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RESEARCH

Migraine and cognitive decline among women: prospective cohort study

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Abstract

Objective To evaluate the association between migraine and cognitive decline among women.

Design Prospective cohort study.

Setting Women's Health Study, United States.

Participants 6349 women aged 65 or older enrolled in the Women's Health Study who provided information about migraine status at baseline and participated in cognitive testing during follow-up. Participants were classified into four groups: no history of migraine, migraine with aura, migraine without aura, and past history of migraine (reports of migraine history but no migraine in the year prior to baseline).

Main outcome measures Cognitive testing was carried out at two year intervals up to three times using the telephone interview for cognitive status, immediate and delayed recall trials of the east Boston memory test, delayed recall trial of the telephone interview for cognitive status 10 word list, and a category fluency test. All tests were combined into a global cognitive score, and tests assessing verbal memory were combined to create a verbal memory score.

Results Of the 6349 women, 853 (13.4%) reported any migraine; of these, 195 (22.9%) reported migraine with aura, 248 (29.1%) migraine without aura, and 410 (48.1%) a past history of migraine. Compared with women with no history of migraine, those who experienced migraine with or without aura or had a past history of migraine did not have significantly different rates of cognitive decline in any of the cognitive scores: values for the rate of change of the global cognitive score between baseline and the last observation ranged from –0.01 (SE 0.04) for past history of migraine to 0.08 (SE 0.04) for migraine with aura when compared with women without any history of migraine. Women who experienced migraine were also not at increased risk of substantial cognitive decline (worst 10% of the distribution of decline). When compared with women without a history of migraine, the relative risks for the global score ranged from 0.77 (95% confidence interval 0.46 to 1.28) for women with migraine without aura to 1.17 (0.84 to 1.63) for women with a past history of migraine.

Conclusion In this prospective cohort of women, migraine status was not associated with faster rates of cognitive decline.

Introduction

Migraine is a chronic-intermittent primary headache disorder that affects about 20% of the female population.[1] Up to one third of those with migraine experience aura (that is, transient neurology symptoms mainly of the visual field) before or during a migraine attack. Besides the headache, migraine is believed to usually be a benign condition. However, previous studies have linked migraine, especially migraine with aura, to an increased risk of ischaemic stroke.[2] In addition to increasing the risk of stroke, migraine has also been associated with an increased prevalence of clinically silent brain lesions.[3-5] In the general population, silent brain lesions have been shown to be a risk factor for dementia and cognitive decline,[6] leading to speculation that migraine may be a progressive brain disorder.[7] Determining if there is an association between migraine and cognitive decline among women is important because women are more likely than men to experience migraines[1] and also have a higher prevalence of dementia.[8] If an association between migraine and cognitive decline does exist, preventing the onset of migraines may be one way to slow the progression of cognitive decline. Additionally, interventions aimed at preserving cognitive function could be targeted to women who experience migraine.

Although several cross sectional studies[9-19] and a few prospective studies[20-22] have examined the association between migraine and cognitive decline, many were small or were unable to stratify

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the association between migraine and cognitive decline by aura status. Using data from the Women's Health Study, we examined the association between migraine subtypes and cognitive decline during four years of follow-up.

Methods

The Women's Health Study was a randomised, placebo controlled clinical trial designed to test the effects of low dose aspirin and vitamin E in the primary prevention of cardiovascular disease and cancer. The design and results of the study have been reported previously.[23-25] Briefly, at baseline (1992-95), 39 876 US female health professionals age 45 or older without a history of cardiovascular disease, cancer, or other major illnesses were enrolled. The clinical trial ended in March 2004, and the women are currently being followed in an observational study.

In 1998, a cognitive subcohort of women participating in the Women's Health Study was started.[26 27] Women were eligible to participate if they were aged 65 or older. Of the 7175 women eligible to participate, 6377 completed the initial cognitive assessment. Two additional follow-up assessments were done, each about two years apart. Of those who completed the initial assessment, 5845 (91.7%) completed at least one follow-up assessment and 5073 (79.5%) completed all assessments. About 8% of participants did not complete any follow-up assessments owing to death (2%), being unreachable (1%), or refusal (5%).

