Original Article

Cephalalgia
An International Journal of Headache

International Headache Society

The retinal microcirculation in migraine: The Rotterdam Study

Cephalalgia
2018, Vol. 38(4) 736–743

DOI: 10.1177/0333102417708774
journals.sagepub.com/home/cep

SAGE

Ke-xin Wen[1], Unal Mutlu[1,2], M Kamran Ikram[1,3], Maryam Kavousi[1], Caroline CW Klaver[1,2], Henning Tiemeier[1,4], Oscar H Franco[1] and M Arfan Ikram[1,3,5]

Abstract

Background: To explore the role of microvascular pathology in migraine, we investigated the association between migraine and retinal microvascular damage.

Methods: We included 3270 participants (age $\geq$ 45 years, 63% women) from the population-based Rotterdam Study (2006–2009). Participants with migraine were identified using a validated questionnaire based on ICHD-II criteria (n = 562). Retinopathy signs were graded on fundus photographs. Retinal arteriolar and venular caliber were measured by semi-automatic assessment of fundus photographs. Associations of migraine with retinopathy and retinal microvascular calibers were examined using logistic and linear regression models, respectively, adjusting for age, sex, and cardiovascular risk factors.

Results: Migraine was not associated with the presence of retinopathy (odds ratio (OR): 1.09, 95% confidence interval (CI) 0.62; 1.92). In the fully adjusted model, adjusting for the companion vessel, persons with migraine did not differ in retinal arteriolar or venular caliber compared to persons without migraine (mean difference in standardized arteriolar caliber −0.05 (95%CI −0.13; 0.03); in standardized venular caliber −0.00 (95%CI −0.09; 0.08)). Migraine subtypes, including migraine with aura, were also not associated with retinal microvascular damage.

Conclusions: Our findings suggest that migraine is not associated with retinopathy or difference in retinal microvascular caliber. Further studies are needed to confirm these results.

Keywords

Epidemiology, cohort studies, headache, microvascular disease, retinopathy, retinal microvascular caliber

Date received: 7 November 2016; revised: 23 February 2017; 29 March 2017; accepted: 31 March 2017

Introduction

Migraine is a chronically recurring headache disorder that affects up to 14% of adults in Europe (1). Despite the high individual and societal burden of migraine, the exact pathogenesis remains elusive. Migraine has been shown to have a substantial vascular component. It is associated with an increased risk of cerebrovascular disease such as stroke (2–4) and markers of cerebrovascular damage such as white matter lesions (5). It has also been identified as a risk factor for coronary heart disease (2). Large vessel disease biomarkers such as atherosclerosis are linked to cerebrovascular disease (6,7) and have been extensively studied in migraine (8–10), but have not yet elucidated common mechanisms. Increasing evidence shows that microvascular pathology also contributes to stroke and coronary heart disease (11,12). In parallel, microvascular damage has also been implicated in the development of migraine (13) and may provide an important insight into mechanisms of migraine. Microvascular damage visible on retinal vascular imaging, including retinal vessel

[1]Department of Epidemiology, Erasmus MC University Medical Center, Rotterdam, The Netherlands
[2]Department of Opthalmology, Erasmus MC University Medical Center, Rotterdam, The Netherlands
[3]Department of Neurology, Erasmus MC University Medical Center, Rotterdam, The Netherlands
[4]Department of Psychiatry, Erasmus MC University Medical Center, Rotterdam, The Netherlands
[5]Department of Radiology, Erasmus MC University Medical Center, Rotterdam, The Netherlands

Corresponding author:
M Arfan Ikram, Department of Epidemiology, Erasmus MC University Medical Center PO Box 2040, 3000 CA Rotterdam, The Netherlands.
Email: m.a.ikram@erasmusmc.nl

diameter and retinopathy signs, has been demonstrated as a useful marker for studying the microcirculation in cerebrovascular diseases (14). However, only a few studies have examined the link between migraine and retinal markers of microvascular damage (15,16), and the nature of the association remains uncertain. Therefore, in a large population-based cohort study, we investigated the status of the retinal microvascular circulation, as represented by retinopathy signs and retinal vessel diameter, in persons with migraine.

Methods

Settings and study population

This study was based in the Rotterdam Study, a prospective population-based cohort among the middle-aged and elderly inhabitants of the district of Ommoord in Rotterdam, The Netherlands (17). We included participants from the third cohort (RS-III) initiated in 2006 (n = 3892). Participants were assessed by home interview and physical examination and extensive examination at the research facility from 2006 to 2009. Time between migraine assessment and retinal imaging averaged 6.4 weeks (standard deviation 9.6).

