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Migraine with aura and risk of silent brain infarcts and white matter hyperintensities: an MRI study

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A small number of population-based studies reported an association between migraine with aura and risk of silent brain infarcts and white matter hyperintensities in females. We investigated these relations in a population-based sample of female twins. We contacted female twins ages 30–60 years identified through the population-based Danish Twin Registry. Based on questionnaire responses, twins were invited to participate in a telephone-based interview conducted by physicians. Headache diagnoses were established according to the International Headache Society criteria. Cases with migraine with aura, their co-twins, and unrelated migraine-free twins (controls) were invited to a brain magnetic resonance imaging scan performed at a single centre. Brain scans were assessed for the presence of infarcts, and white matter hyperintensities (visual rating scales and volumetric analyses) blinded to headache diagnoses. Comparisons were based on 172 cases, 34 co-twins, and 139 control subjects. Compared with control subjects, cases did not differ with regard to frequency of silent brain infarcts (four cases versus one control), periventricular white matter hyperintensity scores [adjusted mean difference (95% confidence interval): −0.1 (−0.5 to 0.2)] or deep white matter hyperintensity scores [adjusted mean difference (95% confidence interval): 0.1 (−0.8 to 1.1)] assessed by Scheltens' scale. Cases had a slightly higher total white matter hyperintensity volume compared with controls [adjusted mean difference (95% confidence interval): 0.17 (−0.08 to 0.41) cm^3] and a similar difference was present in analyses restricted to twin pairs discordant for migraine with aura [adjusted mean difference 0.21 (−0.20 to 0.63)], but these differences did not reach statistical significance. We found no evidence of an association between silent brain infarcts, white matter hyperintensities, and migraine with aura.

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Introduction

Migraine is a common disorder afflicting ∼10–15% of the population (Rasmussen *et al.*, 1991; Lipton *et al.*, 2001). About one-third of migraineurs experience transient neurological symptoms known as auras, which characterize a variant known as migraine with aura. Population-based studies indicate that migraine, and in particular migraine with aura, may be a risk factor for subclinical (silent) brain infarcts and white matter hyperintentisies (WMHs) (Kruit *et al.*, 2004, 2005; Scher *et al.*, 2009; Kurth *et al.*, 2011; Palm-Meinders *et al.*, 2012; Hamedani *et al.*, 2013; Monteith *et al.*, 2014). These findings caused considerable concern as WMHs have been associated with increased risk of stroke, dementia, and death (Debette and Markus, 2010) and furthermore, raised the question whether migraine, a condition so common as to be encountered by all physicians regardless of specialty, is a chronic progressive brain disorder (Lipton and Pan, 2004). Although the number of population-based studies assessing the association between migraine and risk of silent infarcts and WMH is relatively small and their results somewhat difficult to reconcile (Bashir *et al.*, 2013), most studies support the notion that migraine with aura, particularly in females, is associated with an increased risk of WMHs and silent infarcts. Motivated by these studies, we conducted a cross-sectional population-based study, which was nested within the population-based Danish Twin Registry and specifically targeted towards women with migraine with aura. We used established diagnostic headache criteria and state of the art neuroimaging techniques to clarify whether migraine with aura conveys an increased risk for silent infarcts and WMHs.

Materials and methods

Study population and assessment of headache diagnoses

We recruited subjects through the Danish Twin Registry, the oldest and most complete national twin registry worldwide (Skytthe *et al.*, 2006). We identified female twins born 1931 to 1982 who, based on earlier responses to a previously used questionnaire (Gaist *et al.*, 2005), were classified as: screen positive for migraine with aura, co-twins to females screen positive for migraine with aura, or screen negative for migraine of any type. We enrolled females from these three groups in our study by a two-step procedure. First, the twins received a brief questionnaire on health and lifestyle issues (sent out in waves from February 2011 to April 2014). Non-responders received one reminder. Second, we invited eligible questionnaire responders to participate in a semi-structured phone interview conducted by five trained physicians and focused on headache history. Based on interview responses, each subject's headaches were classified according to the International Classification of Headache Disorders, 3rd edition beta version (ICHD-3beta; Headache Classification Committee of the International Headache Society, 2013). Twins with definite migraine with aura and their co-twins were invited to participate, if eligible according to study criteria (Supplementary Table 1). We only recruited potential controls among screen negative twins that were also classified as non-migraineurs according to the telephone interview with a single exception (a twin originally classified as co-twin to a sister with migraine with aura, where interview revealed that neither of the twins had ever suffered from any form of migraine). Any information revealing an exclusion criterion (Supplementary Table 1) led to exclusion at any stage of the study. Eligible subjects were invited to participate in the MRI part of the study at the Danish Research Centre for Magnetic Resonance, Copenhagen University Hospital Hvidovre. Subjects received no financial reward for participating.

We did not match controls to cases based on age. To achieve a balanced age distribution in cases and controls, we assessed the age of potential participants within 5-year age strata twice during the recruitment period. If a control:case ratio of ≥1 was achieved within an age-stratum, no further controls within this age-group were invited to participate. This only resulted in a small number of potential controls not being included in the study (Fig. 1). Thus, control recruitment was based solely on the stratum-specific numbers of cases and occurred independent of the MRI scan results. Finally, four eligible cases identified at the end of the study period were not included owing to a sufficient number of participating cases.