Assessment of migraine

On the baseline questionnaire we asked the women "Have you ever had migraine headaches?" and "In the past year, have you had migraine headaches?" We also asked the women who reported experiencing migraine headaches within the past year about the characteristics of their attacks, including the presence of aura or any indication that a migraine was coming. Using the women's responses to these questions, we divided them into four categories: no migraine history, migraine with aura (women who indicated experiencing migraine within the year before baseline and who reported the presence of aura or any indication that a migraine was coming), migraine without aura, and a past history of migraine (women who reported ever having migraine headache but not experiencing migraine headache within the year before baseline). Previous validation studies in the Women's Health Study have shown good agreement between self reported migraine and the *International Classification of Headache Disorders* I and II.[28 29] For this analysis we excluded the 28 women who did not provide information on migraine status at baseline. The figure⇓ shows the number of women included and excluded at each stage of the design.

Assessment of outcomes

Interviewers blinded to the participant's migraine status administered the telephone cognitive assessment. The assessment was composed of five separate tests: telephone interview for cognitive status, immediate and delayed recall trials of the east Boston memory test, delayed recall trial of the telephone interview for cognitive status 10 word list, and a category fluency task. The telephone interview for cognitive status assesses global cognitive function and is a telephone adaptation of the mini-mental state examination.[30] Scores range from 0 to 41 points, and the test is shown to have high reliability and validity for measuring cognitive function.[31] The east Boston memory test assesses verbal memory with scores ranging from 0 to 12 points.[32] The delayed recall of the telephone interview for cognitive status 10 word list also assesses verbal memory.

The category fluency test assesses language and executive functioning[26 33] by asking women to name as many animals as possible in one minute. The validity of the telephone assessment compared with face to face interviews has been shown in previous studies (r=0.81 comparing our brief telephone administered cognitive assessment with face to face interviews composed of 21 tests).[26 34]

To create a global cognitive score we averaged z scores for performance on each of the five tests. For the 0.4% of participants who did not complete all five tests we used the mean of the z scores of the completed tests. We created a verbal memory composite score by averaging the z scores of the immediate and delayed recalls of both the east Boston memory test and the telephone interview for cognitive status 10 word list. Both of these composite scores have been used in previous studies in the Women's Health Study.[26 27 33 34] Finally, we also examined separately scores on the telephone interview for cognitive status as an additional measure of global cognition and scores on the category fluency task as executive function is particularly affected by clinical or subclinical stroke.

Statistical analysis

We calculated means for continuous baseline characteristics and frequencies for categorical baseline characteristics. At each cognitive assessment we used repeated measures analyses to examine mean performance. We adjusted for several potential confounders, as measured at baseline: age (continuous), smoking status (never, former, current), alcohol consumption (≤3 drinks per month, 1-6 drinks per week, ≥1 drinks per day), body mass index (<25, 25-29.9, ≥30 kg/m²), educational attainment (less than a bachelors degrees versus bachelors degree or above), use of postmenopausal hormones (never, current, or past), history of high cholesterol levels (yes or no), treatment for high cholesterol levels (yes or no), history of hypertension (yes or no), treatment for hypertension (yes or no), diabetes (yes or no), and history of oral contraceptive use (yes or no).

To examine change in cognitive functioning over time we used general linear models of response profiles. Similar to previous studies done using data from the Women's Health Study,[26 27 33] we modelled time nominally rather than linearly (since there was not a linear relation between time and cognitive performance) and modelled the effect of migraine status over time (the joint effects of migraine and time) by using interaction terms between migraine status and time. All models were fitted using maximum likelihood and accounted for the longitudinal correlation within participants by using an unstructured covariance matrix. We carried out age and multivariable adjusted analyses. The multivariable analysis adjusted for the same potential confounders as the repeated measures analysis of means with the exception of excluding treatment for high cholesterol levels for the global score and category fluency outcomes due to problems with model convergence. We also tested for effect modification by age (dichotomised at the median age of 75 years), history of hypertension, cardiovascular disease (all incident occurrences from baseline to the end of the cognitive substudy), baseline score for the global score, verbal score, telephone interview for cognitive status, and category fluency score (dichotomised at the median), perceived change in memory (worse versus no change or improvement), and educational attainment. The testing was done by including a three way interaction term for each variable with migraine status and time in separate age adjusted models.

