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Cumulative exposure to estrogen may increase the risk of migraine in women

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Abstract

Background: Migraine is a common disorder, particularly affecting women during their reproductive years. This female preponderance has been linked to exposure to female sex hormones.

Methods: We used self-reported data from women born in 1943–1965 enrolled in the Norwegian Women and Cancer Study to examine the differences between women with migraine and women without migraine in a prospective design with respect to both endogenous and exogenous female sex hormone exposure.

Results: In total, 62,959 women were included in the study, of whom 24.8% reported previous migraine (n = 15,635). Using a Cox proportional hazards model, we found that higher age at menarche reduced the risk of migraine (hazards ratio (HR) = 0.96, 95% confidence interval (CI) = 0.95–0.98) and that oral contraceptive use and parity increased the risk of migraine (HR = 1.12, 95% CI = 1.06–1.18 and HR = 1.37, 95% CI = 1.29–1.46, respectively).

Conclusions: Older age at menarche appears to reduce migraine risk, whereas oral contraceptive use and having children appear to increase the risk. Further research is required to investigate the causality of these associations.

Keywords

Childbirth, estrogen, menarche, migraine, oral contraceptives, premenstrual syndrome

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Introduction

Migraine is a common, debilitating disease; in 2019, according to the Global Burden of Disease Study, migraine was the second highest cause of disability, and first among young adults (1). Migraine not only causes individual suffering, but also places a strain on society in terms of economics and employment. The prevalence of migraine in European adults has been estimated at around 15% (2), and a similar figure has been identified in the Norwegian population, with a one-year prevalence of 12% (3).

Prior to puberty, the prevalence of migraine is approximately 7.5% (4), with a similar figure for males and females. However, after puberty, the condition is more common in females than males, with a one-year prevalence of about 17% among women and 8% in men (2). In one study, the lifetime prevalence of migraine was three times higher in women than in men, at 25% compared to 8% (5).

Puberty distinctly changes the prevalence of migraine in women, with fluctuations in female sex hormone levels considered to play an important role. During the menstrual cycle, a decrease in progesterone levels induces menstruation, whereas a rapid decrease in estrogen levels occurs around the time of menstruation. It has been hypothesized that the decrease in estrogen levels increases the susceptibility to attacks of migraine without aura, although the exact

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mechanisms remain unclear (6–8). However, the "estrogen withdrawal hypothesis" has been challenged, and a causal relationship between declining estrogen levels and migraine remains to be determined (9). Nonetheless, women strongly associate their migraine with menstruation; a large cross-sectional study from 2021 found that women reported menstruation as the most common trigger for migraine (10). By contrast, high estrogen levels are associated with an increased risk of migraine attacks with aura (11). Migraine generally improves during the second and third trimesters of pregnancy (12), which may be attributed to the high and stable levels of estrogen and progesterone present in this period. However, migraine with aura may worsen or occur *ex novo* during pregnancy. Moreover, lower and stable estrogen levels, as seen after well-established menopause, are associated with migraine improvement and consequent decrease in prevalence (13). In the perimeopausal period, frequent and erratic hormonal fluctuations may worsen migraine (14). The premenstrual syndrome (PMS) is a combination of physical, psychological and cognitive symptoms, such as breast tenderness, headache, and mood swings, which occurs in 48–90% of menstruating women (15). Symptoms of PMS appear during the luteal phase of the menstrual cycle and cease soon after the onset of menstruation. Studies have shown conflicting results regarding PMS and migraine. One study found a correlation between the severity of PMS symptoms and menstrual migraine (15), whereas another did not find a relationship between the two conditions (16).

Migraine in women undoubtedly fluctuate with natural changes in female sex hormones; however, whether cumulative exposure to estrogen increases the risk of migraine remains unclear. In some women, the onset of migraine coincides with menarche, whereas in others, migraine appears to start during pregnancy (17,18). The prevalence of migraine is higher in women with early menarche than in those with later menarche (19). Furthermore, the use of oral contraceptives (OCs) containing estrogen has also been linked to a higher prevalence of migraine (20).

In the present study, we used self-reported data from the Norwegian Women and Cancer Study (NOWAC) to examine possible differences in women with and without migraine in a prospective design with respect to both endogenous and exogenous female sex hormone exposure.

Methods

The study population of NOWAC

The NOWAC study is a national, population-based, prospective cohort study initiated in 1991. The cohort consists of 172,478 Norwegian women aged 30–70 years at recruitment. The participants responded to questionnaires sent by mail with repeated measures two or three times after six to eight years. Participants were randomly sampled from the national population register to ensure adequate representativeness in estimating both relative and absolute risks (21). The study, which has been described in detail elsewhere (22), was initiated to investigate possible associations between Norwegian women's lifestyles, particularly the use of OCs, and cancer. The cohort is linked to the Norwegian National Cancer Registry and the Norwegian Cause of Death Registry. The overall response rate was 52.7% and written informed consent was obtained from all participants. The NOWAC study was licensed by the Norwegian Data Inspectorate (2002/2241) and approved by the Regional Committee for Medical and Health Research Ethics (REC-635219).

