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Increased Risk of Multiple Sclerosis among Women with Migraine in the Nurses' Health Study II

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Abstract

Background—The prospective Nurses' Health Study II (NHS-II), which enrolled over 116,000 female nurses, provides a unique opportunity to test the hypothesis of whether migraine is associated with MS and to explore the temporal aspects of the interrelationship.

Objectives—To calculate relative risk of MS among NHS-II participants with and without migraine; to estimate odds ratio of being diagnosed with migraine in women with and without pre-existing MS.

Methods—Cox proportional hazards regression was used to estimate rate ratios and 95% CIs of being diagnosed with MS in women with and without pre-existing migraine adjusted for potential confounders. Multi-variate adjusted odds ratio of being diagnosed with migraine in women with and without pre-existing MS were estimated using logistic regression.

Results—The prevalence of migraine in women with MS at baseline (26%, $p=0.11$) and those diagnosed with MS after enrolment (29%, $p<0.0001$) was higher than in the non-MS cases (21%). The relative risk of developing MS in migraineurs was 1.39 times higher than in non-migraineurs (95% CI: 1.10-1.77 ($p=0.008$)). The absolute risk of developing MS in women-migraineurs over a 15-year follow-up was 0.47%, and 0.32% among non-migraineurs. The odds of being diagnosed with migraine was higher in women with pre-existing MS compared to those without MS, but did not reach statistical significance (OR=1.57, 95% CI: 0.97-2.52; $p=0.06$).

Conclusions—Using a large, population-based cohort of women-nurses, history of migraine was associated with an increased risk of MS. However, the difference in absolute risk of MS in migraineurs and non-migraineurs was small.

Keywords

Multiple Sclerosis [41]; Migraine [101]; Natural history studies (prognosis) [58]; Risk factors in epidemiology [59]

Introduction

The possibility of a link between migraine and MS was suggested over a half-century ago by Compston and McAlpine who observed that 2% of patients with MS experienced migraine within three months of MS onset [1]. Since then, nine case-control studies have been conducted with the aim of determining whether migraine prevalence is increased in MS

patients. In four of these studies migraine was more common in MS patients than healthy controls or non-MS neurological controls [2][3][4][5][6], while the other four studies found no increase in migraines among MS patients [7][8][9][10]. The prevalence of migraine among MS patients ranged from 21-69%. The relatively wide range and conflicting results are perhaps not surprising given differences in study methodology (e.g., lifetime prevalence vs. point prevalence), case definitions, timing, location, patient and control selection, and small sample size.

The studies of migraine in MS suffer from two main limitations: they are cross-sectional surveys and thus do not yield information regarding the temporal relationship between migraine and MS; all but one of these studies ([9]) were tertiary clinic-based and are therefore subject to selection and Berkman's biases [11].

A methodologically rigorous, large-scale, non-clinic based, prospective study could help resolve the controversy of whether migraine is associated with MS and shed light on the temporal relationship between the two disorders. Therefore, we sought to examine the association between MS and migraine among women in the Nurses' Health Study II (NHS-II), a prospective cohort of over 116,000 women that has been extensively used to investigate risk factors in MS [12][13][14][15][16][17].

Materials and Methods

Participants

The NHS-II is a cohort of 116,671 female, married, registered nurses, aged 25 to 42 years and living in one of 14 states across the US. The women completed an enrollment questionnaire in 1989 and updated their medical and lifestyle information via questionnaire every two years thereafter.

Ascertainment of MS diagnosis

The ascertainment of MS cases has been described recently [16]. In brief, women who self report an MS diagnosis are asked permission for study investigators to contact their treating neurologist and obtain a copy of medical records pertaining to the diagnosis. When study neurologists applied Poser criteria for diagnosis of MS to the clinical and laboratory data, 93% of all definite and probable diagnoses were confirmed [16]. Thus, women are considered as having definite or probable diagnosis of MS according to Poser criteria as reported by the neurologist or after review of medical records by the study neurologist. At baseline in 1989, 140 women had MS ('prevalent cases'). Between 1989 and 2005, there were 402 new diagnoses of probable or definite MS ('incident cases'). Among the incident cases, 244 had MS symptom onset after 1989 and 114 had symptom onset before 1989, but were diagnosed after 1989, while 44 had an unknown date of symptom onset. The subset of 244 incident cases who developed MS symptoms after the baseline will be referred to as 'MS onset after baseline cases'.

Migraine status

In 1989 (baseline), 1993, and 1995, women were asked to report if they ever had a physician-diagnosed migraine headache.