We assigned women with missing information on body mass index (n=149) to a separate category. For other covariates, the

number of women with missing information was small (<100 for each variable), so we assigned them to the never/rarely or no use categories or, in the case of education, we used information on years of education to impute their highest educational attainment.

We carried out additional analyses using logistic regression to determine if migraine increased the risk of "substantial" cognitive decline. Substantial cognitive decline was defined as the worst 10% of the distribution of decline from the initial to the final cognitive assessment of the whole study cohort. We adjusted for all variables included in our previous analyses of mean scores and also adjusted for the time between entry into the Women's Health Study and third cognitive assessments.

All models were fit using SAS 9.1. All probability values were two tailed, and we considered P<0.05 to be statistically significant.

Results

Of the 6349 women, 853 (13.4%) reported any migraine; of these, 195 (22.9%) reported migraine with aura, 248 (29.1%) migraine without aura, and 410 (48.1%) a past history of migraine. Table 1⇓ shows the baseline characteristics of the participating women. Women who experienced migraine with aura were less likely to consume alcohol than women in the other migraine categories. Women who reported a past history of migraine had less education than women without any history of migraine, migraine with aura, or migraine without aura. Women with no history of migraine were more likely to have diabetes. Women with migraine without aura were the least likely to exercise.

The mean follow-up time for the cognitive substudy was 3.4 years. Table 2⇓ shows the average test scores at each cognitive assessment by migraine status adjusted for potential confounders. The global scores, verbal scores, or telephone interview for cognitive status scores did not differ significantly among the migraine categories. For the category fluency test, the scores differed significantly among the migraine groups at the second and third cognitive testing. Overall, cognitive performance seemed to be similar or even slightly better for women in the migraine groups than for women with no history of migraine.

Table 3⇓ presents the results from age and multivariable adjusted longitudinal analyses. All of the interaction terms between migraine categories and time were close to the null and non-significant, providing no evidence of differences in rates of cognitive decline for those with no history of migraine compared with women who experienced migraine with or without aura or had a past history of migraine.

The risk of substantial cognitive decline in women who experienced migraine with or without aura or had a past history of migraine was not increased (table 4⇓) compared with those with no history of migraine. In secondary analyses, we found no evidence of significant effect modification by history of hypertension, baseline score, perceived change in memory, or educational attainment. Statistically significant effect modification by age (less than or higher than the median of 75 years) was observed for the telephone interview for cognitive status (P=0.02). This result seemed to be driven by a greater rate of cognitive decline at the third time point among those with a past history of migraine who were older than the median age (β coefficient −0.85) compared with those who were younger than the median age (β coefficient 0.07). No statistically significant effect modification by median age was observed for the other cognitive outcomes. Statistically significant effect

modification by cardiovascular disease was observed on the category fluency test (P=0.01). Among women who experienced migraine with aura, those who also experienced a cardiovascular event had greater rates of decline (β coefficient −2.76 at the second time point and β coefficient −2.43 at the third time point) than those who did not experience a cardiovascular event (β coefficient −0.50 at the second time point and β coefficient 0.70 at the third time point). No statistically significant effect modification by cardiovascular event was observed for the other cognitive outcomes.

Discussion

Results from this large, prospective cohort study among women provide no evidence that migraine is associated with greater rates of cognitive decline when compared with women without a history of migraine. This result did not differ according to migraine aura status or past history of migraine. We also did not observe meaningful effect modification of this lack of association for most of our migraine groups. We did observe some effect modification by age for those with a past history of migraine, suggesting that older women had faster rates of decline on the telephone interview for cognitive status than younger women. Additionally, among women with migraine with aura, those who experienced a cardiovascular event had faster rates of decline on the category fluency test than those without a cardiovascular event.