All participants who provided information on migraine in the questionnaire (n = 3892) and had data from retinal imaging were included in the current study. Exclusion criteria were: Persons classified as ''probable migraine'' (fulfilling all but one of the migraine criteria (n = 177)); persons missing data on retinopathy (n = 445); persons missing data on retinal vessel diameter (n = 326). The population for analysis included participants with data on migraine and retinopathy (n = 3270, age range 45–89 years) and data on migraine and retinal vessel diameter (n = 2944, age range 45–89 years)) (Supplementary Figure 1).

The Rotterdam Study has been approved by the Medical Ethics Committee of the Erasmus MC according to the Population Studies Act: Rotterdam Study. All participants provided written informed consent.

Assessment of migraine

Migraine was assessed at the home interview through administration of the migraine questionnaire by trained interviewers; 634 participants completed the questionnaire by phone interview. The migraine questionnaire was based on the migraine headache criteria from the International Classification of Headache Disorders, second edition (ICHD-II) (18), and was modified from the questionnaire validated for use in the Genetic Epidemiology of Migraine (GEM) study in Leiden (19). This questionnaire had a specificity of 0.93 and a sensitivity of 0.36. The migraine questionnaire assessed lifetime occurrence of headache attacks that fulfilled the diagnostic criteria of more than five headache attacks, with a duration of 4–72 hours (when untreated), with typical migraine headache characteristics, and accompanying symptoms of photophobia or nausea.

As described previously (20), the migraine headache criteria in our questionnaire differed moderately from the ICHD-II criteria: We asked participants if they had ever experienced headache with severe pain, affecting their activities, instead of moderate to severe pain intensity. In addition, migraine with aura was classified as at least five (instead of two) headaches fulfilling all migraine headache criteria in combination with headache accompanied by aura symptoms lasting between five to 60 minutes (20). All individuals who met the criteria (20) for any lifetime history of migraine, including migraine with and without aura, were classified as persons with migraine. Persons with migraine were also dichotomized into active migraine (<1 year since last attack) or non-active migraine (>1 year since last attack).

Assessment of retinopathy and retinal microvascular calibers

Retinopathy and retinal microvascular calibers were assessed in RS-III as a part of a full eye examination in the research center, including self-reported ophthalmic history and simultaneous stereoscopic fundus color photography of the optic disc (20° field, Topcon Optical Company, Tokyo, Japan) after pharmacological mydriasis (21).

Retinopathy signs were graded on fundus photographs of both eyes by two trained research physicians. Retinopathy was defined as the presence of soft or hard exudates, micro-aneurysms, macular edema, cotton wool spots, dot, blot or flame shaped hemorrhages, artery or vein branch occlusion, and laser coagulation scars (21). For intra-rater and inter-rater agreement (n = 113), fundus photographs were checked for quality and the presence of retinopathy signs by two experienced graders. These graders, each having 20 years of experience, divided their work and graded all fundus photographs particularly focusing on retinopathy signs. Consensus sessions and between-grader comparisons were performed regularly, and weighted κ coefficients ranged from 0.52 to 0.96 for various retinopathy signs.

For retinal microvascular calibers, per participant the fundus photograph of one eye with the best quality was analyzed using the Retinal Vessel Measurement System (Retinal Analysis, Optimate, WI; Department of Ophthalmology and Visual Science, University of Wisconsin-Madison) (23), and a separate summary value was calculated for the arteriolar and venular

calibers (in μm) after correction for differences in magnification due to the refractive status of the eye (24–26). We verified, in a random subsample of 100 participants, that individual measurements in the left and right eye were similar. Measurements were performed by two raters blinded to participant characteristics. For inter-rater and intrarater agreement (n = 100) the Pearson's correlation coefficients were 0.85 and 0.86 for arteriolar calibers, and 0.87 and 0.87 for venular calibers, respectively (27). Persons who did not undergo ophthalmic examination, or had fundus images on both eyes that could not be graded, were excluded.