Covariates

Multivariate analyses were adjusted for latitude of residence age 15 (north, middle, south), ethnicity (Scandinavian, Southern European, other Caucasian, other), pack-years smoking (never, <10, 10-24, >24), body mass index (BMI) at age 18 (<18.5 kg/m², 21-22.9, 23-24.9,

25-26.9, 27-29.9, ≥ 30), and supplemental vitamin D intake in 1991 (0, $<400\text{IU/d}$, $\geq 400\text{IU/d}$) as described previously [14][17].

Statistical analysis

Comparisons of migraine prevalence in MS cases vs. non-cases were done using a chi-squared test. In the prospective analyses examining the risk of MS associated with history of migraine, women were followed from the date they returned the baseline questionnaire to the earliest of: date of MS diagnosis (or onset), date of death, or June 2005. Analyses were conducted using report of migraine at baseline and ever reporting migraine (1989, 1993, or 1995). Cox proportional hazards regression stratified by age (in months) and 2-year time periods (frequency of the questionnaires) was used to estimate rate ratios (RRs) and 95% confidence intervals (CIs).

We also conducted analyses examining whether women with MS were more likely to have migraine headaches. This analysis excluded any case of MS that onset after 1989 ($n=244$) and any woman who reported having physician-diagnosed migraine in 1989 ($n=17,893$). This restriction increased the likelihood that the MS preceded the migraine. Because we do not have information on the date of migraine diagnosis, we could not do a prospective analysis using Cox proportional hazards regression. Instead, we used multivariate logistic regression, adjusted for same variables as above (age, latitude of residence, ethnicity, smoking history at baseline (ever vs. never), BMI at age 18 (<18.5 , $18.5-<25$, $25-<30$, $>30\text{ kg/m}^2$), supplemental vitamin D) to estimate the odds ratio of being diagnosed with migraine in women with and without pre-existing MS.

Analyses were conducted using SAS software, version 9.1 (SAS Institute Inc, Cary, NC). A p value <0.05 was considered significant.

The study has been approved by the institutional review board of Brigham and Women's Hospital, Boston.

Results

Prevalence of migraine in the NHS-II

At baseline, 17,893 (15.4%) women reported having physician-diagnosed migraine. There were no differences between migraineurs and non-migraineurs with respect to age, body mass index at age 18, latitude of residence at age 15, Scandinavian ancestry and smoking status (Table 1). By 1995 an additional 6,407 women reported a physician-diagnosed migraine. 'Cumulative migraine prevalence' in the NHS-II through 1995 was 20.9%.

Frequency of migraine among prevalent MS cases

At baseline, 140 women (0.1% of the sample) had a diagnosis of MS ('prevalent MS cases'), and 27 of them (19.3%) had a co-existing diagnosis of migraine. As of 1995, the last available migraine status update in NHS-II, 10 additional prevalent MS cases reported being diagnosed with migraine by a physician. Thus, the number of migraineurs in the prevalent MS group rose to 37 (26%), which is higher than the cumulative prevalence of migraine among non-MS cases (21%), though the difference did not reach significance ($p=0.11$).

Prevalence of migraine at baseline and at last migraine status follow-up (in 1995) in the non-MS, 'prevalent MS', 'incident MS' and 'MS onset after baseline' groups is shown in Figure 1.

Frequency of migraine among incident MS cases

There were 402 women who were diagnosed with MS after the baseline ('incident MS cases'), of whom 84 (20.9%) had a pre-existing diagnosis of migraine. In analyses adjusted for age, body mass index at age 18, smoking history, vitamin D intake, latitude of residence and ancestry, women who reported having a history of migraine at baseline had a 39% increased risk of MS ($p=0.008$) (Figure 2). The difference in absolute risk of developing MS among women with migraine at baseline and those without was small: 0.47% (84 out of 17,893) in migraineurs v. 0.32% (318 out of 98,778) in non-migraineurs over 15.5 years of follow-up.

In addition to the 84 cases in the incident MS group with a diagnosis of migraine at baseline, 32 new cases of physician-diagnosed migraine were reported as of 1995, for a total of 116 migraine cases, yielding a cumulative migraine frequency in the incident MS cohort of 28.9%.

Of the 32 de novo migraine diagnoses, 21 were reported prior to MS diagnosis and 11 after MS diagnosis. Thus, in the group of women with incident MS and migraine, 91% (105/116 women) were diagnosed with migraine before they were diagnosed with MS.