Comparisons with other studies

Cross sectional studies have shown mixed results on the association between migraine status and lower cognitive functioning. Some studies have shown no differences among those with and without migraine,[9-14] whereas others have shown evidence of worse cognitive functioning among those who experience migraine.[15-19] However, owing to their cross sectional nature, none of these studies could examine the association between migraine and cognitive decline, a more meaningful outcome than cognition at any single time point.

The prospective studies on the association between migraine and cognitive decline among adults have not found greater rates of cognitive decline among people with migraine compared with people without migraine.[20-22] The Baltimore cohort of the National Institute of Health Mental Health Epidemiology Catchment Area study found that although adults with migraine overall and those with migraine with aura who were aged 50 or older at baseline showed lower baseline scores on tests of delayed and immediate recall, they actually showed less decline in those tests over time compared with people aged 50 or older at baseline who did not have migraines. Rates of decline did not differ between people aged less than 50 at baseline with migraine and those without.[21] The Maastricht Ageing Study did not find differences between people with and without migraine in decline on the mini-mental state examination, immediate and delayed recall of tests with 15 word lists, or other tests for simple and complex speed.[20] Finally, the Epidemiology of Vascular Ageing Study found no evidence of greater cognitive decline among people who experienced migraine on any of a wide variety of cognitive tests. For the Wechsler adult intelligence scale-revised, there was evidence that people who experienced migraine declined less over time than those with no history of severe headache. There was also little evidence that the presence of white matter hyperintensities or brain infarction modified the association between migraine and cognitive decline.[22]

In the present study we also found little evidence that cognitive function among those who experienced migraine declined more

than those without a history of migraine. Since this study was much larger than previous studies, we were able to examine the impact of migraine with aura, migraine without aura, and past history of migraine. Examining the association between migraine and cognitive decline by aura status is important because migraine with aura has been linked to more deleterious effects on the brain, particularly ischaemic vascular changes.[4] Additionally, we were able to carry out other subgroup analyses by age or the presence of cardiovascular disease, which could not be done in previous studies.

Strengths and limitations of the study

The strengths of this study include its large prospective design, standardised assessment of migraine status, information on migraine with and without aura, and the availability of validated cognitive function measures[26 34] at multiple time points, which allowed us to examine change in cognitive function over time.

Several limitations should be considered when interpreting our results. Our cohort was composed of women aged 65 and older, mostly white, female health professionals, which might limit the ability to generalise our results to other cohorts. However, we do not believe that the biological mechanisms linking migraine with cognitive decline would be different in our cohort compared with other populations. Since migraine was self reported, women may incorrectly report their migraine status. However, all participants were health professionals who are known to report health information accurately. Furthermore, validation studies have shown good agreement between self reported migraine and the *International Classification of Headache Disorders* I and II.[28 29] Although our study was not able to examine the impact of migraine on cognitive decline among men, potential effects of migraine on subsequent conditions, such as cognitive decline, are of particular interest in women because of the longer life expectancy among women.

Overall we did not observe a large amount of cognitive decline among our participants, possibly because of the age of the participants and the short follow-up period. Additionally, although the telephone interview for cognitive status does not seem to show a ceiling effect as strong as that seen for the mini-mental state examination,[35] it is possible that the women in our cohort may not have been declining enough for our "global score" to detect changes in cognitive status. However, other studies using this cohort have detected risk factors for cognitive decline, such as type 2 diabetes, longer duration of diabetes, educational status, and income,[33 36] which suggests that our study period was long enough to observe a meaningful cognitive decline. Given that the Baltimore Epidemiology Catchment Area Study had a much longer period of follow-up than our study (1993 to 2005) and also did not find evidence of worse decline among people who experience migraine further helps to ameliorate concerns that the women in our study may not have been followed for long enough to detect decline. Cognitive assessment was done several years after the start of the trial, so there could be possible bias due to loss to follow-up if women who experienced migraine were more likely to be lost to follow-up before the start of cognitive testing and had lower cognitive scores than women remaining in the cohort. However, only a small percentage of women (1.5%) were lost to follow-up between baseline and cognitive assessment[27] so any bias would be relatively small. We did have some loss to follow-up over the course of our study, but the percentage of women lost to follow-up in the migraine categories was similar to that among the women with no history of migraine. Finally, although this study is larger than many previous studies, we may not have

had enough participants in our migraine categories to detect small differences in cognitive decline among our groups.