The questionnaires

The participants received questionnaires containing detailed questions on their lifestyle, health status and diet. The length of the questionnaire and specific questions changed over the years. Questions were added or removed as the research questions changed. However, the core questions (including body height and weight, education, smoking, physical activity, alcohol consumption, and use of OCs and hormone replacement therapy) were consistent. Among other specific topics, the questionnaires covered socioeconomic factors, diet, self-reported health and various diseases including migraine. The participants were asked if they had ever had migraine (yes or no) and at what age their migraine began (if "yes", "how old were you when they started?"). A subsample (n = 24,323) received a questionnaire that contained more detailed questions about migraine. These questions were based on the International Classification of Headache Disorders (ICHD-2) criteria for migraine (23) and included age at first and last migraine, migraine frequency, attack duration, typical headache characteristics, aura, accompanying symptoms (phono- and photophobia, nausea) and use of prescription migraine medication.

The questionnaire included detailed information on OC use. A leaflet was included in the questionnaire that contained all OCs available in Norway, with images and brand names. Furthermore, the women were asked to describe their pattern of use in detail with the OC brand name, age at start, and the number of months and/or years they had used the specific OC. Additionally, reproductive factors such as menarche, age at first birth, number of children, months of breastfeeding and PMS were included. The question about PMS was as follows: Do you ever have premenstrual

complaints: none, breast engorgement, depression, or others?

Definition of the subcohort

Of the entire NOWAC cohort, 90,048 women were asked at least once whether they had experienced migraine. Women born before 1943 were excluded from analysis, for several reasons. First, women born in 1927–1942 were part of a different subcohort and were given slightly different questionnaires. Second, OCs were introduced to Norway in 1967; consequently, women born before 1943 reported significantly lower OC use. Finally, a larger proportion of these women had missing values for age at migraine onset, and we considered that, as a result of their older age when answering the questionnaires, the risk of recall bias was higher. The remaining sample consisted of 62,959 women; most participants in this subcohort were between 40 and 60 years of age when they returned the first questionnaire.

Statistical analysis

The aims of the statistical analysis were to explore whether there were any differences between women with and without migraine regarding endogenous and exogenous female sex hormone exposure, as well as to investigate whether increased hormone exposure (early menarche, childbirth and combined oral contraceptive use) increased the risk of migraine.

To assess the presence of a crude difference in participant characteristics and hormonal exposure according to the prevalence of migraine, the Mann–Whitney *U*-test was used for ordinal variables and the chi-squared test was used for nominal variables. These tests were used to examine the association between migraine and female sex hormone exposure in a cross-sectional design and did not assess the temporal association between endogenous or exogenous hormone exposure and migraine onset.

The continuous variables age at first migraine, birth year, body mass index (BMI), age at menarche, age at first birth and age at first OC use were all categorized into meaningful categories for more appropriate analysis. Age at first migraine was grouped in five-year intervals, although any individuals with age at first migraine before 10 years were grouped together in the first category and any individuals with age at first migraine after 60 years were grouped together in the last category. Birth year was grouped in 10-year intervals. BMI was categorized into underweight (less than $18.5\,kg/m^2$) normal weight ($18.5–25.0\,kg/m^2$), overweight ($25.1–29.9\,kg/m^2$) and obese (more than $30.0\,kg/m^2$). Age at menarche was grouped in one-year intervals, where participants with age at menarche before age 10 where grouped together in the first category and those with age at menarche 17 years or older where grouped together in the last category. Age at first birth was categorized into four categories, where those under 20 years were in the first category, and those over 30 years were in the last category, with the remainder in five-year intervals. Lastly, age at first OC use was grouped the same way as age at first birth.

The data were analyzed prospectively to determine the association between the incidence of migraine and different hormonal exposures using a Cox proportional hazards regression model with age as the time scale. Thus, women who reported ever having had a migraine, yet did not provide any information about age at onset, were not included in this analysis because it would not be possible to assess which occurred first of migraine, menarche, childbirth and OC use. All exposures were entered as time-dependent variables in the Cox model as they occurred during the study period. The beginning of the study period in the Cox model was defined as 10 years of age. Because the study design is prospective, the exposures had to occur before migraine, to exclude all prevalent cases. As one of the exposures in the Cox model was menarche, 10 appeared to be a reasonable age to set as the start.

We assessed year of birth and BMI at 18 years as confounders and adjusted for these factors in the final model. BMI at 18 years was considered a proxy for BMI at the start of the study.

The proportional hazards assumption was assessed by Schoenfeld residuals.

The results were given as hazard ratios (HRs) with corresponding 95% confidence intervals (CI) as measures of association.

Statistical analyses were performed using STATA, version 17 (StataCorp, College Station, TX, USA). By convention, $p < 0.05$ was considered statistically significant.

