

# Migraine and risk of stroke: a national population-based twin study

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Numerous studies have indicated an increased risk for stroke in patients with migraine, especially migraine with aura; however, many studies used self-reported migraine and only a few controlled for familial factors. We aimed to investigate migraine as a risk factor for stroke in a Swedish population-based twin cohort, and whether familial factors contribute to an increased risk. The study population included twins without prior cerebrovascular disease who answered a headache questionnaire during 1998 and 2002 for twins born 1935–58 and during 2005–06 for twins born between 1959 and 1985. Migraine with and without aura and probable migraine was defined by an algorithm mapping on to clinical diagnostic criteria according to the International Classification of Headache Disorders. Stroke diagnoses were obtained from the national patient and cause of death registers. Twins were followed longitudinally, by linkage of national registers, from date of interview until date of first stroke, death, or end of study on 31 Dec 2014. In total, 8635 twins had any migraineous headache, whereof 3553 had migraine with aura and 5082 had non-aura migraineous headache (including migraine without aura and probable migraine), and 44 769 twins had no migraine. During a mean follow-up time of 11.9 years we observed 1297 incident cases of stroke. The Cox proportional hazards model with attained age as underlying time scale was used to estimate hazard ratios with 95% confidence intervals for stroke including ischaemic and haemorrhagic subtypes related to migraine with aura, non-aura migraineous headache, and any migraineous headache. Analyses were adjusted for gender and cardiovascular risk factors. Where appropriate; within-pair analyses were performed to control for confounding by familial factors. The age- and gender-adjusted hazard ratio for stroke related to migraine with aura was 1.27 (95% confidence interval 1.00–1.62),  $P = 0.05$ , and 1.07 (95% confidence interval 0.91–1.26),  $P = 0.39$  related to any migraineous headache. Multivariable adjusted analyses showed similar results. When stratified by gender and attained age of  $\leq 50$  or  $> 50$  years, the estimated hazard ratio for stroke was higher in twins younger than 50 years and in females; however, non-significant. In the within-pair analysis, the hazard ratio for stroke related to migraine with aura was attenuated [hazard ratio 1.09 (95% confidence interval 0.81–1.46),  $P = 0.59$ ]. In conclusion, we observed no increased stroke risk related to migraine overall but there was a modestly increased risk for stroke related to migraine with aura, and within-pair analyses suggested that familial factors might contribute to this association.

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**Abbreviations:** SALT = Screening Across the Lifespan Twin study; STAGE = Swedish Twin Study of Adults: Genes and Environment

## Introduction

Migraine is a complex primary headache disorder, characterized by recurrent headache attacks, affecting ~11% of the population, with a female predominance of 3:1 (Bigal and Lipton, 2009). Approximately one-third of the patients have an initial aura of neurological symptoms, most often a visual scotoma (Lipton *et al.*, 2001). A diagnosis of migraine with or without aura is assigned according to the internationally accepted clinical criteria ICHD-III beta (The International Classification of Headache Disorders, version three beta), by the International Headache Society (Headache Classification Committee of the International Headache Society, 2013). Probable migraine is defined as migraine-like attacks missing one of the features required to fulfil criteria for the subtypes coded above, and not fulfilling criteria for another headache disorder.

The pathophysiology of migraine is complex and incompletely understood, but involves activation of the trigeminovascular system (Silberstein, 2004; Ferrari *et al.*, 2015), whereas the aura most likely is caused by cortical spreading depression followed by inhibition of neuronal activity and changes in cerebral blood flow (Charles and Baca, 2013; Ferrari *et al.*, 2015). Both genetic and environmental factors seem to play a role for the clinical expression of migraine (Russell and Olesen, 1995; Ferrari *et al.*, 2015) and there is a strong familial aggregation in ~50% of migraine patients (Stewart *et al.*, 1997; Svensson Dan, 2004).

Migraine, especially migraine with aura, has been suggested as a risk factor for cardiovascular disease in general as well as for stroke (Kurth, 2007). Numerous studies, including meta-analyses (Etminan *et al.*, 2005; Schurks *et al.*, 2009; Spector *et al.*, 2010), have reported an ~2-fold increased risk for ischaemic stroke and cardiovascular disease among patients with migraine. The most recent meta-analysis that included prospective cohort studies found a relative risk for ischaemic stroke of 1.64 (Hu *et al.*, 2017a). For haemorrhagic stroke the association is less clear. One meta-analysis (Sacco *et al.*, 2013) found a relative risk estimate of 1.48 for haemorrhagic stroke with any migraine, but the meta-analysis of prospective studies found no such association (Hu *et al.*, 2017b). Migraine has also been associated with white matter lesions and silent strokes (Kruit *et al.*, 2010), but data have not been consistent and a recent study showed no association between migraine and silent infarcts or white matter lesions (Gaist *et al.*, 2016). Several of the previous studies had a retrospective design with a possible risk for recall bias, and in the prospective studies, migraine status and stroke were often self-reported leading to risk of misclassification, or the studies were performed in selective populations limiting generalizability.