Covariates

Covariates were selected as cardiovascular and lifestyle factors that may confound the association between migraine and retinal microvascular damage. Education was assessed at study entry and categorized into low (primary education only), intermediate (secondary education) and high (higher vocational education or university) education level. Assessment of cardiovascular risk factors (systolic blood pressure, diastolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, use of antihypertensive medication indicated for hypertension, use of lipid-lowering medication, diabetes mellitus and smoking) has been described previously (28). C-reactive protein was measured in nonfasting frozen serum samples using Rate Near Infrared Particle Immunoassay (Immage Immunochemistry System, Beckman Coulter, Fullerton, CA). The presence of atherosclerotic plaques was assessed by ultrasound at the carotid artery bifurcation, common carotid artery, and internal carotid artery on both sides. Missing values for all covariates were imputed using multiple imputation based on all variables in the full regression model. All missing values were less than 5%. The percentage of missing values for each covariate are described in Supplementary Table 1.

Statistical analysis

Differences in characteristics between groups were tested by ANCOVA for continuous outcomes and logistic regression for categorical outcomes, adjusted for age and sex. Associations of migraine with retinopathy and retinal microvascular calibers were modeled using logistic and linear regression models, respectively, with persons without migraine as the reference group. The covariate C-reactive protein was log-transformed because of its skewed distribution. For analyses on retinopathy, two models were constructed. The first model adjusted for age and sex, and the second model additionally adjusted for education level, smoking, systolic and diastolic blood pressure, C-reactive protein, total cholesterol, high-density lipoprotein cholesterol, lipid-lowering or antihypertensive medication use, the presence of atherosclerotic plaque and diabetes mellitus. For analyses on retinal microvascular caliber, values for retinal microvascular caliber were standardized by calculating z-scores, and three models were constructed. The first adjusted for age and sex, and the second model additionally adjusted for the caliber of the other vessel; the third model additionally adjusted for education level, smoking, systolic and diastolic blood pressure, C-reactive protein, total cholesterol, high-density lipoprotein cholesterol, lipid-lowering or antihypertensive medication use, the presence of atherosclerotic plaque and diabetes mellitus. Arterial and venular calibers are highly correlated and are associated with clinical outcomes in opposite directions (29). This may lead to confounding when the calibers are modeled alone. Therefore, adjusting the model for the caliber of the accompanying (other) vessel allows for correction of this potential confounder. We also investigated retinopathy and retinal microvascular caliber in migraine subtypes, including migraine with aura and active migraine. The potential interaction of migraine with age and sex on retinopathy or microvascular caliber was assessed by inclusion of interaction terms in the regression models and by stratified analyses. Results for retinopathy are presented as odds ratios (OR) with 95% confidence intervals (CI). Results for retinal microvascular calibers are presented as betas that correspond to mean difference in standardized arteriolar or venular caliber with 95% CI. Statistical significance was considered to be two-sided p-values <0.05. No adjustment was made for multiple testing due to the exploratory nature of the study. All statistical analyses were performed using the statistical software package SPSS (IBM Corp., Armonk, New York, USA), version 21.0 for Windows.

Results

Table 1 presents the descriptives of the study population. In all, 562 persons were classified as persons with definite migraine, of which 126 participants had migraine with aura and 307 had active migraine. Persons with migraine were younger than those without migraine and a higher percentage were women (Table 1). After adjusting for age and sex, a lower percentage of persons with migraine were current smokers, while a higher percentage were former smokers and used lipid-lowering medication.

Amongst persons without migraine, 3.3% had retinopathy while amongst persons with migraine 2.8% had retinopathy (Table 1). After multivariate adjustment, persons with migraine were not more likely to have retinopathy (OR 1.09, 95% CI 0.62; 1.92) compared

Table 1. Descriptives of the study population (n = 3270).

