | 53.4 | 53.4 | 53.1 | 54.8 |
| **University** | 38.6 | 42.2 | 41.5 | 38.3 |
| **Never smoker** | 47.1 | 50.7 | 50.5 | 49.5 |
| **Past smoker** | 44.1 | 42.4 | 43.0 | 42.5 |
| **Current smoker** | 8.8 | 6.7 | 6.5 | 8.0 |

Abbreviations: BMI = body mass index; CVD = cardiovascular disease; MET = metabolic equivalent.
Values are mean ± SD or % unless indicated otherwise.

**Table 5** Associations Between Different Types of Migraine and Hypertension

| Model | No migraine (n = 37,144, cases = 1,097) | Migraine with aura (n = 498, cases = 25) | Migraine without aura (n = 561, cases = 22) | Unknown migraine type (n = 7,197, cases = 314) |
|---|---|---|---|---|
| 1 | Ref | 1.65 (1.11, 2.45) | 1.39 (0.91, 2.12) | 1.44 (1.27, 1.63) |
| 2 | Ref | 1.54 (1.04, 2.30) | 1.32 (0.87, 2.02) | 1.34 (1.18, 1.52) |

Reported as hazard ratio (95% confidence interval). Adjusted on age (model 1) and on family history of cardiovascular disease, smoking, diabetes, dyslipidemia, education level, ever use of menopausal hormone therapy, body mass index, and total physical activity (model 2).

particularly due to other nonmigraine headaches. However, as migraine with aura would be less likely to be misclassified, as the significant associations with migraine with aura overlapped with migraine without aura, misclassification was likely low. As hypertension cases were primarily based on self-reports, some cases could have been missed, or diagnosis could have been delayed. The cohort is rather homogenous, consisting of a high percentage of high school teachers, and may not be representative of the French population. The cohort for this study consisted only of menopausal women; trends may be different in men and in younger women. As the study is observational, residual and unmeasurable confounding is possible, but is unlikely to explain the observed association. We lacked information on migraine aura in the main analysis, and the secondary analysis, which did include this information, had a shorter follow up and a lower number of cases. Because we lacked information on the frequency of medical visits, we are unable to rule out that some information bias may be present, as was previously mentioned. In this cohort, data on the severity of hypertension are unavailable for the majority of participants, and should be considered a limitation that could be rectified in other cohort studies.

Practitioners should be aware that women with a history of migraine should be considered to be at a higher risk of hypertension.

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## Appendix Authors

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## Appendix *(continued)*

| Name | Location | Contribution |
|---|---|---|
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## References