Results

In total, 62,959 women were included in this study. The lifetime prevalence of migraine was 24.8%, and the mean age of $\pm$SD onset was 25.9 ± 12 years, as shown in Table 1.

A slight trend was observed where the women with self-reported migraine tended to be older than those without migraine. The BMI at 18 years also varied somewhat between the two groups; a tendency towards a lower BMI in women with migraine was observed. Table 1 summarizes the baseline characteristics of women with self-reported migraine compared to women without migraine.

Table 1. Characteristics of the study population (n = 62,969).

Characteristic	All women with migraine, n (%)	Women without migraine, n (%)	*p*-value
	15,635 (24.8)	47,324 (75.2)	
Age at first migraine (years)			
<10	468 (3.7)		
10–19	3863 (30.5)		
20–29	3386 (26.8)		
30–39	2670 (21.1)		
40–49	1782 (14.1)		
50–59	413 (3.3)		
60+	68 (0.5)		
Mean ± SD	25.9 ± 11.9		
Year of birth			<0.001*
1940–49	7677 (49.1)	22,097 (46.7)	
1950–59	7596 (48.6)	23,796 (50.3)	
1960–65	362 (2.3)	1431 (3.0)	
BMI at 18 years			<0.001*
<18.5	2580 (17.4)	6862 (15.3)	
18.6–25	11,515 (77.5)	35,645 (79.7)	
25–30	653 (4.4)	1887 (4.2)	
>30	103 (0.8)	335 (0.8)	
Mean ± SD	20.7 ± 2.6	20.8 ± 2.6	

*Mann–Whitney *U*-test.
BMI, body mass index.

Endogenous hormone exposure

A difference was observed in age at menarche, parity and age at first birth between women with and without self-reported migraine (Table 2). Women with migraine reported earlier menarche. In the Cox model, an HR of 0.96 (95% CI = 0.95–0.98) was found, indicating that the risk of migraine was lower with a higher age of menarche.

Moreover, fewer women with migraine were nulliparous than women without migraine, and women with migraine had their first child earlier than those without migraine. Regarding parity, no difference was found in the effect of giving birth two or more times (data not shown). An HR of 1.37 (95% CI = 1.29–1.46) was found in association with parity, indicating an increased risk of migraine in women who had given birth. Fewer women with migraine reported no PMS symptoms, and more women with migraine reported having more than one PMS symptom. Table 2 summarizes these findings.

Exogenous hormone exposure

An increased risk of migraine was identified in ever users compared to never users of OCs in the Cox model, as seen in Table 3, with an HR of 1.12 (95% CI = 1.06–1.18). However, this association was not statistically significant according to the chi-squared test. Women with migraine more often reported to have used progestin- only oral contraceptives (POC) or both combined oral contraceptives (COC) or POCs, compared to women without migraine. Regarding which type of OC that was used at first ever OC use, more women with migraine reported to have used POCs, and an increased risk of migraine with an HR of 1.19 (95% CI = 1.07–1.31) was found for POC compared to COC with an HR of 1.08 (95% CI = 1.02–1.14).

No significant association was observed in age at first OC use or in OC use before the first childbirth between the two groups. However, a larger proportion of women with migraine reported using OCs for reasons other than contraception and discontinuing OC use for medical reasons. Table 3 summarizes these findings.

Educational level was also considered as a confounder. Because migraine occurred early in the women's lives; however, we chose not to include this in the final Cox model. The education level changed the estimates by less than 1% when the sensitivity analysis was completed.

Migraine with and without aura

In total, 24,323 women (38.6% of the total sample) received the questionnaire that contained detailed questions about migraine. In this subsample, 7215 (29.6%) reported to ever have had migraine and, of these, 17.4% (n = 1250) reported migraine with aura (MA). Compared to women with migraine without aura (MO), women with MA showed a tendency towards younger age at migraine onset and age at menarche. An HR of 0.97 (95% CI = 0.95–0.99) was found for menarche in MO compared to MA, and an HR of 0.98 (95% CI = 0.96–1.0) for MO compared to women without migraine, and HR 0.94 (95% CI = 0.89–0.98) for MA compared to women without migraine. (More women with MA reported ≥1 PMS symptom. Regarding parity, women with MO and MA appeared similar regarding frequency, but the HR for parity was 1.22 (95% CI = 1.12–1.34) for MO compared to MA, as well as 1.19 (95% CI = 1.07–1.32) for MO compared to women without migraine and 1.38 (95% CI = 1.12–1.70) for MA compared to women without migraine. For OC use, an HR of 1.23 (95% CI = 1.13–1.32) was found for women with MO compared to MA, and an HR of 1.23 (95% CI = 1.13–1.34) for MO compared to women without migraine and an HR of 1.21 (95% CI = 1.02–1.45) for MA compared to women without migraine. More women with MA reported POC use, and the HR for POC with first OC use was 1.43 (95% CI = 1.23–1.65) and 1.12 (95% CI = 1.03–1.22) for COC use in MO compared to MA.