MRI

All participants underwent whole-brain MRI using the same 3.0 T MR scanner (Siemens Verio).

Image preprocessing

T_2-weighted images of the whole brain were obtained using a 3D turbo spin echo sequence (repetition time = 3200 ms, echo time = 409 ms, matrix = 256 × 256, 176 sagittal slices with no gap, $1.0 × 1.0 × 1.0$ mm^3 isotropic voxels). FLAIR images of

Twins contacted based on their response to questionnaire items on migraine in 2002

SCREENING POSITIVE FOR MA	SCREENING NEGATIVE FOR MA-- CO-TWIN SCREENING POSITIVE	SCREENING NEGATIVE FOR MIGRAINE
(n = 782; both twins in 63 pairs)	(n = 332)	(n = 1124)

Response to questionnaire in present study

Responders (n = 612) Non-responders (n = 170)
Responders (n = 224) Non-responders (n = 108)
Responders (n = 858) Non-responders (n = 266)

Participated in phone interview

No, not interviewed (n = 172)
No, not interviewed (n = 113)
No, not interviewed (n = 476)

Yes, interviewed (n = 440)
Yes, interviewed (n = 111)
Yes, interviewed (n = 382)

History of CVD (n = 20)
History of CVD (n = 2)
History of CVD (n = 5)

No history of CVD (n = 420)
No history of CVD (n = 109)
No history of CVD (n = 377)

Headache criteria for study group fulfilled

No, excluded (n = 174)
No, excluded (n = 5)
No, excluded (n = 55)

No, reclassified (n = 9)
9 co twin

No, reclassified (n = 26)
25 to MA definite
1 to control[a]

No, reclassified (n = 24)
21 to MA definite
3 to co-twin

Yes, potential case (n = 283)
Yes, potential co-twin (n = 90)
Yes, control (n = 299)

Invited to MRI

No (n = 93)
20 MRI not possible
15 fulfilled other exclusion criteria
4 eligible, but not included (sufficient number of participants)
2 unreachable
52 eligible, did not wish to participate

No (n = 51)
5 MRI not possible
3 fulfilled other exclusion criteria
34 other twin not eligible/participating
9 eligible, did not wish to participate

No (n = 147)
23 MRI not possible
10 fulfilled other exclusion criteria
38 eligible, but not included (sufficient number of participants)
3 erroneously excluded
10 unreachable
63 eligible, did not wish to participate

Yes (n = 190)
Yes (n = 39)
Yes (n = 152)

14 claustrophobia
1 motion distortion
3 abnormal findings

3 claustrophobia
1 missing data
1 non participation of case twin

5 claustrophobia
4 motion distortion
3 abnormal findings
1 missing data

Included in study
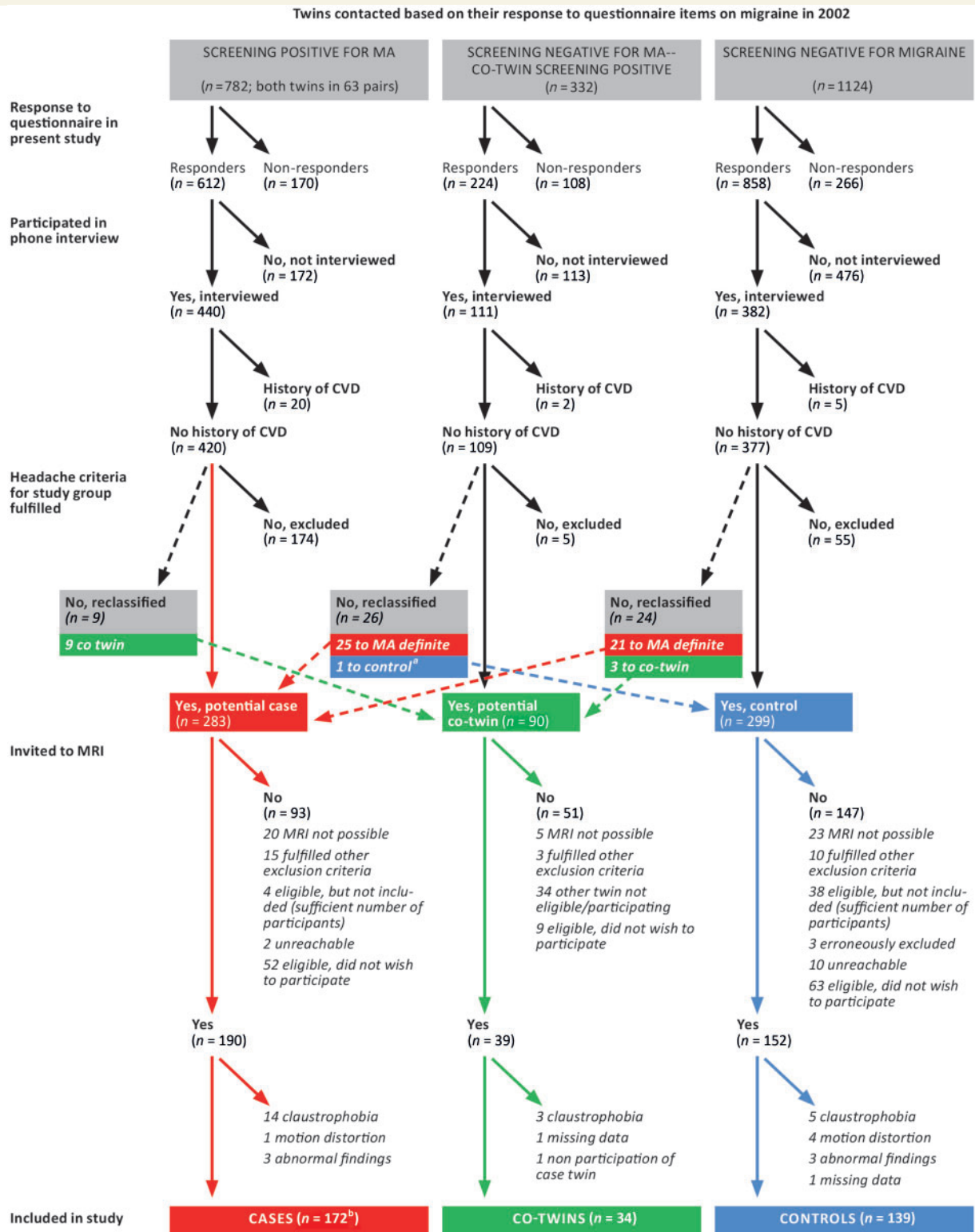
CASES (n = 172[b])
CO-TWINS (n = 34)
CONTROLS (n = 139)