Frequency of migraine in the 'MS onset after baseline' cases

Of the 402 women in the incident MS cohort who were diagnosed with MS after baseline, 244 experienced their first symptom of MS after baseline ('MS onset after baseline cases'). The remainder of the incident cohort, 158 cases, either had symptom onset before the baseline (114 cases) or an unknown symptom onset date (44 cases). In 1989, frequency of migraine among the cases with MS onset after baseline was 18.9% (46/244). During the 1989-1995 period, an additional 20 women in the MS onset after baseline subset reported physician-diagnosed migraine, resulting in a cumulative migraine frequency of 27.1% (66/244). Of the 20 new migraine cases, 14 developed migraine before first MS symptoms and 6 after MS symptoms. Thus, among women with migraine and MS onset after baseline, 91% (60/66) received migraine diagnosis prior to the first symptom of MS.

In analyses adjusted for age, body mass index at age 18, smoking history, vitamin D intake, latitude of residence and ancestry, women in the MS onset after baseline subset who reported having a history of migraine at baseline had a 28% increased risk of MS compared to non-migraineurs, which was not statistically significant ($RR=1.28$; 95% CI (0.92-1.76), $p=0.14$). However, when the analysis was carried out using updated migraine prevalence (as of 1995) rather than baseline migraine prevalence, the migraineurs had a 39% increased risk of MS as compared to women with no migraine history, which was a statistically significant difference ($RR=1.39$; 95% CI (1.03-1.85), $p=0.03$). The relative risks of MS among incident MS cases and MS onset after baseline cases using both baseline and cumulative migraine prevalences are shown in Figure 2.

Relative risk of new migraine diagnosis in patients with and without pre-existing MS

To better understand the interrelationship between migraine and MS, one needs to consider not only whether migraine occurs more frequently among women who will develop MS, but also the reciprocal question of whether women with MS are more likely to develop migraines. To address the latter question, we estimated the odds of having a physician-diagnosed migraine by 1995 in women with no migraine, but positive MS history at baseline. 'Positive MS' history was defined either as a diagnosis of definite/probable MS at baseline, or symptom onset before baseline.

In the subset of 113 patients with pre-baseline diagnoses of MS, but no history of migraine at baseline in 1989, ten women were diagnosed with migraine by 1995 (8.9%), while in the no MS/no migraine cohort of 98,099 women, 6,397 were diagnosed with migraine by 1995 (6.5%). Thus, women with pre-existing MS compared to women with no MS had a 33% increased odds of being diagnosed with migraine during follow-up, but this difference was non-significant ($p=0.4$) (Table 2).

In the subset of cases with MS symptom onset before baseline, 9 out of 73 women were diagnosed with migraine between 1989 and 1995 (12.3%). Since in the no MS/no migraine at baseline group, 6.5% were diagnosed with migraines during 1989-1995 follow-up, the odds ratio of developing MS was 1.9-fold higher in the MS symptom onset group, which trended to, but did not reach statistical significance ($p=0.07$) (Table 2). Combining the prevalent MS and 'MS symptom onset before baseline' groups, the odds ratio of new diagnosis of migraine among MS patients compared to non-MS patients was trending toward significance ($p=0.06$) (Table 2).

Discussion

Analysis of NHS-II, a large cohort of women, provides the strongest evidence to date for an existence of an association between migraine and MS. The cumulative prevalence of migraine among two non-overlapping cohorts of MS patients in NHS-II – 'prevalent MS cases' and 'incident MS cases' – was higher than in the non-MS cases. The relatively modest differences in migraine frequency in the MS and non-MS groups – 26-29% in the MS groups v. 21% in non-MS patients – may explain why previous, smaller-size studies of migraine in MS, being likely under-powered, yielded conflicting results. However, as migraine estimates in NHS-II are only current as of 1995, they should be considered as the "lower bound" of cumulative prevalence. The true prevalence through the end of the follow-up period in 2005 would likely be higher in all groups, and would likely widen the gap between MS and non-MS groups.

The prospective nature of the NHS-II cohort allowed us to investigate the temporal relationship between migraine and MS. In this respect the most instructive results emerge from analysis of the 'MS onset after baseline' cases. These women developed MS during the follow up period, and their migraine status was ascertained prior to the first symptom of MS. The women with pre-existing migraine had a statistically significant 39% higher risk of developing MS compared to non-migraineurs. It is important to emphasize, however, that the *absolute* risk of MS among women-migraineurs was small, 0.47%, which was only 0.15% higher, in absolute terms, than in non-migraineurs over the 15.5 years of follow-up. Migraine can therefore be considered a predictor of MS, but a relatively modest one compared to the more established risk factors such as DRB1*1501 haplotype [12] or history of infectious mononucleosis [18].