Table 2. Endogenous hormones.

Characteristic	All women with migraine, n (%)	Women without migraine, n (%)	*p*-value	HR (95% CI)***
Age at menarche (years)			<0.001*	0.96 (0.95–0.98)
≤10	266 (1.7)	575 (1.2)		
11	1326 (8.6)	3360 (7.2)		
12	3174 (20.6)	9236 (19.8)		
13	4365 (28.3)	13,638 (29.3)		
14	3691 (24.0)	11,726 (25.2)		
15	1873 (12.1)	5813 (12.5)		
16	552 (3.6)	1759 (3.8)		
≥17	166 (1.1)	471 (1.0)		
Mean ± SD	13.2 ± 1.4	13.3 ± 1.3		
Premenstrual syndrome			<0.001*	
No symptoms	1645 (16.9)	7317 (25.3)		
One symptom	4862 (50.0)	14,525 (50.3)		
More than one symptom	3213 (33.1)	7034 (24.4)		
Parity			<0.001**	
Parous	14,484 (92.6)	43,214 (91.3)		1.37 (1.29–1.46)
Nulliparous	1151 (7.4)	4110 (8.7)		
Mean ± SD	2.2 ± 1.1	2.2 ± 1.1		
Age at first birth (years)			<0.001*	
<20	2079 (14.4)	5490 (12.7)		
20–24	7068 (48.9)	20,198 (46.9)		
25–29	3827 (26.5)	12,305 (28.5)		
≥30	1471 (10.2)	5107 (11.9)		
Mean ± SD	23.8 ± 4.4	24.1 ± 4.5		

*Mann–Whitney *U*-test.
**Chi-squared test.
***Hazard ratio (HR) (95% confidence interval (CI)) (Cox proportional hazards model) mutually adjusted for the exposures, birth year and BMI at age 18 years.

For type of OC at first use in women with MO compared to women without migraine, an HR of 1.15 (95% CI = 1.05–1.26) was found for COC and an HR of 1.44 (95% CI = 1.22–1.69) was found for POC. In women with MA compared to women without migraine, an HR of 1.03 (95% CI = 0.85–1.24) was found for COC and an HR of 1.41 (95% CI = 1.02–1.94) was found for POC. More women with MA had stopped using OC for medical reasons. Table 4 summarizes these findings.

Discussion

Both endogenous and exogenous exposure to female sex hormones appear to affect migraine occurrence in women. In the present study, we found a marginally lower age of menarche in women with self-reported migraine compared to women without self-reported migraine, notably when we did not consider whether migraine or menarche occurred first. However, we also found that a higher age at menarche resulted in a slightly lower risk of migraine in the Cox model, which did take account of which event occurred first. These results are consistent with the findings of previous studies, in which early menarche was associated with an increased prevalence of migraine (19). Our findings suggest that older age at menarche may play a protective role against the development of migraine.

We also demonstrated that fewer women with migraine were nulliparous than women without migraine. Women with migraine also presented a slightly lower age at first birth than those without migraine. The Cox model suggests an association between increased risk of migraine in parous women compared to nulliparous women. We did not observe an increase in risk with an increase in the number of children. Most women with established migraine prior to pregnancy report fewer migraine during pregnancy, particularly during the third trimester (24,25). A possible explanation for the increase in migraine prevalence in parous women is that pregnancy may have triggered the onset of migraine in some women; however, this association is uncertain because we did not find an increased risk of migraine with an increasing number of pregnancies, and because migraine commonly occurs during the reproductive age. Another potential explanation for parous women having a higher risk of migraine is that having a child is a major life event that often causes significant changes in everyday life, such as irregular sleep or sleep deprivation,

Table 3. Exogenous hormones.

Characteristic	All women with migraine, n (%)	Women without migraine, n (%)	*p*-value	HR (95% CI)***
Oral contraceptive Status			0.111**	
Ever used	9821 (64.1)	29,563 (63.4)		1.12 (1.06–1.18)
Never used	5497 (35.9)	17,067 (36.6)		
Type of oral contraceptive use			0.003**	
Combination oral contraceptives (COC)	6340 (75.7)	19,833 (77.4)		
Progestin-only oral contraceptives (POC)	1027 (12.3)	3015 (11.8)		
Both COC and POC	1005 (12.0)	2771 (10.8)		
Type of oral contraceptive first used			0.003**	
COC	5589 (84.6)	17,475 (86.1)		1.08 (1.02–1.14)
POC	1014 (15.4)	2819 (13.9)		1.19 (1.07–1.31)
Missing information	9032	27,030		
Age at first use (years)			0.451*	
<20	2459 (25.3)	7204 (24.6)		
20–24	4616 (47.5)	14,051 (48.1)		
25–29	1918 (19.8)	5930 (20.3)		
≥ 30	721 (7.4)	2053 (7.0)		
Mean $\pm$ SD	22.5 ± 4.2	22.5 ± 4.2		
Use before first birth			0.485**	
Yes	3019 (41.4)	8832 (41.9)		
No	4267 (58.6)	12,245 (58.1)		
Other use than contraception			<0.001**	
Yes	905 (14.5)	1990 (10.6)		
No	5490 (85.5)	16,798 (89.4)		
Stopped use for medical reasons			<0.001**	
Yes	1470 (23.1)	2775 (14.7)		
No	4896 (76.9)	16,087 (85.3)		