Clinical implications

Results of this study do not suggest that women with migraine with or without aura or with a past history of migraine have an increased risk of cognitive decline. Based on the results from this study and from previous studies using a wide variety of cognitive tests and various approaches to assessing migraine status, migraine does not seem to lead to functional impairments of the brain. Based on these results, patients with migraine and their treating doctors should be reassured that migraine may not have long term consequences on cognitive function. We did observe greater rates of cognitive decline in the subgroup of women who experience migraine with aura and had a history of cardiovascular disease compared with women who experience migraine with aura and did not have history of cardiovascular disease. However, because of the multiple subgroup analyses, this result should be interpreted with caution and further research is warranted to determine whether the interplay of migraine and cardiovascular disease leads to faster cognitive decline, and whether preventive strategies can be applied.

Unanswered questions and future research

Migraine is a complex disease and has been linked with various comorbidities, such as stroke and other vascular disease events. However, the mechanisms underlying these associations are not fully understood. Evaluating the interrelations between migraine and other diseases remains an important research target to establish strategies to positively influence the course of disease and to optimise treatment strategies.

What is already known on this topic

Several cross sectional studies and a few prospective cohort studies have examined the association between migraine and cognition

Many of these studies were, however, small or unable to stratify the association by migraine aura status

What this study adds

Results from this large, prospective cohort study among women provide no evidence that women who experience migraine with aura or migraine without aura have greater rates of cognitive decline than women without a history of migraine

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Tables

Table 1| Baseline characteristics of 6349 women according to migraine status. Values are numbers (percentages) of women unless stated otherwise

Characteristic	No migraine history (n=5496)	Migraine With aura (n=195)	Migraine Without aura (n=248)	Past history of migraine (n=410)
Mean (SD) age at study randomization (years)	66.3 (4.1)	65.9 (3.9)	65.3 (3.6)	66.4 (4.13)
Mean age (SD) at baseline cognitive interview (years)	71.9 (4.1)	71.6 (3.9)	71.0 (3.5)	72.1 (4.1)
Body mass index:				
<25	2670 (48.6)	99 (50.8)	127 (51.2)	213 (52.0)
25-29.9	1860 (33.8)	70 (35.9)	83 (33.5)	136 (33.2)
≥30	833 (15.2)	21 (10.8)	34 (13.7)	54 (13.2)
History of hypertension	2188 (39.8)	75 (38.5)	91 (36.7)	192 (46.8)
Antihypertensive drug use	1230 (22.4)	40 (20.5)	56 (22.6)	100 (24.4)
History of high cholesterol levels	2346 (42.7)	98 (50.3)	110 (44.4)	117 (43.2)
Cholesterol lowering drug use	349 (6.4)	14 (7.2)	11 (4.4)	22 (5.4)
Oral contraceptive use	1860 (33.8)	79 (40.5)	84 (33.9)	160 (39.0)
Postmenopausal hormone use:				
Never	2258 (41.1)	48 (24.6)	84 (33.9)	143 (34.9)
Past	1055 (19.2)	43 (22.1)	46 (18.6)	91 (22.2)
Current	2175 (39.6)	104 (53.3)	118 (47.6)	174 (42.4)
Alcohol consumption:				
Rarely/never	2611 (47.5)	98 (50.3)	122 (49.2)	193 (47.1)
1-3 drinks/month	626 (11.4)	25 (12.8)	34 (13.7)	55 (13.4)
1-6 drinks/week	1569 (28.6)	50 (25.6)	76 (30.7)	110 (26.8)
≥1 drinks per day	686 (12.5)	22 (11.3)	16(6.5)	52 (12.7)
Vigorous physical activity:				
Rarely/never	2369 (43.1)	81 (41.5)	120 (48.4)	164 (40.0)
<1/week	887 (16.1)	37 (19.0)	43 (17.3)	72 (17.6)
1-3 times/week	1575 (28.7)	54 (27.7)	60 (24.2)	125 (30.5)
≥4 times/week	662 (12.1)	23 (11.8)	24 (9.7)	48 (11.7)
Smoking status:				
Never	2863 (52.1)	102 (52.3)	141 (56.9)	219 (53.4)
Former	2072 (37.7)	74 (38.0)	88 (35.5)	153 (37.3)
Current	556 (10.1)	19 (9.7)	18 (7.3)	38 (9.3)
Diabetes	202 (3.7)	3 (1.5)	5 (2.0)	10 (2.4)
Highest attained education:				
LPVN, associates degree, registered nurse	3598 (65.5)	130 (66.7)	173 (69.8)	295 (72.0)
Bachelor's degree or higher education	1810 (32.9)	65 (33.3)	70 (28.2)	114 (27.8)
Mean (SD) baseline telephone interview for cognitive status score	34.2 (2.7)	34.3 (2.6)	34.4 (2.5)	34.4 (2.6)
Mean (SD) baseline immediate EBMT	9.6 (1.6)	9.6 (1.6)	9.6 (1.5)	9.7 (1.7)
Mean (SD) baseline delayed EBMT	9.3 (1.8)	9.4 (1.7)	9.3 (1.6)	9.4 (1.7)
Mean (SD) baseline immediate 10 word list recall	4.8 (1.8)	4.9 (1.8)	4.9 (1.8)	5.0 (1.7)
Mean (SD) baseline delayed 10 word list recall	3.0 (2.1)	2.9 (1.9)	3.0 (2.1)	3.1 (2.0)
Mean (SD) baseline category fluency score	17.5 (4.9)	18.2 (5.1)	18.0 (5.0)	17.8 (5.0)