	No migraine (n = 2708)	Definite migraine (n = 562)	*p*-value
Age (years)	57.0 (6.8)	56.1 (6.3)	0.006*
Female	1383 (51.1%)	449 (79.9%)	<0.001*
Education level			
Low	737 (27.2%)	158 (28.1%)	0.38
Intermediate	1240 (45.8%)	253 (45.0%)	0.66
High	731 (27.0%)	151 (26.9%)	0.13
Smoking			
Never	789 (29.1%)	186 (33.1%)	0.91
Current	765 (28.2%)	116 (20.6%)	0.003*
Former	1154 (42.6%)	260 (46.3%)	0.012*
Systolic blood pressure (mmHg)	133.0 (19.3)	131.1 (18.9)	0.80
Diastolic blood pressure (mmHg)	82.5 (11.1)	82.8 (10.9)	0.14
C-reactive protein (mg/L) (log-transformed)	0.12 (0.5)	0.13 (0.5)	0.64
Total cholesterol (mmol/L)	5.5 (1.1)	5.7 (1.1)	0.52
High-density lipoprotein cholesterol (mmol/L)	1.4 (0.4)	1.5 (0.4)	0.17
Lipid-lowering medication use	600 (22.2%)	135 (24.0%)	0.010*
Antihypertensive use	627 (23.2%)	139 (24.7%)	0.07
Atherosclerotic plaque (yes)	979 (36.2%)	178 (31.7%)	0.65
Diabetes mellitus (yes)	275 (10.2%)	48 (8.5%)	0.94
Retinopathy (yes)	90 (3.3%)	16 (2.8%)	
Mean arteriolar caliber (μm)	158.5 (15.6)	157.3 (15.6)	
Mean venular caliber (μm)	239.7 (23.0)	238.0 (22.9)	
Migraine with aura	NA	126 (22.4%)	

Values are presented as mean (standard deviation) or count (percentages). n = number of persons. Reported values are obtained from the first imputed dataset. Percentage of missing values imputed for each covariate are described in Supplementary Table 1 (S1). Differences in characteristics between groups were tested by ANCOVA for continuous outcomes and logistic regression for categorical outcomes, adjusted for age and sex. Difference compared to persons without migraine: *$p < 0.05$.

Table 2. Retinopathy in persons with migraine compared to persons without migraine.

	n: N	Model 1	*p*-value	Model 2	*p*-value
No migraine	90: 2618	1.00 (reference)		1.00 (reference)	
Migraine	16: 546	0.99 (0.57; 1.73)	0.98	1.09 (0.62; 1.92)	0.77
Migraine with aura	5: 121	1.40 (0.55; 3.56)	0.48	1.65 (0.63; 4.30)	0.31
Migraine without aura	11: 425	0.87 (0.46; 1.67)	0.68	0.96 (0.50; 1.85)	0.90
Active migraine	9: 298	1.11 (0.54; 2.27)	0.78	1.31 (0.63; 2.72)	0.47
Non-active migraine	7: 248	0.86 (0.39; 1.90)	0.71	0.90 (0.40; 2.01)	0.79

Values given are odds ratios and 95% CI (from logistic regression) in persons with migraine and migraine subtypes for retinopathy, compared to persons without migraine. n = number of persons with retinopathy; N = number of persons without retinopathy. Model 1: adjusted for age and sex. Model 2: additionally adjusted for education level, smoking, systolic and diastolic blood pressure, C-reactive protein, total cholesterol, high-density lipoprotein cholesterol, lipid-lowering or antihypertensive medication use, presence of atherosclerotic plaque and diabetes mellitus. Difference compared to persons without migraine: *$p < 0.05$.

to persons without migraine (Table 2). Migraine subtypes, including migraine with aura, were not associated with a higher prevalence of retinopathy (Table 2).

The presence of migraine was associated with a lower arteriolar caliber in the age and sex adjusted model (−0.10, 95% CI −0.20; −0.01); the difference in venular caliber was in the same direction, but non-significant (−0.06, 95% CI −0.16; 0.04) (Table 3). However, these differences were attenuated in both arteriolar and venular caliber after adjustment for the other vessel and further adjustment for cardiovascular risk factors. Analyses of migraine subtypes did not demonstrate any difference in the estimates (Table 3).

Table 3. Adjusted mean difference in retinal microvascular caliber between persons with and without migraine.