*Mann-Whitney *U*-test.
**Chi-squared test.
***Hazard ratio (HR) (95% confidence interval (CI)) (Cox proportional hazards model) mutually adjusted for the exposures, birth year and BMI at age 18 years.

increased responsibilities and increased levels of stress; previous studies have reported a higher risk of chronic headaches associated with major life changes (26).

In the present study, we suggest a greater risk of migraine in women who had used OCs. Women with migraine were also more likely to use contraception for other indications than contraception, and had stopped OC use for medical reasons. Headaches, including migraine, are known side effects of OCs, and studies have shown that OC use can both exacerbate and improve migraine (27). We could not determine whether the women with migraine in the present study had different patterns of OC use (i.e. whether they started or continued using OCs because it improved migraine, or discontinued OC use because it worsened migraine). However, it is a possible assumption that some of the women who reported discontinued use of OCs for medical reasons did so because it worsened their migraine. Because headaches and migraine are known to be possible side effects of OCs, it is also possible that different prescription practices contributed to the differences in the patterns of OC use. In Norway, women with migraine with aura are advised not to use combined hormonal contraception as a result of the associated increased risk of stroke and thromboembolic events (28). Regarding type of OC used, women with migraine had more often used either POCs exclusively or both COCs and POCs, compared to women without migraine. By contrast to previous studies, we found an increased risk of migraine amongst those who had used POCs as first ever OC compared to COCs (29). However, our results must be interpreted with caution because there were many women with missing values, and fewer POC users compared to COC users.

The methodological limitations of the present study must be considered. First, the diagnosis of migraine and its subtypes was not made using the diagnostic gold standard, fulfilling the diagnostic criteria after evaluation by a physician/neurologist, but by responses to questionnaires. However, the simple question "Have you ever had migraine?" was validated with a substantial chance-corrected agreement rate (kappa $= 0.77$) (30). Furthermore, the prevalence of migraine found in the NOWAC study was similar to that found in

Table 4. Migraine with and without aura.

Characteristic	Migraine without aura (MO)	Migraine with aura (MA)	No migraine	*p*-value	HR (95% CI)*** MO vs. no migraine	HR (95% CI)*** MA vs. no migraine	*p*-value MO vs. MA	HR (95% CI)*** MO vs. MA
Migraine	5965 (82.6)	1250 (17.4)	17108 (73.4)					
Age at first migraine (years)				<0.001**			<0.001*	
<10	130 (3.1)	44 (3.7)						
10–19	1126 (26.5)	402 (33.9)						
20–29	1062 (25.0)	303 (25.6)						
30–39	967 (22.8)	201 (17.0)						
40–49	689 (16.4)	136 (11.5)						
50–59	220 (5.2)	79 (6.7)						
60+	42 (1.0)	20 (1.7)						
Mean ± SD	27.7 ± 12.5	26.1 ± 13.4						
Age at menarche (years)				0.001**	0.98 (0.96–1.0)	0.94 (0.89–0.98)	<0.001*	0.97 (0.95–0.99)
≤10	58 (1.2)	18 (1.5)	198 (1.2)					
11	427 (8.7)	124 (10.0)	1188 (7.1)					
12	980 (20.1)	270 (21.8)	3401 (20.2)					
13	1435 (29.4)	350 (28.3)	4955 (29.4)					
14	1143 (23.4)	283 (22.9)	4233 (25.1)					
15	621 (12.7)	139 (11.2)	2127 (12.6)					
16	168 (3.4)	44 (3.5)	578 (3.4)					
≥17	54 (1.1)	10 (0.8)	168 (1.0)					
Mean ± SD	13.2 ± 1.4	13.1 ± 1.4	13.3 ± 1.3					
Premenstrual syndrome				<0.001**			0.002*	
No symptoms	821 (18.2)	170 (14.8)	4153 (26.6)					
One symptom	2274 (50.3)	571 (49.8)	7780 (49.7)					
More than one symptom	1424 (31.5)	406 (35.4)	3713 (23.7)					
Parity				0.141**	1.19 (1.07–1.32)	1.38 (1.12–1.70)	0.439**	1.22 (1.12–1.34)
Parous	4586 (92.7)	1151 (92.1)	15715 (91.9)					
Nulliparous	360 (7.3)	99 (7.9)	1393 (8.1)					
Mean ± SD	2.2 ± 1.1	2.2 ± 1.1	2.2 ± 1.1					
Oral contraceptive Status				0.026**	1.23 (1.13–1.34)	1.21 (1.02–1.45)	0.202**	1.23 (1.13–1.32)
Ever	3314 (67.7)	864 (69.6)	11,259 (66.4)					
Never	1579 (32.3)	377 (30.4)	5689 (33.6)					
Oral contraceptive type				0.230**			0.175**	
Combination oral contraceptives (COC)	2192 (74.7)	559 (71.8)	7586 (75.2)					
Progestin-only oral contraceptives (POC)	368 (12.5)	101 (13.0)	1248 (12.4)					
Both	374 (12.8)	118 (15.2)	1255 (12.4)					

(continued)

Table 4. Continued.