LPVN=licensed practical nurse/licensed vocational nurse; EBMT=east Boston memory test.

Numbers may not add up to 100% because of rounding or missing data.

Table 2| **Multivariable adjusted mean cognitive scores and standard errors at each follow-up assessment (about two years apart) by migraine status**

Cognitive tests at assessment points	No history of migraine		Migraine with aura		Migraine without aura		Past history of migraine		
	No of participants	Adjusted mean* (SE)	No of participants	Adjusted mean* (SE)	No of participants	Adjusted mean* (SE)	No of participants	Adjusted mean* (SE)	Overall P value
Global score†:									
First	5496	–0.02 (0.03)	195	0.01 (0.05)	248	–0.01 (0.05)	410	0.05 (0.04)	0.11
Second	4902	0.05 (0.04)	174	0.08 (0.06)	220	0.07 (0.06)	370	0.12 (0.05)	0.30
Third	4496	–0.02 (0.04)	167	0.08 (0.07)	202	0.04 (0.06)	337	0.03 (0.05)	0.15
Verbal score†:									
First	5496	–0.03 (0.03)	195	–0.02 (0.06)	248	–0.03 (0.05)	410	0.05 (0.05)	0.18
Second	4902	0.12 (0.04)	174	0.17 (0.07)	220	0.14 (0.06)	370	0.16 (0.05)	0.69
Third	4496	0.08 (0.04)	167	0.17 (0.07)	202	0.12 (0.07)	337	0.13 (0.06)	0.31
Telephone interview for cognitive status:									
First	5483	34.18 (0.13)	195	34.24 (0.23)	248	34.29 (0.21)	408	34.48 (0.18)	0.17
Second	4898	33.85 (0.14)	174	33.80 (0.25)	220	33.95 (0.24)	370	33.88 (0.20)	0.94
Third	4496	33.88 (0.16)	167	33.86 (0.27)	202	34.02 (0.26)	337	33.99 (0.22)	0.84
Category fluency test:									
First	5476	17.22 (0.24)	195	17.86 (0.42)	247	17.58 (0.39)	407	17.63 (0.33)	0.09
Second	4898	17.52 (0.27)	174	17.51 (0.47)	220	17.72 (0.44)	370	18.43 (0.37)	0.01
Third	4495	16.82 (0.28)	167	17.94 (0.48)	202	17.46 (0.45)	337	17.05 (0.39)	0.01

P values from analysis of covariance comparing no history of migraine, migraine with aura, migraine without aura, and past history of migraine.