Stroke, like migraine, is a complex disease influenced by both environmental and genetic factors, and genetic markers associated with an increased risk of stroke have also been implicated in migraine (Tietjen *et al.*, 2009; Zhang

*et al.*, 2012; Li and Qin, 2014; Malik *et al.*, 2015), indicating that the association between migraine and stroke may in part be explained by genetic factors. Of the previous studies on migraine and stroke, no prospective study and only a few case-control studies controlled for a family history of migraine or stroke (Chang *et al.*, 1999; Donaghy *et al.*, 2002b), and none attempted to disentangle whether the risk increase was confounded by familial factors. We aimed to evaluate migraine, with or without aura and probable migraine, as a risk factor for stroke (ischaemic or haemorrhagic) in a prospective Swedish population-based twin cohort, and whether a potential increased risk may be explained by familial factors.

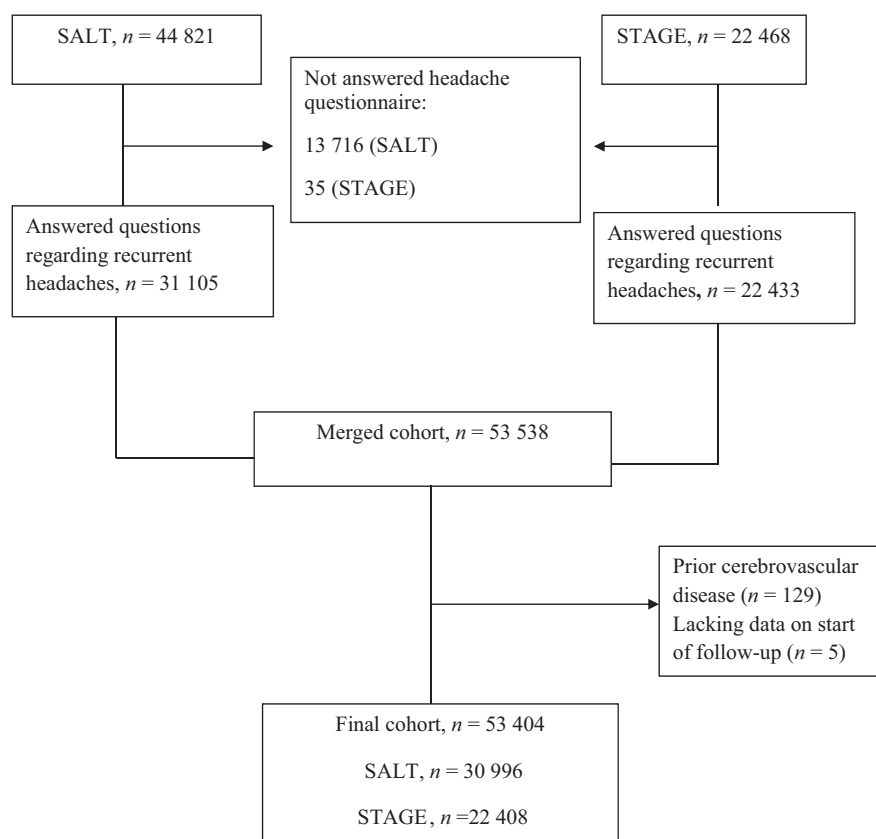
## Materials and methods

### Study design and population

The study design was a prospective twin study, and the study population consisted of twins from two cohorts within the Swedish Twin Registry (Lichtenstein *et al.*, 2002). In the Screening Across the Lifespan Twin study (SALT), all twins in the Swedish Twin Registry born 1958 or earlier were contacted for telephone interviews and they answered questions regarding demographics, lifestyle factors and medical history. In the SALT headache study (Svensson Dan, 2004), a subset of participants born between 1935 to 1958 ( $n = 31\,105$ ) answered questions on recurrent headaches enabling a diagnosis of primary headaches according to ICHD criteria. Data were collected between 1998 and 2002. In the Swedish Twin Study of Adults: Genes and Environment study (STAGE), similar data were collected for twins born between 1959 and 1985 ( $n = 22\,433$ ) using a web-based questionnaire during 2005 and 2006. The data collection in SALT and STAGE is described in detail elsewhere (Lichtenstein *et al.*, 2006). Individuals were excluded from the study population if information on date of study entry was missing ( $n = 5$ ), or a diagnosis of stroke prior to the start of follow-up was found in the national patient register ( $n = 129$ ). In total, 53 404 individuals were included in the final cohort (Fig. 1). Of these, 30.2% of the twin pairs were monozygotic, 33.5% were same-sexed dizygotic, and 34.4% opposite sexed. In 1.9% of the twin pairs, zygosity was unknown. There were 38 908 twins complete twin pairs. The study was approved by the regional ethics board, Stockholm, Sweden.