Figure 1 Flow-chart of recruitment and participation in Women with Migraine with Aura Neuroimaging (WOMAN) study.
CVD = cerebrovascular disorder; MA = migraine with aura.
[a]No migraine in twin or co-twin.
[b]Includes 20 case-case twin pairs.

the whole brain were obtained using a 3D turbo inversion recovery sequence (repetition time = 5000 ms, echo time = 395 ms, inversion time = 1800 ms, matrix = 256 × 256, 176 sagittal slices with no gap, $1.0 \times 1.0 \times 1.0$ mm³ isotropic voxels).

Images were preprocessed using pipelines implemented in Matlab SPM8 (Wellcome Department of Cognitive Neurology, University College London, UK) routines to obtain anatomical point correspondence between images. For WMH delineation the FLAIR images were co-registered to the T₂-weighted image using a six-parameter rigid transformation and both images were then resliced to $1 \times 1 \times 1$ mm³ resolution.

Image assessment

All images were assessed by a consultant radiologist with experience in neuroradiology who was blinded to headache diagnoses and clinical data. A brain infarct was defined as a non-mass parenchymal defect, with a vascular distribution, isointense to CSF signal on all sequences and a hyperintense rim on FLAIR images. Number, location, and size of infarcts were recorded. White matter hyperintensities were defined as clearly hyperintense areas relative to surrounding white matter on both FLAIR and T₂-weighted images and identified by simultaneous inspection of both aligned images. We used three measures to assess WMH burden. First, we graded WMHs according to a modified version of Fazekas visual score [0 (no WMH), 1, 2, and 3] (Pantoni *et al.*, 2005). Second, we applied a slightly modified version of Scheltens' semiquantitative scale (Scheltens *et al.*, 1993; Kruit *et al.*, 2004). Periventricular WMHs were assessed in three regions (frontal and posterior horns and bands) and rated as 0 (no periventricular WMH); 1 (pencil-thin lining); 2 (smooth halo or thick lining); or 3 (large confluent lesions). The three regional scores were summed up to a total score (range, 0–9). Deep WMHs were rated by lobe location, number, and size, as measured with a calliper in the JIM image analysis package on the FLAIR image and summed to a final score (range, 0–24). Third, local thresholding was applied and WMH volumes for the whole brain were quantified semi-automatically using the JIM image analysis package, Version 6.0, (Xinapse Systems Ltd., Northants, UK, www.xinapse.com) and FSLUTILS (Smith *et al.*, 2004), Version 5.0.5. For all measures, visual identification was carried out by a single trained rater.

Potential confounders

Information on potential confounders and other covariates was collected through the initial postal questionnaire, the telephone interview, and a second brief questionnaire the twins completed on the day of their brain scan. Information on the twins' zygosity—classified as monozygotic, dizygotic same sex, and dizygotic opposite sex—was provided by the Danish Twin Registry (Skytthe *et al.*, 2006).

Education level was categorized into 'low' in females who reported <12 years of schooling and <3 years of vocational training. Other sociodemographic characteristics were likewise dichotomized [residency in capital and environs (Greater Copenhagen), cohabitation, currently employed]. Smoking history was defined as 'ever' or 'never'. For ever smokers we also calculated pack-years of exposure. The number of alcoholic drinks per week was classified as follows: 0, 1–4, 5–9, and 10 + . Ever use and number of years of oral contraceptive use were recorded.