What can account for the higher rate of MS among women with migraine compared to those without? One possible explanation is that the association is due to errors in diagnosis of MS in migraineurs: women with migraine may have been more likely to be seen by a neurologist, evaluated with brain MRI, and misdiagnosed with 'MS' on the basis of non-specific radiographic findings in combination with a history of transient (usually) visual or sensory neurologic deficits. We consider this scenario to be unlikely for two reasons: first, diagnosis of MS was made according to non-MRI-based Poser criteria, which are considered to be more specific for MS than the (partly) MRI-based McDonald criteria; secondly an association between migraine and MS was found also among women with a definite diagnosis of MS (data not shown). It could also be argued that the association may be due to detection bias [19]: abnormalities on brain MRI in a migraine patient would lead to greater

scrutiny of the patient's past neurologic history and subsequent symptoms, and would facilitate an earlier diagnosis of MS compared to non-migraineurs, who might not come to attention of a neurologist until more obvious signs of MS are manifest. We believe that this consideration is also unlikely to have significantly influenced the results since Poser criteria for MS adopted in NHS-2 do not take into consideration MRI findings. Furthermore, the age at diagnosis of MS in migraineurs (42.5 years) and non-migraineurs (42.1) was similar in our cohort.

Another interpretation for the apparent higher risk of MS among migraineurs is that migraine-like headache may be the presenting symptom of MS, rather than a concurrent diagnosis. Headache is not usually considered an MS symptom, though it is the most common indication for brain MRI in 'radiographically isolated syndrome' [20] and has been reported at MS onset in 1-2% of patients [1][27]. The available data does not allow us to determine whether migraine in a 'pre-symptomatic' MS phase is a primary or secondary headache, but the fact that migraine generally predates MS by many years, and the rarity of migraine at MS onset would seem to indicate that in most cases migraine is more likely to be a pre-existing diagnosis.

Our results that migraine increases the risk of subsequent MS are in line with two previous small case-control studies [5][6]. A number of potential mechanisms may account for this observation. One possibility is that migraine, and specifically migraine with aura, may lead to subtle increase in permeability of the blood-brain barrier and neuroinflammation [21], thereby exposing antigen in the privileged central nervous system compartment to circulating T cells and contributing to their sensitization to myelin products. This model might explain how a non-immune mediated condition such as migraine might play a role in the pathogenesis of presumably autoimmune disease, such as MS. Unfortunately, we did not have information in this study on whether the migraine was with or without aura. This hypothesis, purely speculative at present, lends itself to experimental verification. It is also possible that migraine may skew cytokine profile in a way that may predispose to autoimmune reaction in CNS. In this connection it is interesting to observe that certain cytokines, such as IL-10 and TNF α , tend to be overexpressed in both migraine attacks and during an MS relapse [7][26]. Other possibilities will need to be considered as well, such as existence of shared environmental and genetic risk factors [22].

We also observed a trend for migraine to be diagnosed more frequently in MS patients compared to non-MS cases, but this trend did not reached statistical significance. Various hypotheses have been put forth to explain how MS can predispose to migraine [23], but the antecedent question of whether or not such a predisposition exists cannot be established with the evidence at hand.

Our study has a number of strengths compared to prior investigations of MS and migraine. The diagnoses of MS were validated through a study neurologist and review of records; the study involves a large, non clinic-based sample; it employs a prospective cohort design, which allowed us to ascertain the temporal order of emergence of migraine and MS in a subset of enrollees. There are also several limitations. First, the NHS-II enrolled only women of similar professional and socio-economic background, nearly all of whom were Caucasian. Thus, our results may not be generalizable to MS patients with different demographic characteristics (men, non-Caucasians, older patients, etc.). On the other hand, the prevalence of migraine in our sample of women was nearly identical to that in large Internet-based in the National Health and Wellness Study, in which migraine were reported by 29% of respondents with MS, a significantly higher rate than among non-MS cases [24]. Second limitation is that the diagnosis of migraine was based on self-report, but did not make use of a validated diagnostic tool for patient-reported migraine, such as the one used in