### Diagnosis of migraine

The questionnaires in SALT and STAGE included similar questions mapping on to the ICHD criteria for primary headaches. The first question was whether individuals have, or had had, recurrent headache episodes not caused by infection or other evident cause. Additional questions covered characteristics of recurrent headaches (unilateral pain, moderate to severe intensity, pounding, aggravation by physical activity), associated symptoms (nausea, vomiting, increased sensitivity for sound and light) and presence of aura symptoms (at least two episodes with temporary, short lasting disturbance of vision followed by headache). In SALT, there was a question on



**Figure 1** Description of study population ( $n = 67\,289$ ).

duration of headache, while this question was lacking in STAGE. The headache questions were validated in a subset of participants in SALT through telephone interviews by experienced neurologists specialized in headache disorders, showing a positive predictive value of 87% for migraine diagnosis (Svensson, 2004). Based on the questionnaire, an algorithm was constructed to identify individuals with migraine headache with or without visual aura according to the ICHD-III criteria in both cohorts. In SALT, migraine patients were further categorized as migraine with or without aura, and probable migraine. As information on duration of headache was missing in STAGE, we could only subcategorize migraine patients as migraine with aura or probable migraine in this cohort (Fig. 2). Twins with migraine aura without subsequent headache could not be identified with this methodological approach (because, if they answered no regarding past or present recurring headaches, no further migraine-related questions were asked).

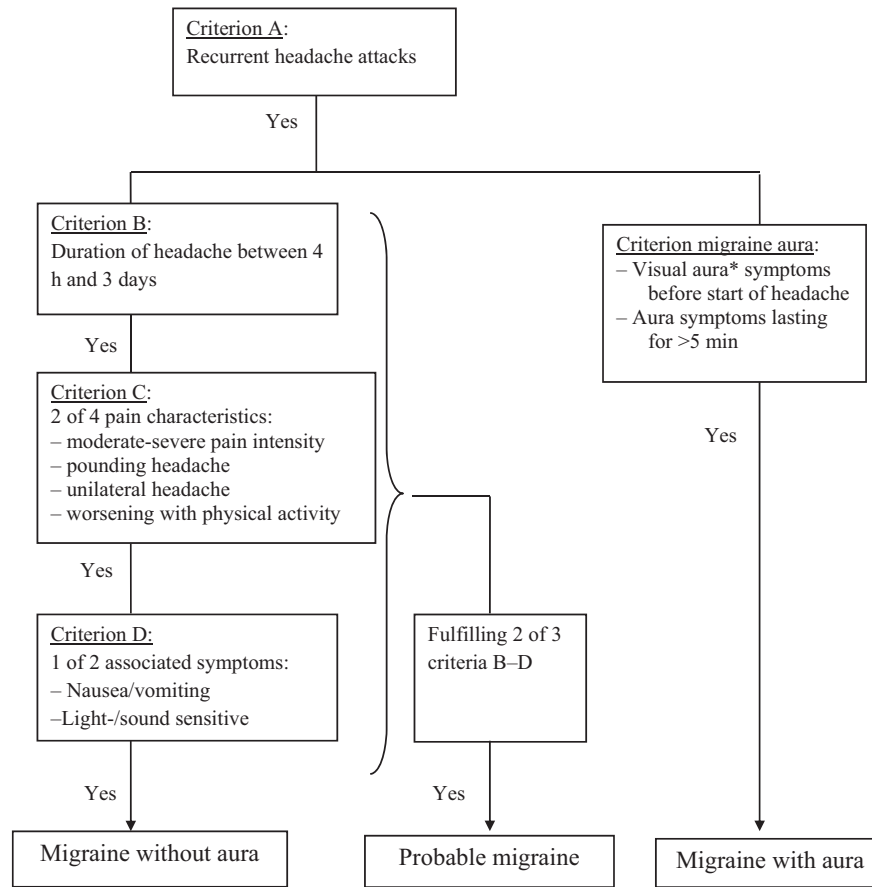
Based on the diagnostic algorithm we defined three diagnostic categories in the merged cohort that were used in the analyses; migraine with aura, non-aura migraineous headache and any migraine. The category non-aura migraineous headache included twins fulfilling criteria for migraine without aura and probable migraine without co-existing migraine with aura. The category any migraine included twins with migraine with aura plus twins with non-migraineous headache (Fig. 3).