	Number	Model 1	*p*-value	Model 2	*p*-value	Model 3	*p*-value
				Arterioles			
No migraine	2439	0.00 (*reference)*		0.00 (*reference)*		0.00 (*reference)*	
Migraine	505	−0.10 (−0.20; −0.01)	0.039*	−0.07 (−0.15; 0.01)	0.10	−0.05 (−0.13; 0.03)	0.20
Migraine with aura	112	−0.15 (−0.34; 0.03)	0.11	−0.10 (−0.26; 0.06)	0.21	−0.10 (−0.25; 0.05)	0.18
Migraine without aura	393	−0.09 (−0.20; 0.02)	0.09	−0.06 (−0.16; 0.03)	0.16	−0.04 (−0.12; 0.05)	0.40
Active migraine	277	−0.08 (−0.20; 0.05)	0.23	−0.04 (−0.14; 0.07)	0.51	−0.05 (−0.15; 0.05)	0.34
Non-active migraine	228	−0.14 (−0.27; −0.01)	0.040*	−0.12 (−0.23; −0.01)	0.039*	−0.06 (−0.17; 0.05)	0.29
				Venules			
No migraine	2439	0.00 (*reference)*		0.00 (*reference)*		0.00 (*reference)*	
Migraine	505	−0.06 (−0.16; 0.04)	0.22	−0.01 (−0.09; 0.08)	0.85	−0.00 (−0.09; 0.08)	0.92
Migraine with aura	112	−0.10 (−0.29; 0.09)	0.30	−0.02 (−0.18; 0.14)	0.80	−0.01 (−0.17; 0.15)	0.92
Migraine without aura	393	−0.05 (−0.16; 0.06)	0.34	−0.00 (−0.10; 0.09)	0.92	−0.00 (−0.09; 0.09)	0.92
Active migraine	277	−0.08 (−0.21; 0.05)	0.21	−0.04 (−0.15; 0.07)	0.46	−0.02 (−0.12; 0.09)	0.76
Non-active migraine	228	−0.04 (−0.18; 0.10)	0.57	0.04 (-0.08; 0.15)	0.56	0.01 (−0.10; 0.12)	0.85

Values given are mean difference and 95% confidence intervals (from linear regression) in standardized arteriolar and venular calibers of persons with migraine compared to persons without migraine. Model 1: age and sex adjusted. Model 2: additionally adjusted for the other retinal vessel. Model 3: additionally adjusted for education level, smoking, systolic and diastolic blood pressure, C-reactive protein, total cholesterol, high-density lipoprotein cholesterol, lipid-lowering or antihypertensive medication use, presence of atherosclerotic plaque and diabetes mellitus. Different compared to persons without migraine: $^*p < 0.05$.

Table 4. Retinopathy and retinal microvascular caliber in persons with migraine compared to persons without migraine, stratified on age and sex.

	n/N	Retinopathy	*p*-value	n/N	Arteriolar caliber	*p*-value	Venular caliber	*p*-value
		OR (95% CI)			Mean difference (95% CI)		Mean difference (95% CI)	
Age ≤ 65	529/2487	0.91 (0.50; 1.68)	0.77	478/2259	−0.03 (−0.11; 0.05)	0.41	−0.00 (−0.09; 0.08)	0.09
Age > 65	33/221	0.59 (0.11; 3.31)	0.55	27/180	−0.29 (−0.59; 0.02)	0.07	−0.06 (−0.38; 0.26)	0.72
p-interaction		0.99			0.59		0.23	
Men	113/1325	0.79 (0.30; 2.09)	0.64	98/1168	0.15 (−0.10; 0.31)	0.07	−0.04 (−0.21; 0.13)	0.64
Women	449/1383	1.00 (0.49; 2.01)	0.99	407/1271	−0.11(−0.20; −0.02)	0.015*	−0.00 (−0.10; 0.09)	0.96
p-interaction		0.78			0.005		0.58	

Values given for retinopathy are odds ratios and 95% confidence intervals (from logistic regression) in persons with migraine for retinopathy compared to persons without migraine. Values given for arterioles and venules are mean difference and 95% confidence intervals (from linear regression) of standardized arteriolar and venular calibers of persons with migraine compared to persons without migraine. All estimates were obtained from the model adjusted for age, sex, education level, smoking, systolic and diastolic blood pressure, C-reactive protein, total cholesterol, high-density lipoprotein cholesterol, lipid-lowering or antihypertensive medication use, presence of atherosclerotic plaque and diabetes mellitus; the model for arteriolar and venular caliber was additionally adjusted for the other vessel caliber. n = number of persons with migraine, N = number of persons without migraine. Different compared to persons without migraine: $^*p < 0.05$.

When investigating interaction effects, no significant interaction of migraine with age or sex on the association of migraine with retinopathy was found (Table 4). There was also no interaction of migraine with age in the association with the arteriolar or venular calibers. However, there was interaction between migraine and sex on arteriolar caliber (p-value for interaction = 0.005). Specifically, mean arteriolar caliber was narrower in women with migraine compared to women without migraine (−0.11, 95% CI −0.20; −0.02), whereas in men with migraine the mean difference in arteriolar caliber compared to men without migraine was in the opposite direction (0.15, 95% CI −0.10; 0.31). No migraine-sex interaction was found on venular caliber (p-value for interaction = 0.58).