Characteristic	Migraine without aura (MO)	Migraine with aura (MA)	No migraine	*p*-value	HR (95% CI)*** MO vs. no migraine	HR (95% CI)*** MA vs. no migraine	*p*-value MO vs. MA	HR (95% CI)*** MO vs. MA
Type of OC first used				0.395**			0.620**	
COC	1913 (83.9)	509 (83.0)	6703 (84.7)		1.15 (1.05–1.26)	1.03 (0.85 –1.24)		1.12 (1.03–1.22)
POC	368 (16.1)	104 (17.0)	1212 (15.3)		1.44 (1.22–1.69)	1.41 (1.02–1.94)		1.43 (1.23–1.65)
Missing	2660	637	9185					
Age at first OC use (years)				0.001**			0.008*	
<20	848 (26.3)	245 (29.3)	2724 (24.8)					
20–24	1529 (47.3)	420 (50.3)	5438 (49.5)					
25–29	632 (19.5)	132 (15.8)	2082 (18.9)					
≥30	224 (6.9)	38 (4.6)	753 (6.8)					
Mean ± SD	22.4 ± 4.1	21.8 ± 3.7	22.4 ± 4.1					
OC use before first birth				0.005**			0.001**	
Yes	1356 (45.5)	401 (52.0)	4727 (47.1)					
No	1625 (54.5)	370 (48.0)	5315 (52.9)					
OC use other than contraception				<0.001**			0.004**	
Yes	400 (13.2)	135 (17.3)	1081 (10.5)					
No	2623 (86.7)	647 (82.7)	9214 (89.5)					
Stopped OC use for medical reasons				<0.001**			0.011**	
Yes	599 (20.0)	189 (24.1)	1474 (14.2)					
No	2402 (80.0)	595 (75.9)	8885 (85.8)					

*Mann–Whitney *U*-test.

**Chi-squared test.

***Hazard ratio (HR) (95% confidence interval (CI)) (Cox proportional hazards model) mutually adjusted for the exposures, birth year and BMI at age 18 years.

other reports (2,3,5). Additionally, a recent validation study was conducted to assess the agreement between new validated questions about migraine, based on the International Headache Society's diagnostic criteria (23), compared to the simple question ("Have you ever had migraine?") in a subcohort of the NOWAC; this study found a kappa value of 0.71, indicating good consistency across the series (unpublished results, Bugge NS and Braaten T). It should also be noted that a respondent may develop migraine during the study period, which makes perfect agreement improbable.

In the present study, most participants were between 40 and 60 years of age when they returned the first questionnaire. A possible limitation of the study is the accuracy of the reported age at menarche and first migraine because of the elapsed time from the event to the questionnaire. Nevertheless, menarche is an important event in most women's lives, and it is reasonable to assume that women would have a good recollection of when it happened. Furthermore, there is no reason to believe that women with migraine have a better or worse recall of age at menarche; therefore, it is unlikely that systematic differences between the two groups would exist. Similarly, for age at first migraine onset, it may be reasonable to assume that a woman has some recollection of this. However, 19.0% (n = 2976) of the participants did not report age at first migraine in the present study. Childhood migraine is often seen as somewhat different from adult migraine and this condition is often not acknowledged until long after its onset. Therefore, the exact onset of migraine can be difficult for women to determine.

The present study used a prospective design to ascertain whether migraine or different hormonal exposures occurred first. However, the women returned the questionnaires when they were between 40 and 50 years old and the data were therefore collected retrospectively; consequently, we cannot dismiss the possibility of recall bias.

Numerous studies have examined the relationship between migraine and hormones, particularly between menstruation and migraine (31). In the present study, we could only distinguish between migraine with and without aura for one third of the sample. MO and MA behave differently according to estrogen levels and hormonal life events, and the lack of subclassification for all participants in this study is a limitation. The results from the subsample where it was distinguished between MO and MA displayed a slight earlier onset of both age at first migraine and menarche in patients with MA and a stronger relation to COC use, supporting the general view that high levels of estrogen predispose for the occurrence. One could thus contemplate higher levels of naturally occurring estrogen in subjects with migraine aura (32), with the consequence of earlier menarche and earlier onset of migraine, and eventually an increased risk of stroke. This is a hypothesis that potentially could be tested in future studies. Further support for an increased estrogen/testosterone-ratio in migraine aura can perhaps be found at the other end of the migraine onset distribution. Migraine aura, often without headache, has a tendency to occur in the elderly, especially in men (33).