*Adjusted for age, smoking status, alcohol consumption, body mass index, educational attainment, postmenopausal hormone use, history of high cholesterol levels, treatment for high cholesterol levels, history of hypertension, treatment for hypertension, diabetes, and past oral contraceptive use.

†Scores measured in standardised units.

Table 3| Age and multivariate adjusted associations between rate of change in cognitive function by migraine status

Migraine status and assessments	Global score*		Verbal score*		Telephone interview for cognitive status		Category fluency score	
	Coefficient (SE)	P value	Coefficient (SE)	P value	Coefficient (SE)	P value	Coefficient (SE)	P value
Age adjusted								
First assessment (reference)	—	—	—	—	—	—	—	—
Second assessment	0.07 (0.01)	<0.01	0.13 (0.01)	<0.01	–0.11 (0.04)	0.01	0.54 (0.07)	<0.01
Third assessment	0.02 (0.01)	0.06	0.10 (0.01)	<0.01	–0.12 (0.04)	0.01	0.03 (0.07)	0.70
No migraine (reference)	—	—	—	—	—	—	—	—
Migraine with aura:	0.03 (0.04)	0.47	0.01 (0.05)	0.83	0.05 (0.19)	0.80	0.65 (0.36)	0.07
Second assessment	–0.02 (0.05)	0.68	0.02 (0.05)	0.72	–0.12 (0.21)	0.58	–0.77 (0.39)	0.05
Third assessment	0.05 (0.05)	0.29	0.06 (0.06)	0.28	–0.11 (0.22)	0.61	0.36 (0.40)	0.37
Migraine without aura:	0.0045 (0.04)	0.90	–0.02 (0.04)	0.67	0.05 (0.16)	0.75	0.34 (0.32)	0.28
Second assessment	0.03 (0.04)	0.48	0.05 (0.05)	0.36	0.09 (0.19)	0.64	–0.12 (0.33)	0.71
Third assessment	0.08 (0.04)	0.09	0.08 (0.05)	0.15	0.26 (0.20)	0.19	0.28 (0.34)	0.41
Past history of migraine:	0.07 (0.03)	0.03	0.07 (0.03)	0.047	0.24 (0.13)	0.06	0.35 (0.25)	0.16
Second assessment	–0.0047 (0.03)	0.89	–0.03 (0.04)	0.46	–0.24 (0.16)	0.13	0.44 (0.29)	0.13
Third assessment	–0.01 (0.04)	0.74	–0.01 (0.04)	0.72	–0.13 (0.16)	0.42	–0.09 (0.27)	0.74
Multivariable adjusted†								
First assessment (reference)	—	—	—	—	—	—	—	—
Second assessment	0.07 (0.01)	<0.01	0.13 (0.01)	<0.01	–0.11 (0.04)	0.01	0.54 (0.07)	<0.01
Third assessment	0.02 (0.01)	0.07	0.09 (0.01)	<0.01	–0.12 (0.04)	0.01	0.02 (0.07)	0.77
No migraine (reference)	—	—	—	—	—	—	—	—
Migraine with aura:	0.03 (0.04)	0.49	0.01 (0.05)	0.85	0.04 (0.18)	0.83	0.65 (0.36)	0.07
Second assessment	–0.02 (0.05)	0.69	0.02 (0.05)	0.71	–0.11 (0.21)	0.59	–0.77 (0.39)	0.05
Third assessment	0.05 (0.05)	0.28	0.06 (0.06)	0.28	–0.11 (0.22)	0.62	0.37 (0.40)	0.36
Migraine without aura:	0.01 (0.04)	0.75	–0.01 (0.04)	0.77	0.07 (0.16)	0.65	0.36 (0.31)	0.24
Second assessment	0.03 (0.04)	0.48	0.05 (0.05)	0.35	0.09 (0.19)	0.64	–0.12 (0.33)	0.72
Third assessment	0.08 (0.04)	0.09	0.08 (0.05)	0.15	0.25 (0.20)	0.21	0.28 (0.34)	0.41
Past history of migraine:	0.08 (0.03)	0.01	0.08 (0.03)	0.03	0.29 (0.13)	0.02	0.42 (0.25)	0.09
Second assessment	–0.0047 (0.03)	0.89	–0.03 (0.04)	0.46	–0.24 (0.16)	0.13	0.44 (0.29)	0.13
Third assessment	–0.01 (0.04)	0.75	–0.01 (0.04)	0.72	–0.13 (0.16)	0.43	–0.09 (0.27)	0.75