On the day of the brain scan we recorded the twins' height and weight, their blood pressure (measured in the upper arm before and after the MRI), and withdrew a blood sample to determine cholesterol and glycated haemoglobin values. The height and weight were used to calculate body mass index (BMI; weight in kilograms divided by the square of height in metres). The lowest of the two blood pressure measures was used. Hypertension was defined as systolic blood pressure of ⩾160 mmHg or a diastolic blood pressure of ⩾95 mmHg, or current use of antihypertensive drugs. Diabetes was defined as self-reported physician diagnosed diabetes, or a measurement of glycated haemoglobin of 44 mmol/mol (6.5%) or higher. Twins were classified as having a history of coronary artery disease if they reported a history of physician diagnosed angina or myocardial infarction.

Sample size calculations

We made the same assumptions regarding the prevalence of WMHs (20%) and silent brain infarcts (5%) in controls as a previous study (Kruit *et al.*, 2004). We aimed to include at least 130 cases and 130 control subjects in our study, which would provide us with 90% power to detect an odds ratio of 2.5 or greater for WMHs and an odds ratio of 4.0 or greater for silent brain infarcts (two-tailed test, alpha 0.05).

Statistical analyses

To assess the influence of non-participation in the present study, we compared means and distributions of characteristics in postal questionnaire and interview participants and non-participants. In these, and all other analyses, the inference was adjusted for cluster effects within twin pairs (robust estimation of variance).

Individual-based analyses

We used χ^2 and *t*-test to compare distributions. Using linear regression, we assessed the difference in periventricular WMH, and deep WMH scores, and WMH volume in females with migraine with aura compared with migraine-free control subjects. Regression analyses were adjusted for age, smoking, alcohol use, and hypertension (Model 1), and residency in Greater Copenhagen, education level, BMI, cholesterol level, and ever use of oral contraceptives (Model 2). To not overlook non-linear relationships between WMH volume and migraine with aura, we also performed quintile regression of WMH volume.

To explore potential effect measure modification, we performed analyses stratified by age (dichotomized according to median age of subjects), life time number of migraine with aura attacks (<10, 10–49, 50–100, >100), and active migraine with aura (migraine with aura attacks reported in the 12 months preceding the interview).

Within-pair analyses

In twin pairs discordant for migraine with aura we calculated the difference in periventricular WMH and deep WMH scores and WMH volume within each twin pair. We also assessed the difference in MRI changes using multivariate linear regression as described above (Models 1 and 2), although in analyses stratified by zygosity we only adjusted for the factors corresponding to Model 1 due to small sample sizes.

Table 1 Characteristics of study participants

Characteristic	Cases n = 172	Controls n = 139	P-value[a]	Co-twins n = 34	P-value[b]
Age at time of MRI scan, years	48.1 ± 6.6	47.8 ± 7.9	0.8	49.7 ± 5.6	0.07
Zygosity, n (%)					
Monozygotic	71 (41.3)	55 (39.6)		17 (50.0)	
Dizygotic, same sex	67 (39.0)	49 (35.3)		17 (50.0)	
Dizygotic, opposite sex	34 (19.8)	35 (25.2)	0.5	NA	
Residency in Greater Copenhagen, n (%)	65 (37.8)	59 (42.5)	0.4	10 (29.4)	0.3
Married or cohabiting, n (%)	139 (80.8)	103 (74.1)	0.2	30 (88.2)	0.3
Currently employed[c], n (%)	149 (86.6)	121 (87.1)	0.9	29 (85.3)	0.8
Low education level[d], n (%)	56 (32.6)	34 (24.5)	0.1	12 (35.3)	0.7
Smoker, ever, n (%)	84 (48.8)	69 (49.6)	0.9	14 (41.2)	0.4
Smoker, pack-years[e]	11.8 ± 11.6	11.7 ± 11.7	0.9	12.9 ± 9.0	0.7
Alcohol, drinks per week, n (%)					
0	38 (22.1)	15 (10.8)		9 (26.5)	
1–4	93 (54.1)	71 (51.1)		12 (35.3)	
5–9	32 (18.6)	34 (24.5)		10 (29.4)	
10 +	9 (5.2)	19 (13.7)	0.007	3 (8.8)	0.2
BMI[f,g]	24.8 ± 4.2	24.7 ± 4.4	0.8	25.2 ± 5.1	0.7
Blood pressure[g,h] mmHg					
Systolic	134.1 ± 17.1	133.0 ± 18.1	0.6	138.12 ± 18.6	0.2
Diastolic	85.4 ± 11.6	84.0 ± 11.8	0.3	85.9 ± 11.7	0.8
Total cholesterol[g], mmol/l	5.2 ± 1.0	5.1 ± 1.0	0.7	5.0 ± 1.0	0.4
LDL-cholesterol[g,i], mmol/l	2.8 ± 0.8	2.8 ± 0.8	0.6	2.8 ± 0.8	0.9
Glycated haemoglobin[g], mmol/mol	34.9 ± 3.6	35.6 ± 4.4	0.2	34.9 ± 3.9	0.9
Hypertension[j], n (%)	56 (32.6)	31 (22.3)	0.047	12 (35.3)	0.7
Diabetes[k], n (%)	1 (0.6)	3 (2.6)	–	0	–
Coronary artery disease[l], n (%)	3 (1.7)	1 (0.7)	–	0	–
Oral contraceptive use[m]					
Ever use, n (%)	144 (85.2)	114 (82.6)	0.5	29 (87.9)	0.7
Years of use	11.3 ± 8.4	11.3 ± 8.5	0.9	11.1 ± 8.7	0.9

Plus minus values are means ± standard deviation.