Discussion

In this population-based cohort study, we found that lifetime migraine was not associated with markers of retinal microvascular damage. Importantly, migraine was not associated with either subclinical markers or clinical retinal microvascular damage, as shown by retinal vessel caliber and retinopathy, respectively. Findings from previous studies on these associations have been equivocal. One previous study, reporting increased presence of retinopathy in persons with migraine (16), had a higher prevalence of retinopathy of around 7.7% for persons with migraine without aura compared to 2.8% for all persons with migraine in our study population, despite a comparable age range. Retinopathy could be underestimated in our study population as the use of only fundus photographs centered on the macula excludes damage visible in other retinal fields. This may partially underlie the different findings. Additionally, persons with migraine or other headaches were found to have smaller mean arteriolar caliber (15,16) and venular caliber than those without migraine (16). These studies had mixed results for migraine subtypes: Persons with migraine with aura were found to have smaller arteriolar and venular caliber (16), while the other study found only persons with migraine without aura had smaller arteriolar caliber (15). Notably, we found similar estimates to previous studies when modeling the retinal vessel calibers separately, whereas the differences became non-significant after modeling the arteriolar and venular caliber simultaneously. The retinal vessel calibers are highly correlated, but are associated in opposite directions with cardiovascular disease (29). Therefore, simultaneous modeling of both retinal vessels ensured adjustment for confounding by this correlation, which could have influenced the previous findings.

The reported associations between microvascular damage and increased risk of hypertension, coronary atherosclerosis and coronary heart disease (12,30–33) may provide further indications regarding the mechanisms of a potential association between migraine and cardiovascular disease (2,3). Migraine has also been associated with microvascular pathology in the brain in the form of cerebral microbleeds (13). However, we were unable to identify a link between migraine and extracerebral microvascular damage. One explanation may be that our study population was much younger than the population investigated for microbleeds, and thus may have a lower load of microvascular damage. Furthermore, migraine may not be unequivocally associated with vascular pathology traditionally linked to cardiovascular disease. Persons with migraine in our study had a comparable cardiovascular risk profile to persons without migraine, supporting this theory. Persons with migraine have a shared genetic risk of stroke (4), and stroke has been strongly linked to changes in retinal microvasculature (34). However, persons with migraine have a lower genetic risk of coronary artery disease (35), and in these persons cerebral perfusion may be increased interictally (20). The fact that we did not find an association between migraine and retinal vessel damage indicates that the shared etiology of migraine and stroke may not be explained by well-established pathways such as atherosclerosis. Alternatively, persons with severe migraine may be non-participants in our study, and therefore the effects of chronic migraine could be underestimated. Analysis of migraine subgroups indicated that persons with active migraine were at a greater (non-significant) risk of retinopathy than those with non-active migraine, suggesting that any risk of retinopathy due to migraine may only be present in the active period. Similarly, the association of migraine and stroke is strongest in young women (36). However, our analysis of migraine subgroups may have been insufficiently powered to draw conclusions from. Finally, when we explored the effects of age and sex on the association between migraine and microvascular markers, women with migraine appeared to have narrower arterioles than women without migraine. However, as the estimate amongst men was considerably in the opposite direction (although non-significant), effect modification by sex may be a spurious finding.

Our study has a number of limitations. Firstly, the migraine questionnaire used an adapted ICHD-II migraine criteria (20), which could have misclassified persons with moderate migraine headache but not severe headache into the control group. Those with migraine with aura could have been misclassified as persons with migraine without aura due to limited information on aura symptoms. This misclassification may have led to an underestimation of our effects. Furthermore, retinopathy may be underestimated, as previously explained. Due to limited information,

we were unable to adjust for potential confounding effects of pain medication use in our study. Additionally, in subgroup analyses, the numbers in each group may have been too small to obtain adequate estimates. Finally, the cross-sectional design of the study precludes causal interpretation of our findings. Strengths of this study include the large population-based sample and use of both pre-clinical and clinical markers of retinal microvascular damage. Furthermore, adjustment of retinal microvascular caliber by the other vessel caliber allowed for correction of confounding from the positive correlation of the arteriolar and venular calibers (29).

In conclusion, we did not find persons with migraine or migraine with aura to be more likely to have retinopathy than persons without migraine, and there was no difference in retinal arteriolar or venular caliber between the two groups. More studies are needed to corroborate the findings and understand the role of microvascular pathology in migraine.