the American Migraine Prevalence and Prevention (AMPP) study [25]. The detailed nature of the instrument used in the AMPP made impractical its inclusion in the NHS-II questionnaire, which asks targeted questions about wide range of medical conditions. It is hoped that the number of false-positive and false-negative responses has been kept to a minimum by restricting the study to medical professionals who would be expected to have increased awareness and better understanding of migraine and easier access to health care compared to the general population. It was reassuring that self-reported migraine prevalence in NHS-II among non-MS cases was within the range of what was reported by women in the general population in the AMPP: 28.1% in the 30-39 age group and 25.5% in the 40-49 age group [25]. Another limitation of our study relates to lack of information about migraine onset and migraine type which precluded a more in-depth analyses of the temporal interrelationship between various migraine types and MS. Finally, the number of MS cases in NHS-2 may be an underestimate as we employed the more specific, but less sensitive Poser criteria, rather than the newer, revised McDonald criteria. Since the estimated lifetime risk of MS in our cohort was high – nearly 1:250 women [16], it is doubtful that many cases were missed because the more restrictive criteria were used. Furthermore, the use of Poser criteria has the advantage of decreasing the chances of misdiagnosis due to presence of non-specific white matter lesions on brain MRI that have been described in migraineurs.

In conclusion, our work confirms an existence of an association between migraine and MS that was previously reported by some [2][3][4][5][6][24], but not all investigators. It also supports the idea that migraine is a risk factor for, or at least a predictor of, MS as suggested by two small case-control series [5][6]. Further research is needed to test the various hypotheses that may explain the association between migraine and MS.

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References

1. Compston N, McAlpine D. Some aspects of the natural history of disseminated sclerosis. *Q J Med.* 1952; 21:135–167. [PubMed: 14941968]
2. Watkins SM, Espir M. Migraine and multiple sclerosis. *J Neurol Neurosurg Psychiatry.* 1969; 32:35–37. [PubMed: 5774132]
3. Rolak LA, Brown S. Headaches and multiple sclerosis: a clinical study and review of the literature. *J Neurol.* 1990; 237:300–302. [PubMed: 2230844]
4. Kister I, Caminero AB, Monteith TS, et al. Migraine is comorbid with multiple sclerosis and associated with a more symptomatic MS course. *J Headache Pain.* 2010; 11(5):417–25. [PubMed: 20625916]
5. Martínez Sobrepera HJ, Cabrera Gómez JA, Tuero Iglesias A. Exogenous factors in the aetiology of multiple sclerosis in Cuba. A study of cases and controls. *Rev Neurol.* 2001; 33:931–937. [PubMed: 11785004]
6. Zorzon M, Zivadinov R, Nasuelli D, et al. Risk factors of multiple sclerosis: a case-control study. *Neurol Sci.* 2003; 24:242–247. [PubMed: 14658040]
7. Vacca G, Marano E, Brescia Morra V, et al. Multiple sclerosis and headache co-morbidity. A case-control study. *Neurol Sci.* 2007; 28:133–135. [PubMed: 17603764]
8. Putzki N, Pfriem A, Limmroth V, et al. Prevalence of migraine, tension-type headache and trigeminal neuralgia in multiple sclerosis. *Eur J Neurol.* 2009; 16:262–267. [PubMed: 19138330]
9. Nicoletti A, Patti F, Lo Fermo S, et al. Headache and multiple sclerosis: a population-based case-control study in Catania, Sicily. *Cephalalgia.* 2008; 28:1163–1169. [PubMed: 18727645]
10. Warren S, Warren KG. Multiple sclerosis and associated diseases: a relationship to diabetes mellitus. *Can J Neurol Sci.* 1981; 8:35–39. [PubMed: 7225955]