[a]Cases versus controls. χ^2 for proportions and t-test for means. The inference was adjusted for twin pair cluster effects.

[b]Cases versus co-twins. χ^2 or Fisher's exact test for proportions and t-test for means. The inference was adjusted for twin pair cluster effects.

[c]Women on maternity leave from full or part-time employment included as employed.

[d]Education level was defined as low in females with <12 years of schooling and <3 years of vocational training.

[e]Only current or past smoker included. Data on pack-years of smoking were missing for five cases and three controls.

[f]BMI, the weight in kg divided by the square of the height in meters.

[g]Measured on the day the MRI was performed.

[h]Data on systolic and diastolic blood pressure missing for five controls.

[i]Low density lipoprotein. Not measured in three cases due to high triglyceride level (>4 mmol/l).

[j]Hypertension was defined as systolic blood pressure of ⩾160 mmHg, or diastolic blood pressure of ⩾95 mmHg, or current use of antihypertensive drugs for hypertension.

[k]Diabetes was defined as self-reported physician diagnosed diabetes in postal questionnaire, or glycated haemoglobin of 44 mmol/mol (6.5%) or higher.

[l]Self-reported physician diagnosed angina pectoris or myocardial infarct in postal questionnaire.

[m]Self-reported in postal questionnaire. Data on ever use of oral contraceptive use were missing on three cases, one co-twin, and one control. Data on number of years of oral contraceptive use were missing in seven cases, two co-twins, and four controls.

All analyses were performed using Stata SE 14 (StataCorp, College Station, TX, USA).

The study was approved by the Ethics Committee of the Region of Southern Denmark and the Danish Data Protection Agency. Written informed consent was obtained from all participants. The study is registered at clinicaltrials.gov (NCT02047695).

Results

We posted questionnaires to 2238 twins. Based on their responses, we excluded 761 of 1694 twins who returned the questionnaire (Fig. 1). The remaining 933 twins were telephone interviewed. After the telephone interview we excluded 27 of these twins due to a history of cerebrovascular episodes, which in all but one twin had been symptomatic. A further 524 twins were excluded because they did not fulfil the headache criteria, fulfilled an exclusion criterion, or did not wish to participate. Reasons for exclusion at the various stages of the study are presented in Supplementary Fig. 1. Responders to the questionnaire lived more frequently in the Greater Copenhagen area than non-responders. Also, among screen negative twins, responders were older than non-responders (Supplementary Table 2). Based on questionnaire responses we excluded 761 twins (Fig. 1). Eligible twins not participating in the interview

were similar to participating twins for a range of characteristics, but had received fewer years of schooling and vocational education (Supplementary Table 3). Among screen negative co-twins, interview non-participants were more frequently current smokers, reported migraine or migraine with aura less frequently, and had fewer headache days in the past year, compared with participants (Supplementary Table 3). Non-participating screen negative twins reported a lower consumption of alcohol, compared with participating twins from the same group. Eligible twins that declined the brain scan invitation (or could not be reached) were similar with twins that accepted the invitation with regard to a range of characteristics; however, non-participating controls had received fewer years of schooling and were less frequently diagnosed with tension-type headache compared with controls who accepted the scan invitation (Supplementary Table 4).

In all, 190 cases, 39 co-twins, and 152 control subjects attended a study visit for a brain scan. Thirty-five of these twins were excluded due to scan-related issues, i.e. claustrophobia (*n* = 22), technical problems (*n* = 7), or abnormal findings (demyelinating lesions: two cases and two controls; glioma: one control; large arachnoid cyst: one case) (Fig. 1). A co-twin of a twin-sister who had been excluded during this final process was also excluded. Hence, the present MRI study was based on 172 cases, 34 co-twins, and 139 controls. On average, cases were scanned 8 months and controls 5.5 months after completing the baseline questionnaire. Similar small differences were present for time from interview on headache history to brain scan (cases: mean 6.1 months; controls: 3.7 months).

Cases were similar to their co-twins and the unrelated controls with regard to demographic characteristics and risk factors, although cases reported lower weekly alcohol consumption than controls (Table 1). Also, 32.6% of cases were classified as hypertensive, compared with 22.3% of controls (*P* = 0.047). Headache characteristics of cases did not vary substantially by pairwise participation (Supplementary Table 5).

Silent brain infarcts were present in four cases of which two infarcts were located below the tentorium. One control subject's scan showed a silent supratentorial infarct. The frequency of silent infarcts did not differ significantly between the case and control group (*P* = 0.29). An additional sub-analysis of twin pairs discordant for migraine with aura showed also no difference in frequency of silent infarcts, but this result was based on infarcts in one case and one co-twin from different pairs.