Public health relevance

- Persons with migraine do not appear to be at greater risk of retinopathy.
- Persons with migraine did not differ in retinal microvascular damage compared to persons without migraine.

Acknowledgements

The invaluable contributions of inhabitants, general practitioners and pharmacists of Ommoord are gratefully acknowledged.

Declaration of conflicting interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Ke-xin Wen and Dr Franco work in ErasmusAGE, a center for aging research funded by Nestlé Nutrition (Nestec Ltd), Metagenics Inc and AXA. Dr Kavousi is supported by the VENI grant (91616079) from the Netherlands Organization for Health Research and Development (ZonMW). Professor Ikram received grants from the Netherlands Heart Foundation, ZonMW, Internationaal Parkinson Fonds, and Internationale Stichting Alzheimer Onderzoek.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The Rotterdam Study is supported by the Erasmus MC University Medical Center and Erasmus University Rotterdam, the Netherlands Organisation for Scientific Research (NWO), The Netherlands Organisation for Health Research and Development (ZonMW), the Research Institute for Diseases in the Elderly (RIDE), the Netherlands Genomics Initiative (NGI), the Ministry of Education, Culture and Science, the Ministry of Health, Welfare and Sports, the European Commission (DG XII), and the Municipality of Rotterdam. None of the funding organizations or sponsors were involved in the design and conduct of the study; collection, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

References

1. Stovner LJ and Andree C. Prevalence of headache in Europe: A review for the Eurolight project. *J Headache Pain* 2010; 11: 289–299.
2. Kurth T, Winter AC, Eliassen AH, et al. Migraine and risk of cardiovascular disease in women: Prospective cohort study. *BMJ* 2016; 353: i2610.
3. Guidetti D, Rota E, Morelli N, et al. Migraine and stroke: ''Vascular'' comorbidity. *Front Neurol* 2014; 5: 193.
4. Malik R, Freilinger T, Winsvold BS, et al. Shared genetic basis for migraine and ischemic stroke: A genome-wide analysis of common variants. *Neurology* 2015; 84: 2132–2145.
5. Kruit MC, van Buchem MA, Launer LJ, et al. Migraine is associated with an increased risk of deep white matter lesions, subclinical posterior circulation infarcts and brain iron accumulation: The population-based MRI CAMERA study. *Cephalalgia* 2010; 30: 129–136.
6. Gronewold J, Bauer M, Lehmann N, et al. Coronary artery calcification, intima-media thickness, and ankle-brachial index are complementary stroke predictors. *Stroke* 2014; 45: 2702–2709.
7. Bos D, Ikram MA, Elias-Smale SE, et al. Calcification in major vessel beds relates to vascular brain disease. *Arterioscler Thromb Vasc Biol* 2011; 31: 2331–2337.
8. Goulart AC, Santos IS, Bittencourt MS, et al. Migraine and subclinical atherosclerosis in the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil). *Cephalalgia* 2016; 36: 840–848.
9. Hamed SA, Hamed EA, Ezz Eldin AM, et al. Vascular risk factors, endothelial function, and carotid thickness in patients with migraine: Relationship to atherosclerosis. *J Stroke Cerebrovasc Dis* 2010; 19: 92–103.
10. Stam AH, Weller CM, Janssens AC, et al. Migraine is not associated with enhanced atherosclerosis. *Cephalalgia* 2013; 33: 228–235.
11. Wong TY, Klein R, Couper DJ, et al. Retinal microvascular abnormalities and incident stroke: The Atherosclerosis Risk in Communities Study. *Lancet* 2001; 358: 1134–1140.
12. Wong TY, Klein R, Klein BE, et al. Retinal microvascular abnormalities and their relationship with