## Diagnosis of cerebrovascular disease

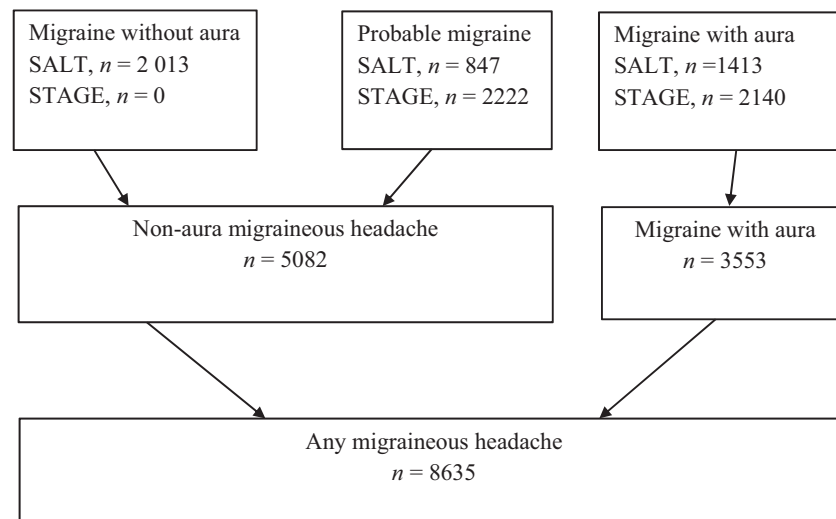
The Swedish Twin Registry was cross-linked to the national patient register and cause-of-death register (National Board of health and welfare). The patient register covers all hospital discharges in Sweden since 1987 and outpatient visits at hospital-based clinics since 2001 (Ludvigsson *et al.*, 2011). Each record includes one primary diagnosis and up to eight secondary diagnoses, as well as date of admission and discharge or date of outpatient visit. The national cause-of-death register covers the entire of Sweden and contains diagnoses of causes of death; both major and contributory causes. In both registers, data are updated continuously and diagnoses are coded according to the International Classification of Diseases (ICD) using ICD-10 since 1998. We recorded all first stroke diagnoses from study entry until 31 December 2014 in these registries using ICD-10 codes for cerebral ischaemia (I63.0–I63.9 and G46.0–G46.8) and intracerebral haemorrhage I61.0–I61.9. Both primary and secondary diagnoses were considered.

## Cerebrovascular risk factors

Presence of cerebrovascular risk factors including previous cardiovascular disease was mainly obtained from the medical history questionnaire used both in SALT and STAGE (hypertension yes/no, diabetes yes/no, hyperlipidaemia yes/no, angina pectoris yes/no, myocardial infarction yes/no,



**Figure 2 Algorithm for identifying twins with migraine (migraine with aura, migraine without aura, probable migraine).** \*Visual disturbance such as flickering of light, zigzag lines moving in the visual field.



**Figure 3 Assignment to analysis group depending on migraine diagnosis.**

peripheral artery disease yes/no). For atrial fibrillation, the questionnaire asked for ‘irregular heartbeat or so called atrial fibrillation’, hence, we assumed that misdiagnosis between benign palpitations and atrial fibrillation might occur. Therefore, presence of atrial fibrillation was assigned if a diagnosis was found (ICD-10 I48.0–I48.9) in the national patient register during the study period.