The WMH rating in cases was similar to that of controls according to evaluations by Fazekas score (Fig. 2) and Scheltens' score (Fig. 2 and Table 2). Adjusting for potential confounders had little impact on the Scheltens' scale evaluations with regard to periventricular WMH scores {adjusted mean difference [95% confidence interval (CI): −0.1 (−0.5 to 0.2)}, or deep WMH scores [adjusted mean difference (95% CI): 0.1 (−0.8 to 1.1)]. Cases had a slightly higher total volume of WMHs compared with

controls [adjusted mean difference (95% CI): 0.17 (−0.08 to 0.41)]. The results on WMHs remained largely unchanged in analyses stratified by median age, number of lifetime migraine with aura attacks, and active migraine (attacks within prior year) (Supplementary Table 6). Furthermore, quantile regression also was consistent with the presented results for total volume of WMHs.

In analyses restricted to discordant twin pairs, females with migraine with aura had slightly higher visual rating scale scores than their co-twins (Fig. 3). These differences were, however, similar to the results of the case-control analyses for both periventricular WMH [adjusted mean
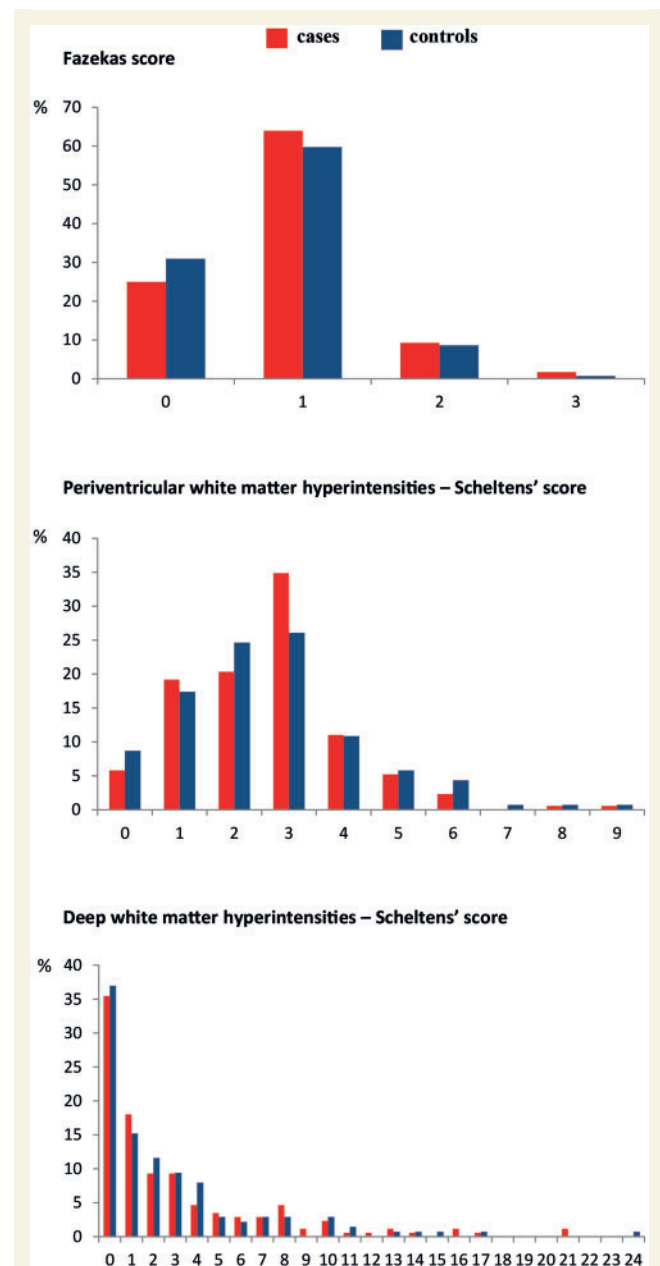

Figure 2 White matter hyperintensity scores assessed by visual rating scales in 172 females with migraine with aura (cases) and 139 migraine-free female control subjects.

difference (95% CI): 0.6 (−0.09 to 1.3)] and deep WMH scores [adjusted mean difference (95% CI): 0.4 (−1.0 to 1.8)]. This was also true of the within pair differences in volumetric scores [adjusted mean difference (95% CI): 0.21 (−0.20 to 0.63) cm³]. These differences were, with a single exception (adjusted mean difference in periventricular WMH score), further diminished in analyses stratified by zygosity (Table 2).

Discussion

In this large population-based study of female twins, migraine with aura did not increase the risk of silent infarcts overall or of infarcts in the posterior circulation territory. The burden of deep WMHs, periventricular WMHs, and overall WMHs did not significantly differ in migraineurs compared with non-migraineurs in case-control analyses, or in intra-pair analyses in twin pairs discordant for migraine with aura.