hypertension, cardiovascular disease, and mortality. *Surv Ophthalmol* 2001; 46: 59–80.
13. Arkink EB, Terwindt GM, de Craen AJ, et al. Infratentorial microbleeds: Another sign of microangiopathy in migraine. *Stroke* 2015; 46: 1987–1989.
14. Patton N, Aslam T, Macgillivray T, et al. Retinal vascular image analysis as a potential screening tool for cerebrovascular disease: A rationale based on homology between cerebral and retinal microvasculatures. *J Anat* 2005; 206: 319–348.
15. Liew G, Mitchell P, Wong TY, et al. Retinal vascular caliber and migraine: The Blue Mountains Eye Study. *Headache* 2006; 46: 997–1004.
16. Rose KM, Wong TY, Carson AP, et al. Migraine and retinal microvascular abnormalities: The Atherosclerosis Risk in Communities Study. *Neurology* 2007; 68: 1694–1700.
17. Hofman A, Brusselle GG, Darwish Murad S, et al. The Rotterdam Study: 2016 objectives and design update. *Eur J Epidemiol* 2015; 30: 661–708.
18. Olesen J and Steiner TJ. *International Classification of Headache Disorders*. Vol. 75(suppl 1), 2nd edn. Cephalalgia, 2004, pp.808–811.
19. Launer LJ, Terwindt GM and Ferrari MD. The prevalence and characteristics of migraine in a population-based cohort: The GEM study. *Neurology* 1999; 53: 537–542.
20. Loehrer E, Vernooij MW, van der Lugt A, et al. Migraine and cerebral blood flow in the general population. *Cephalalgia* 2015; 35: 190–198.
21. Mutlu U, Ikram MA, Hofman A, et al. N-terminal Pro-B-type natriuretic peptide is related to retinal microvascular damage: The Rotterdam Study. *Arterioscler Thromb Vasc Biol* 2016; 36: 1698–1702.
22. Bird AC, Bressler NM, Bressler SB, et al. An international classification and grading system for age-related maculopathy and age-related macular degeneration. The International ARM Epidemiological Study Group. *Surv Ophthalmol* 1995; 39: 367–374.
23. Hubbard LD, Brothers RJ, King WN, Clegg LX, Klein R, Cooper LS, et al. Methods for evaluation of retinal microvascular abnormalities associated with hypertension/sclerosis in the Atherosclerosis Risk in Communities Study. *Ophthalmology* 1999; 106: 2269–2280.
24. Parr JC and Spears GF. Mathematic relationships between the width of a retinal artery and the widths of its branches. *Am J Ophthalmol* 1974; 77: 478–483.
25. Knudtson MD, Lee KE, Hubbard LD, et al. Revised formulas for summarizing retinal vessel diameters. *Curr Eye Res* 2003; 27: 143–149.
26. Littmann H. [Determining the true size of an object on the fundus of the living eye] Zur Bestimmung der wahren Grosse eines Objektes auf dem Hintergrund eines lebenden Auges. *Klin Monbl Augenheilkd* 1988; 192: 66–67. (in German).
27. Mutlu U, Ikram MK, Wolters FJ, et al. Retinal microvasculature is associated with long-term survival in the general adult Dutch population. *Hypertension* 2016; 67: 281–287.
28. Kavousi M, Elias-Smale S, Rutten JH, et al. Evaluation of newer risk markers for coronary heart disease risk classification: A cohort study. *Ann Intern Med* 2012; 156: 438–444.
29. Liew G, Sharrett AR, Kronmal R, et al. Measurement of retinal vascular caliber: Issues and alternatives to using the arteriole to venule ratio. *Invest Ophthalmol Vis Sci* 2007; 48: 52–57.
30. Wong TY, Klein R, Sharrett AR, et al. Retinal arteriolar narrowing and risk of coronary heart disease in men and women. The Atherosclerosis Risk in Communities Study. *JAMA* 2002; 287: 1153–1159.
31. McGeechan K, Liew G, Macaskill P, et al. Meta-analysis: Retinal vessel caliber and risk for coronary heart disease. *Ann Intern Med* 2009; 151: 404–413.
32. Cheung N, Wang JJ, Klein R, et al. Diabetic retinopathy and the risk of coronary heart disease: The Atherosclerosis Risk in Communities Study. *Diab Care* 2007; 30: 1742–1746.
33. Rong J, Yu CQ, Yang P, et al. Association of retinopathy with coronary atherosclerosis determined by coronary 64-slice multidetector computed tomography angiography in type 2 diabetes. *Diab Vasc Dis Res* 2013; 10: 161–168.
34. Ong YT, De Silva DA, Cheung CY, et al. Microvascular structure and network in the retina of patients with ischemic stroke. *Stroke* 2013; 44: 2121–2127.
35. Winsvold BS, Nelson CP, Malik R, et al. Genetic analysis for a shared biological basis between migraine and coronary artery disease. *Neurol Genet* 2015; 1: e10.
36. Schurks M, Rist PM, Bigal ME, et al. Migraine and cardiovascular disease: Systematic review and meta-analysis. *BMJ* 2009; 339: b3914.