Furthermore, we observed that women with migraine reported more PMS symptoms than those without migraine. The definition of PMS varies; however, there is a requirement for a symptom-free interval between the end of menstruation and ovulation to distinguish it from other conditions. Therefore, using OCs that suppress ovulation violates this definition and, in our analysis, we did not exclude women who might have used hormonal contraceptives. It is also possible that some women with presumptive migraine who reported more PMS symptoms actually experienced non-migrainous headaches related to their PMS. Another aspect is the similarities between symptoms of PMS and the prodromal phase of migraine attacks, which has previously been described (34). In the present study, we did not know whether women had menstrual migraine or not, nor the timely relationship between PMS and the migraine headache, and therefore this cross-sectional design is not well suited for determining a relationship between the two, with prospective diary studies being more reliable to define a relationship (35).

Previous studies have shown no difference in estrogen levels between women with and without migraine, and prophylactic treatment of women with menstrual migraine with estrogen has shown divergent results (36,37). The present study provided analyses of a large data set to support the idea that the cumulative doses of estrogen during the reproductive years of a woman's life might affect the risk of migraine development. We suggest that the risk of migraine increases with parity and OC use and decreases with an older age at menarche. We do not have information about the exact timing of each migraine attack and its possible relation to hormonal events, nor whether it was influenced by menstruation, childbirth or OC use. However, our findings show that estrogen may play a role in the onset of migraine. Estrogen alone cannot explain the sex gap in migraine prevalence. More research is needed to further explain the mechanisms involved in migraine in women, including the role of other hormones such as progesterone and oxytocin, as well as the way in which sex hormones impact both the onset and course of the disease (27).

Conclusions

Older age at menarche is associated with reduced risk of migraine, whereas using OCs and parity may appear to increase its risk. Further research is required to explore the causality of these associations.

Clinical implications

- Women with migraine have a slight lower age at menarche compared to women without migraine.
- Women with migraine reported more PMS symptoms compared to women without migraine.
- Women with migraine more often reported to use OCs for other reasons than contraceptive, compared to women without migraine, and also more often reported to discontinue OC use for medical reasons.
- Women with MA had a lower age at first migraine, earlier age at menarche, more PMS symptoms and more often discontinued OC use for medical reasons, compared to women with MO.

Declaration of conflicting interests

The authors declare that there are no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Ethical statement

Written informed consent was obtained from all participants. The NOWAC study was licensed by the Norwegian Data Inspectorate (2002/2241) and approved by the Regional Committee for Medical and Health Research Ethics (REC-635219).

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References

1. Steiner TJ and Stovner LJ. Global epidemiology of migraine and its implications for public health and health policy. *Nat Rev Neurol* 2023; 19: 109–117.
2. Stovner LJ and Andree C. Prevalence of headache in Europe: a review for the Eurolight project. *J Headache Pain* 2010; 11: 289–299.
3. Hagen K, Zwart JA, Vatten L, et al. Prevalence of migraine and non-migrainous headache-head-HUNT, a large population-based study. *Cephalalgia* 2000; 20: 900–906.
4. Abu-Arafeh I, Razak S, Sivaraman B, et al. Prevalence of headache and migraine in children and adolescents: a systematic review of population-based studies. *Dev Med Child Neurol* 2010; 52: 1088–1097.
5. Rasmussen B, Jensen R, Schroll M, et al. Epidemiology of headache in a general population: a prevalence study. *J Clin Epidemiol* 1991; 44: 1147–1157.
6. MacGregor EA. Oestrogen and attacks of migraine with and without aura. *Lancet Neurol* 2004; 3: 354–361.
7. Pavlovic JM, Akcali D, Bolay H, et al. Sex-related influences in migraine. *J Neurosci Res* 2017; 95: 587–593.
8. Somerville BW. The role of estradiol withdrawal in the etiology of menstrual migraine. *Neurology* 1972; 22: 355–365.
9. Raffaelli B, Do TP, Chaudhry BA, et al. Menstrual migraine is caused by estrogen withdrawal: revisiting the evidence. *J Headache Pain* 2023; 24: 131
10. van Casteren DS, Verhagen IE, Onderwater GL, et al. Sex differences in prevalence of migraine trigger factors: A cross-sectional study. *Cephalalgia* 2021; 41: 643–648.
11. Chauvel V, Multon S and Schoenen J. Estrogen-dependent effects of 5-hydroxytryptophan on cortical spreading depression in rat: Modelling the serotonin-ovarian hormone interaction in migraine aura. *Cephalalgia* 2018; 38: 427–436.
12. Allais G, Chiarle G, Sinigaglia S, et al. Migraine during pregnancy and in the puerperium. *Neurol Sci* 2019; 40: 81–91.
13. Linde M, Stovner JL, Zwart JA, et al. Time trends in the prevalence of headache disorders. The Nord-Trondelag Health Studies (HUNT 2 and HUNT 3). *Cephalalgia* 2011; 31: 585–596.
14. MacGregor EA. Menstrual and perimenopausal migraine: A narrative review. *Maturitas* 2020; 142: 24–30.
15. Martin VT, Wernke S, Mandell K, et al. Symptoms of premenstrual syndrome and their association with migraine headache. *Headache* 2006; 46: 125–137.
16. Vetvik KG, MacGregor AE, Lundqvist C, et al. Symptoms of premenstrual syndrome in female migraineurs with and without menstrual migraine. *J Headache Pain* 2018; 19: 97.
17. Granella F, Sances G, Zanferrari C, et al. Migraine without aura and reproductive life events: a clinical epidemiological study in 1300 women. *Headache* 1993; 33: 385–389.
18. Cupini LM, Matteis M, Troisi E, et al. Sex-hormone-related events in migrainous females. A clinical comparative study between migraine with aura and migraine without aura. *Cephalalgia* 1995; 15: 140–144.
19. Aegidius KL, Zwart JA, Hagen K, et al. Increased headache prevalence in female adolescents and adult women with early menarche. The Head-HUNT Study. *Eur J Neurol* 2011; 8: 321–328.
20. Aegidius KL, Zwart JA, Hagen K, et al. Oral contraceptives and increased headache prevalence. *Neurology* 2006; 66: 349–353.
21. Lund E, Kumle M, Braaten T, et al. External validity in a population-based national prospective study – the Norwegian Women and Cancer study (NOWAC). *Cancer Causes Control* 2003; 14: 1001–1008.