Only few population-based studies have examined the relationship between migraine with aura and silent infarcts or WMHs (Kruit *et al.*, 2006; Scher *et al.*, 2009; Kurth *et al.*, 2011; Palm-Meinders *et al.*, 2012; Hamedani *et al.*, 2013). In the CAMERA study, migraine with aura was associated with a strikingly increased risk of silent infarcts in the posterior circulation territory [odds ratio (OR) 13.7,
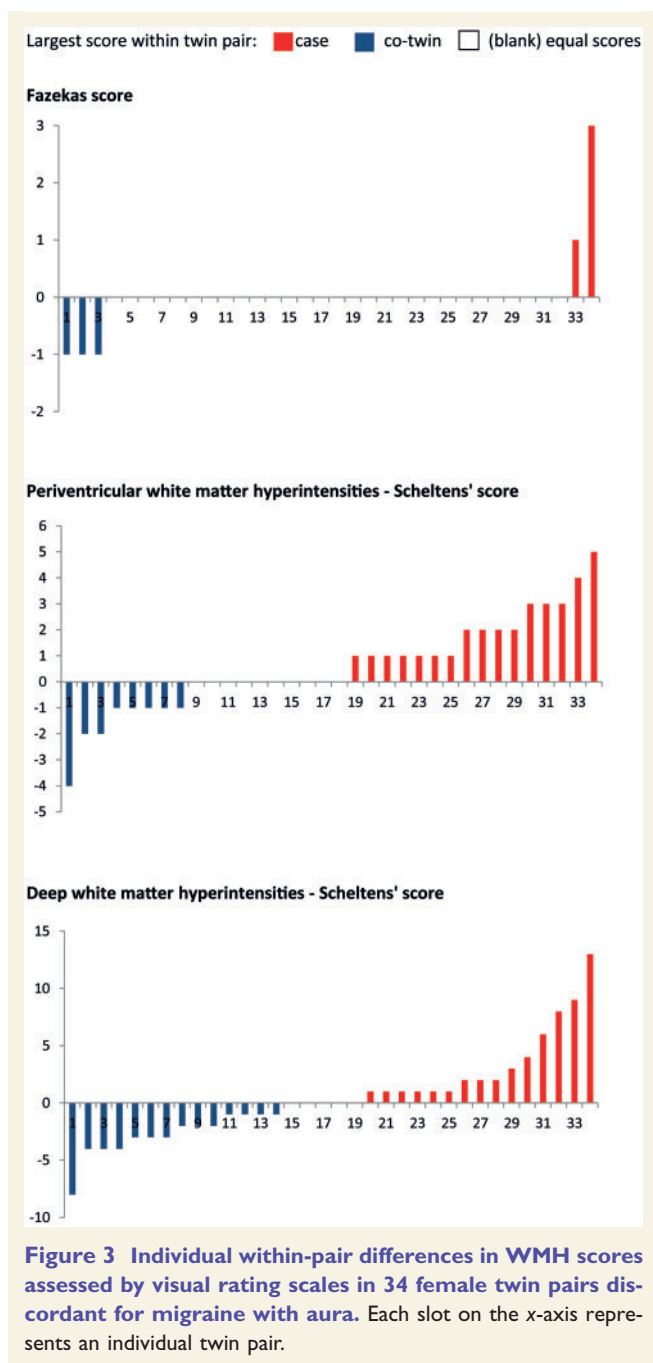
95% CI 1.7–112], particularly in the cerebellum (Kruit *et al.*, 2005), and in females, an increased risk of a load of deep WMHs (OR 2.0, 95% CI 1.0–4.3), compared with non-migraineur controls (Kruit *et al.*, 2004). In a study in Iceland with subjects with headache histories collected at midlife and brain scans performed at late life, a history of migraine with aura increased the risk of silent infarct-like lesions in the cerebellum in females with migraine with aura (OR 1.9, 95%CI 1.4–2.6) (Scher *et al.*, 2009). Two other studies reported an increased prevalence of silent infarcts in migraine with aura subjects, but located outside the cerebellum (Kurth *et al.*, 2011; Monteith *et al.*, 2014), and in one of these studies no association between migraine with aura and WMHs was found (Monteith *et al.*, 2014). A recent meta-analysis of population-based studies showed an association between WMHs and migraine with aura, but not for migraine without aura (Bashir *et al.*, 2013). The association of infarct-like lesions was greater for migraine with aura than for migraine without aura, but no association was found for migraine with aura and migraine without aura compared to controls. Only two studies performed repeat MRI assessments of participants at baseline and after follow-up. In a 9-year follow-up of CAMERA participants, migraine was not associated with incident infarct lesions and an increase in deep WMH burden was only seen in females with migraine without aura, but not in subjects with migraine with aura (Palm-Meinders *et al.*,

Table 2 White matter hyperintensities in Danish female twins by migraine with aura diagnosis