1. MacGregor EA. Migraine, menopause and hormone replacement therapy. *Post Reprod Health* 2018;24:11–18.
2. Victor T, Hu X, Campbell J, Buse D, Lipton R. Migraine prevalence by age and sex in the United States: a life-span study. *Cephalalgia* 2010;30:1065–1072.
3. Scher AI, Terwindt GM, Picavet HSJ, Verschuren WMM, Ferrari MD, Launer LJ. Cardiovascular risk factors and migraine: the GEM population-based study. *Neurology* 2005;64:614–620.
4. Winter A, Berger K, Buring J, Kurth T. Body mass index, migraine, migraine frequency and migraine features in women. *Cephalalgia* 2009;29:269–278.
5. Mahmoud AN, Mentias A, Elgendy AY, et al. Migraine and the risk of cardiovascular and cerebrovascular events: a meta-analysis of 16 cohort studies including 1 152 407 subjects. *BMJ Open* 2018;8:e020498.
6. Kurth T, Winter AC, Eliassen AH, et al. Migraine and risk of cardiovascular disease in women: prospective cohort study. *BMJ* 2018;31:i2610.
7. Kurth T, Gaziano JM, Cook NR, Logroscino G, Diener H-C, Buring JE. Migraine and risk of cardiovascular disease in women. *JAMA* 2006;296:283.
8. Kurth T, Rist PM, Ridker PM, Kotler G, Bubes V, Buring JE. Association of migraine with aura and other risk factors with incident cardiovascular disease in women. *JAMA* 2020;323:2281.
9. Kurth T, Schürks M, Logroscino G, Buring JE. Migraine frequency and risk of cardiovascular disease in women. *Neurology* 2009;73:581–588.
10. Liew G, Wang J, Mitchell P. Migraine and coronary heart disease mortality: a prospective cohort study. *Cephalalgia* 2007;27:368–371.
11. Seçil Y, Ünde C, Beckmann YY, Bozkaya YT, Özerkan F, Başoğlu M. Blood pressure changes in migraine patients before, during and after migraine attacks: blood pressure changes during migraine attack. *Pain Pract* 2010;10:222–227.
12. Spalice A, Del Balzo F, Papetti L, et al. Stroke and migraine is there a possible comorbidity? *Ital J Pediatr* 2016;42:41.
13. Etminan M, Takkouche B, Isorna FC, Samii A. Risk of ischaemic stroke in people with migraine: systematic review and meta-analysis of observational studies. *BMJ* 2005;330:63.
14. Schurks M, Rist PM, Bigal ME, Buring JE, Lipton RB, Kurth T. Migraine and cardiovascular disease: systematic review and meta-analysis. *BMJ* 2009;339:b3914.
15. Vetvik KG, MacGregor EA. Sex differences in the epidemiology, clinical features, and pathophysiology of migraine. *Lancet Neurol* 2017;16:76–87.
16. Mattsson P. Hormonal factors in migraine: a population-based study of women aged 40 to 74 years. *Headache* 2003;43:27–35.
17. Kaiser HJ, Meienberg O. Deterioration or onset of migraine under oestrogen replacement therapy in the menopause. *J Neurol* 1993;240:195–197.
18. Broner S, Bobker S, Klebanoff L. Migraine in women. *Semin Neurol* 2017;37:601–610.
19. Ashraf MS, Vongpatanasin W. Estrogen and hypertension. *Curr Sci Inc* 2006;8:368–376.
20. Clavel-Chapelon F; E3N Study Group. Cohort profile: the French E3N cohort study. *Int J Epidemiol* 2015;44:801–809.
21. Lajous M, Tondeur L, Fagherazzi G, de Lauzon-Guillain B, Boutron-Ruault M-C, Clavel-Chapelon F. Processed and unprocessed red meat consumption and incident type 2 diabetes among French women. *Diabetes Care* 2012;35:128–130.
22. Fournier A, Fabre A, Mesrine S, Boutron-Ruault M-C, Berrino F, Clavel-Chapelon F. Use of different postmenopausal hormone therapies and risk of histology- and hormone receptor-defined invasive breast cancer. *J Clin Oncol* 2008;26:1260–1268.
23. Tehard B, van Liere MJ, Com Nougué C, Clavel-Chapelon F. Anthropometric measurements and body silhouette of women: validity and perception. *J Am Diet Assoc* 2002;102:1779–1784.
24. MacDonald C, Madika A, Lajous M, et al. Associations between physical activity and incident hypertension across strata of body mass index: a prospective investigation in a large cohort of French women. *JAHA* 2020;9.
25. Ainsworth BE, Haskell WL, Whitt MC, et al. Compendium of physical activities: an update of activity codes and MET intensities. *Med Sci Sports Exerc* 2000;32(9 Suppl): S498–S504.
26. Law M, Morris JK, Jordan R, Wald N. Headaches and the treatment of blood pressure: results from a meta-analysis of 94 randomized placebo-controlled trials with 24 000 participants. *Circulation* 2005;112:2301–2306.
27. Rist PM, Winter AC, Buring JE, Sesso HD, Kurth T. Migraine and the risk of incident hypertension among women. *Cephalalgia* 2018;38:1817–1824.
28. Entonen AH, Suominen SB, Korkeila K, et al. Migraine predicts hypertension-a cohort study of the Finnish working-age population. *Eur J Public Health* 2014;24:244–248.
29. Gardener H, Monteith T, Rundek T, Wright CB, Elkind MSV, Sacco RL. Hypertension and migraine in the Northern Manhattan Study. *Ethn Dis* 2016;26:323–330.
30. de Hoon J, Willigers J, Troost J, Struijker-Boudier H, Van Bortel L. Cranial and peripheral interictal vascular changes in migraine patients. *Cephalalgia* 2003;23:96–104.
31. Vanmolkot FH, Van Bortel LM, de Hoon JN. Altered arterial function in migraine of recent onset. *Neurology* 2007;68:1563–1570.
32. Zhang Y, Parikh A, Qian S. Migraine and stroke. *Stroke Vasc Neurol* 2017;2:160–167.
33. Liman TG, Bachelier-Walenta K, Neeb L, et al. Circulating endothelial microparticles in female migraineurs with aura. *Cephalalgia* 2015;35:88–94.
34. Mordi I, Mordi N, Delles C, Tzemos N. Endothelial dysfunction in human essential hypertension. *J Hypertens* 2016;34:1464–1472.
35. International Headache Genetics Consortium, Gormley P, Anttila V, Winsvold BS, et al. Meta-analysis of 375,000 individuals identifies 38 susceptibility loci for migraine. *Nat Genet* 2016;48:856–866.
36. Sabia S, Fournier A, Mesrine S, Boutron-Ruault M-C, Clavel-Chapelon F. Risk factors for onset of menopausal symptoms: results from a large cohort study. *Maturitas* 2008; 60:108–121.
37. Hipolito Rodrigues MA, Maitrot-Mantelet L, Plu-Bureau G, Gompel A. Migraine, hormones and the menopausal transition. *Climacteric* 2018;21:256–266.
38. Misakian AL, Langer RD, Bensenor IM, et al. Postmenopausal hormone therapy and migraine headache. *J Women's Health* 2003;12:1027–1036.
39. Aegidius KL, Zwart J-A, Hagen K, Schei B, Stovner LJ. Hormone replacement therapy and headache prevalence in postmenopausal women: The Head-HUNT study. *Eur J Neurol* 2007;14:73–78.
40. Mueller L. Predictability of exogenous hormone effect on subgroups of migraineurs. *Headache* 2000;40:189–193.
41. Manson JE, Hsia J, Johnson KC, et al. Estrogen plus progestin and the risk of coronary heart disease. *N Engl J Med* 2003;349:523–534.
42. Swica Y, Warren MP, Manson JE, et al. Effects of oral conjugated equine estrogens with or without medroxyprogesterone acetate on incident hypertension in the Women's Health Initiative hormone therapy trials. *Menopause* 2018;25: 753–761.
43. Nair GV, Chaput LA, Vittinghoff E, Herrington DM. Heart and Estrogen/Progestin Replacement Study Investigators. Pulse pressure and cardiovascular events in postmenopausal women with coronary heart disease. *Chest* 2005;127:1498–1506.
44. Harman SM, Black DM, Naftolin F, et al. Arterial imaging outcomes and cardiovascular risk factors in recently menopausal women: a randomized trial. *Ann Intern Med* 2014;161:249–260.

# Association of Migraine With Incident Hypertension After Menopause: A Longitudinal Cohort Study

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