22. Lund E, Dumeaux V, Braaten T, et al. Cohort profile: The Norwegian Women and Cancer study-NOWAC-Kvinner og kreft. *Int J Epidemiol* 2007; 37: 36–41.
23. Headache Classification Subcommittee of the International Headache Society. The international classification of headache disorders: 3rd edition. *Cephalalgia* 2013; 33: 629–808
24. Aegidius KL, Zwart JA and Hagen K, et al. The effect of pregnancy and parity on headache prevalence: The Head-HUNT study. *Headache* 2009; 49: 851–859.
25. Sances G, Granella F, Nappi RE, et al. Course of migraine during pregnancy and postpartum: a prospective study. *Cephalalgia* 2003; 23: 197–205.
26. Scher AI, Stewart WF, Buse D, et al. Major life changes before and after the onset of chronic daily headache: a population-based study. *Cephalalgia* 2008; 28: 868–876.
27. Sacco S, Merki-Feld GS, Aegidius KL, et al. European Headache Federation (EHF), the European Society of Contraception and Reproductive Health (ESCRH). Effect of exogenous estrogens and progestogens on the course of migraine during reproductive age: a consensus statement by the European Headache Federation (EHF) and the European Society of Contraception and Reproductive Health (ESCRH). *J Headache Pain* 2018; 19: 76.
28. Steiner TJ, Jensen R, Katsarava Z, et al. Aids to management of headache disorders in primary care (2nd edition). *J Headache Pain* 2019; 20: 57.
29. Merki-Feld GS, Imthurn B, Langner R, et al. Positive effects of the progestin desogestrel 75 μg on migraine frequency and use of acute medication are sustained over a treatment period of 180 days. *J Headache Pain* 2015; 16: 522.
30. Russell MB, Rasmussen BK, Thorvaldsen P, et al. Prevalence and sex-ratio of the subtypes of migraine. *Int J Epidemiol* 1995; 24: 612–618.
31. Vetvik KG and MacGregor AE. Sex differences in the epidemiology, clinical features, and pathophysiology of migraine. *Lancet Neurol* 2017; 16: 76–87.
32. Nagel-Leiby S, Welch KMA, Grunfeld S, et al. Ovarian steroid levels in migraine with and without aura. *Cephalalgia* 1990; 10: 147–152.
33. Vongvaivanich K, Lertakyamanee P, Silberstein SD, et al. Late-life migraine accompaniments: a narrative review. *Cephalalgia* 2015; 35: 894–911.
34. Facchinetti F, Neri I, Martignoni E, et al. The association of menstrual migraine with the premenstrual syndrome. *Cephalalgia* 1993; 13: 422–425.
35. van Casteren DS, Verhagen IE, van der Arend BWH, et al. Comparing perimenstrual and nonperimenstrual migraine attacks using an e-diary. *Neurology* 2021; 97: 1661–1671
36. Martin VT and Behbehani M. Ovarian hormones and migraine headache: understanding mechanisms and pathogenesis–part 2. *Headache* 2006; 46: 365–386.
37. Vetvik KG and MacGregor EA. Menstrual migraine: a distinct disorder needing greater recognition. *Lancet Neurol* 2021; 20: 304–315.