WMH measures	Migraine with aura	No migraine with aura	Difference (95% CI)	Adjusted[a] difference (95% CI)	
				Model 1	Model 2
Cases versus unrelated controls	*n* = 172	*n* = 139			
Scheltens' score[b], mean ± SE					
Periventricular WMH	2.6 ± 0.1	2.6 ± 0.1	−0.02 (−0.4 to 0.3)	−0.1 (−0.5 to 0.3)	−0.1 (−0.5 to 0.2)
Deep WMH	3.0 ± 0.3	2.7 ± 0.3	0.2 (−0.7 to 1.2)	0.1 (−0.8 to 1.0)	0.1 (−0.8 to 1.1)
WMH volume, cm³, mean ± SE	0.39 ± 0.09	0.22 ± 0.06	0.18 (−0.05 to 0.40)	0.16 (−0.08 to 0.40)	0.17 (−0.08 to 0.41)
Twin pairs discordant for migraine with aura					
Monozygotic and dizygotic twins	*n* = 34	*n* = 34			
Scheltens' score, mean ± SE					
Periventricular WMH	2.4 ± 0.3	1.8 ± 0.2	0.6 (−0.05 to 1.2)	0.6 (−0.08 to 1.2)	0.6 (−0.09 to 1.3)
Deep WMH	3.3 ± 0.7	2.8 ± 0.5	0.5 (−1.0 to 1.9)	0.4 (−1.0 to 1.7)	0.4 (−1.0 to 1.8)
WMH volume, cm³, mean ± SE	0.44 ± 0.3	0.16 ± 0.06	0.29 (−0.26 to 0.83)	0.19 (−0.19 to 0.57)	0.21 (−0.20 to 0.63)
Monozygotic twins	*n* = 17	*n* = 17			
Scheltens' score, mean ± SE					
Periventricular WMH	2.1 ± 0.3	1.4 ± 0.2	0.8 (−0.09 to 1.6)	0.8 (−0.1 to 1.7)	NA
Deep WMH	3.1 ± 0.9	2.9 ± 0.8	0.2 (−1.8 to 2.2)	0.02 (−2.3 to 2.4)	NA
WMH volume, cm³, mean ± SE	0.16 ± 0.05	0.15 ± 0.06	0.01 (−0.11 to 0.13)	0.003 (−0.15 to 0.15)	NA
Dizygotic twins	*n* = 17	*n* = 17			
Scheltens' score, mean ± SE					
Periventricular WMH	2.7 ± 0.4	2.3 ± 0.4	0.4 (−0.6 to 1.5)	−0.2 (−1.4 to 0.9)	NA
Deep WMH	3.4 ± 1.0	2.7 ± 0.8	0.7 (−1.6 to 3.0)	−0.8 (−2.9 to 1.3)	NA
WMH volume, cm³, mean ± SE	0.73 ± 0.5	0.17 ± 0.1	0.56 (−0.58 to 1.70)	0.06 (−0.51 to 0.64)	NA

[a]Adjusted for age, smoking, alcohol use, and hypertension (Model 1), and residency, education level, body mass index, cholesterol level, and ever use of oral contraceptives (Model 2). The inference was adjusted for twin pair cluster effects in case-control analyses.
[b]One control not included due to imaging quality issues.

Figure 3 Individual within-pair differences in WMH scores assessed by visual rating scales in 34 female twin pairs discordant for migraine with aura. Each slot on the x-axis represents an individual twin pair.

2012). Another longitudinal study with MRI assessments 8–12 years apart also reported no association between migraine and WMH progression over time (Hamedani *et al.*, 2013). Our results are at odds with several of the cross-sectional studies mentioned above, which may, at least to some extent, be due to methodological issues. We note, however, that our results are in line with the only two studies that were able to evaluate incident structural brain changes in migraineurs (Palm-Meinders *et al.*, 2012; Hamedani *et al.*, 2013).

Contrary to previous studies investigating mixed migraine populations (migraine without aura and migraine with aura patients), the present study was designed to test specific *a priori* hypotheses in a female migraine with aura population. Other study strengths include that we used the population-based Danish Twin Register, which enabled us to identify a large number of well-characterized females with migraine with aura and suitable controls. Also, we were able to exploit the use of twins in analyses restricted to twin pairs discordant for migraine with aura, an approach that strongly reduced or eliminated potential confounding effects of genes and common environment. Headache status was established through telephone interview with physicians according to internationally acknowledged criteria and all subjects were scanned using the same MRI scanner at a single centre.

Our study also had some potential limitations. First, the cross-sectional nature of our study does not allow us to draw conclusions on the sequence of events, e.g. whether migraine with aura onset predated the occurrence of WMHs. As we found no convincing effect of migraine on silent infarcts or WMHs, we believe that this is a minor drawback. Second, non-participation could result in selection bias. However, our analyses comparing participants and non-participants with regard to a number of characteristics, including known risk factors for infarcts and WMHs, indicate no major selection biases. Third, we excluded potential participants with a history of particular disorders, e.g. cluster headache, CNS disorders other than migraine, or cancer. Given the relative rarity of these disorders, we believe that our exclusion criteria only had a minor influence on the generalizability of our results to other populations. Fourth, our use of twins could, in theory, result in non-generalizability, e.g. due to differences in intrauterine and family environments in twins, compared with singletons. A single MRI study of healthy adults found no significant differences between twins and their singleton siblings with regard to overall brain volume, or, after adjustment for intracranial volume, with regard to white and grey matter volume (Hulshoff Pol *et al.*, 2002). A more recent larger study of twins aged 4 to 19 years found no difference in volumetric brain measures in twins compared with unrelated singletons (Ordaz *et al.*, 2010). Also, the prevalence and characteristics of migraine in Danish adult twins does not vary from that of the background population (Ulrich *et al.*, 1999; Gaist *et al.*, 2005). We argue therefore that our findings can be generalized to non-twin populations.

Our study is observational and we can therefore not rule out that unmeasured or insufficiently measured confounders may have influenced our results. With this caveat in mind, we conclude that the present results do not support the notion that female patients suffering from migraine have more silent infarcts and WMHs than females without this headache disorder.

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Supplementary material

Supplementary material is available at *Brain* online.

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