11. Berkson J. Limitation to application of four-fold table analysis to hospital data. *Biom Bull.* 1946; 2:47–53.
12. De Jager PL, Simon KC, Munger KL, Rioux JD, Hafler DA, Ascherio A. Integrating risk factors: HLA-DRB1*1501 and Epstein-Barr virus in multiple sclerosis. *Neurology.* 2008; 70(13 Pt 2): 1113–8. [PubMed: 18272866]
13. Tai AK, O'Reilly EJ, Alroy KA, et al. Human endogenous retrovirus-K18 Env as a risk factor in multiple sclerosis. *Mult Scler.* 2008; 14(9):1175–80. [PubMed: 18701576]
14. Munger KL, Zhang SM, O'Reilly E, Hernán MA, Olek MJ, Willett WC, Ascherio A. Vitamin D intake and incidence of multiple sclerosis. *Neurology.* 2004; 62(1):60–5. [PubMed: 14718698]
15. Gardener H, Munger K, Chitnis T, Spiegelman D, Ascherio A. The relationship between handedness and risk of multiple sclerosis. *Mult Scler.* 2009; 15(5):587–92. [PubMed: 19389750]
16. Hernán MA, Olek MJ, Ascherio A. Geographic variation of MS incidence in two prospective studies of US women. *Neurology.* Nov 10; 1999 53(8):1711–8. [PubMed: 10563617]
17. Munger KL, Chitnis T, Ascherio A. Body size and risk of MS in two cohorts of US women. *Neurology.* Nov; 2009 73(19):1543–50. [PubMed: 19901245]
18. Thacker EL, Mirzaei F, Ascherio A. Infectious mononucleosis and risk for multiple sclerosis: a meta-analysis. *Ann Neurol.* 2006; 59(3):499–503. [PubMed: 16502434]
19. Sackett DL. Bias in analytic research. *J Chron Dis.* 1979; 32:51–63. [PubMed: 447779]
20. Sellner J, Shirmer L, Hemmer B, Mührlau M. The radiologically isolated syndrome: take action when the unexpected is uncovered? *J Neurol.* 2010; 257:1602–11. [PubMed: 20503053]
21. Gursoy-Ozdemir Y, Qiu J, Matsuoka N, et al. Cortical spreading depression activates and upregulates MMP-9. *J Clin Invest.* 2004; 113:1447–1455. [PubMed: 15146242]
22. Kister I, Caminero AB, Herbert J, Lipton RB. Tension-type headache and migraine in multiple sclerosis. *Curr Pain Headache Per.* 2010; 14(6):441–8.
23. Elliott DG. Migraine in multiple sclerosis. *Int Rev Neurobiol.* 2007; 79:281–302. [PubMed: 17531846]
24. Meteliche D, Stewart M, Phillips A, Gupta S, Edwards N, Goren A. Comorbid Illness among Individuals with Multiple Sclerosis. *Neurology.* 2011; 76:S4–A475.
25. Lipton RB, Scher AI, Kolodner K, et al. Migraine in the United States: epidemiology and patterns of health care use. *Neurology.* 2002; 58:885–894. [PubMed: 11914403]
26. Perini F, D'Andrea G, Galloni E, Pignatelli F, Billo G, Alba S, Bussone G, Toso V. Plasma cytokine levels in migraineurs and controls. *Headache.* Jul-Aug;2005 45(7):926–31. [PubMed: 15985111]
27. Freedman MS, Gray TA. Vascular headache: a presenting symptom of multiple sclerosis. *Can J Neurol Sci.* 1989; 16:63–66. [PubMed: 2924210]

Figure 1. Prevalence of migraine at baseline and at last migraine status follow-up (in 1995) in the non-MS, 'prevalent MS', 'incident MS' and 'MS onset after baseline' groups.

Figure 2. Relative risks of MS among incident MS cases and MS onset after baseline cases using both baseline and cumulative migraine prevalences.

Table 1

Characteristics of women with and without physician-diagnosed migraines

	<u>Migraines at enrollment (1989)</u>	
	Yes	No
No. of women	17893 (15%)	98,537 (85%)
Age baseline, mean	35	34
Residence in North tier at age 15 (%)	26	27
Scandinavian ancestry (%)	4	4.4
Ever smoker at enrollment (%)	37	34
BMI at age 18 (kg/m ²), mean	21	21

BMI – body mass index

Table 2

Multivariate* odds ratio of a first migraine diagnosis between 1989-1995 in women with and without pre-existing MS, among women who reported never having a migraine before 1989

	Migraine in 1993-95		Multivariate OR (95% CI)	p value
	Yes	No		
MS diagnosed before baseline				
Yes	10	103	1.33 (0.69-2.54)	0.40
No	6397	91702		
MS onset before 1989				
Yes	9	64	1.90 (0.95-3.83)	0.07
No	6374	91524		
Pooled			1.57 (0.97-2.52)	0.06

* multivariate – adjusted for age (months), latitude of residence age 15 (north, middle, south), ethnicity (Scandinavian, Southern European, other Caucasian, other), smoking (never vs. ever at baseline), BMI at age 18 (<18.5 kg/m², 18.5-<25, 25-<30, ≥30), supplemental vitamin D in 1991(0, <400IU/d, ≥400IU/d)

Abbreviations: OR – odds ratio; CI – confidence interval; BMI – body mass index