Global score and category fluency do not control for treatment for high cholesterol levels owing to problems with model convergence. The coefficients shown are the results of the joint effects of migraine status and the respective follow-up time.

*Measured in standardised units.

†Adjusted for age, smoking status, alcohol consumption, body mass index, educational attainment, postmenopausal hormone use, history of high cholesterol levels, treatment for high cholesterol levels, history of hypertension, treatment for hypertension, diabetes, and past oral contraceptive use.

Table 4| **Multivariable adjusted* relative risk of substantial cognitive decline† by migraine status**

Cognitive test and migraine status	No of women	Relative risk of substantial decline (95% CI)	P value
Global score‡:			
No history of migraine	457	1.00	
Migraine with aura	12	1.09 (0.68 to 1.77)	0.64
Migraine without aura	15	0.77 (0.46 to 1.28)	0.21
Past history of migraine	36	1.17 (0.84 to 1.63)	0.29
Verbal score†:			
No history of migraine	458	1.00	
Migraine with aura	11	0.64 (0.34 to 1.20)	0.25
Migraine without aura	16	0.82 (0.48 to 1.38)	0.83
Past history of migraine	35	1.02 (0.71 to 1.48)	0.29
Telephone interview for cognitive status:			
No history of migraine	505	1.00	
Migraine with aura	20	0.70 (0.39 to 1.28)	0.38
Migraine without aura	17	0.77 (0.45 to 1.32)	0.58
Past history of migraine	44	1.05 (0.73 to 1.51)	0.26
Category fluency score:			
No history of migraine	423	1.00	
Migraine with aura	16	1.03 (0.61 to 1.74)	0.80
Migraine without aura	17	0.89 (0.54 to 1.48)	0.67
Past history of migraine	31	0.98 (0.67 to 1.44)	0.97

*Adjusted for age, smoking status, alcohol consumption, body mass index, educational attainment, postmenopausal hormone use, history of high cholesterol levels, treatment for high cholesterol levels, history of hypertension, treatment for hypertension, diabetes, past oral contraceptive use, and time from entry into the Women's Health Study to last interview.

†Substantial cognitive decline was defined as the worst 10% of the distribution of decline from the initial to the final cognitive assessment of the whole study cohort.

‡Measured in standardised units.

Figure
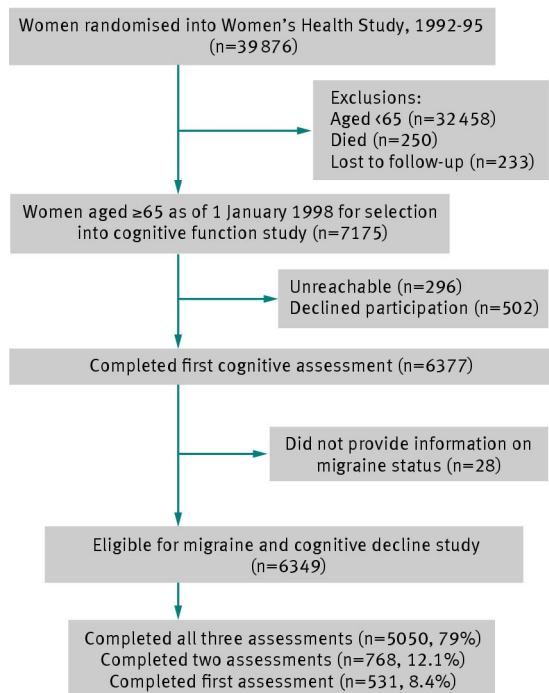
Flow chart of participation in migraine and cognitive decline study among women enrolled in the Women's Health Study