## Statistical analyses

Individuals were followed longitudinally, by linkage of national registers, and risk time was calculated from the date when the interview was finalized, until a first diagnosis of stroke, death or end of follow-up by 31 December 2014, whichever occurred first. For baseline characteristics of demographic data and cardiovascular risk factors, we calculated percentages or means with standard deviation for twins with migraine with aura, non-aura migraineous headache and no migraine respectively. Primary outcome was the combined endpoint of stroke, and secondary analyses were done for ischaemic and haemorrhagic stroke. We estimated hazard ratios with 95% confidence intervals, using the Cox proportional hazards model with attained age as underlying time scale. Assessments were made for migraine with aura, non-aura migraineous headache and any migraineous headache respectively, the reference group being individuals without any migraine headache. We used a cluster-robust sandwich estimator to correct for dependence between observations in the twin data (Lee *et al.*, 1992). The model was initially adjusted for gender, and automatically adjusted for age, since this was the underlying time scale. Both age and gender were considered confounding factors, affecting both the risk of having migraine attacks and subsequent stroke. We thereafter adjusted for established cardiovascular risk factors affecting the likelihood of stroke (current smoking, obesity, hypertension, hyperlipidaemia, diabetes, previous myocardial infarction, previous angina, atrial fibrillation and peripheral artery disease). We also performed analyses including interaction terms for gender and attained age of  $\leq 50$  and  $> 50$  years, enabling calculation of risk estimates for females and males as well as for individuals below and above 50 years of age separately. Where a significant risk estimate was found, we tested for confounding by familial factors by fitting a stratified Cox proportional hazards model, in which each twin pair was considered a stratum. This model conditions on the twin pair, thereby implicitly controlling for all familial confounding factors that are constant within twin pairs, e.g. early childhood environment and genetic factors. An attenuation of the risk estimate in the within-pair analyses would indicate possible confounding by familial factors. The significance level was set to  $P < 0.05$  for all analyses. We used SAS version 9.4 and STATA version 14.1 for statistical analyses.

## Results

The study population consisted of 53 404 Swedish twins with a mean age at entry of 45.3 years [standard deviation (SD) 11.9, range 19.3–65.5] and a gender distribution with a slight female dominance (54.3% females and 45.7% males). In all, 8635 (16.2%) individuals were diagnosed

with any migraineous headache; 6.7% ( $n = 3553$ ) had migraine with aura and 9.5% ( $n = 5082$ ) had non-aura migraineous headache. Individuals with migraine were predominantly female compared to non-migraineurs. Baseline characteristics including prevalence of cerebrovascular risk factors by migraine status are presented in Table 1. Twins with migraine were more prone to have hypertension, peripheral artery disease and to be obese than non-migraineurs, but less prone to have atrial fibrillation. Individuals were followed for a mean of 11.9 years and the total time of observation was 634 468.4 person-years. Mean age at the end of follow-up was 57.2 years (SD 13.9, range 27.3–80.0).

During follow-up, 1297 first strokes were detected in national registers; 1041 ischaemic strokes and 242 haemorrhagic strokes. Most cases were identified in the national patient register only ( $n = 1161$ , 89.5%), while  $n = 34$  (2.6%) were identified in the cause-of-death register only and  $n = 102$  (7.9%) were identified in both. Fourteen cases were diagnosed both as an ischaemic and haemorrhagic event on the same hospital admission. Thirty-eight twins had a record of an ischaemic stroke and a subsequent haemorrhagic stroke, or vice versa. In all, 1073 ischaemic, and 276 haemorrhagic strokes were recorded. Twins with stroke were predominantly males (61.5%). Mean age for stroke diagnosis was 64.1 years (SD 8.4; range 27.3–79.4). Any migraineous headache and non-aura migraineous headache were not associated with an increased risk for stroke in the initial analysis adjusted for attained age and gender [hazard ratio (HR) 1.07 with 95% confidence interval (CI) 0.91–1.26, and HR 0.97 with 95% CI 0.79–1.19, respectively] (Table 2). The multivariable adjusted analysis did not change these results. Migraine with aura was associated with a border-significant, 27% increased risk for stroke in the initial analysis. Multivariable analysis attenuated the risk estimate somewhat. When analysing risks for ischaemic and haemorrhagic stroke, there were no significant associations with migraine in either group (Table 2).

Risk estimates for stroke related to migraine with aura were higher in females than in males, although the interaction term between gender and migraine was non-significant (Table 3). For non-aura migraineous headache and any migraineous headache there were no differences between males and females with regard to stroke risk (Table 3). In the interaction analyses with attained age, stroke risk estimates associated with migraine with aura were higher in twins  $\leq 50$  years than in twins  $> 50$  years, but again, the interaction term was non-significant. Similarly, there were no significant interaction with attained age for non-aura migraineous headache and any migraineous headache. The risk estimate was lower in twins  $\leq 50$  years, however, was non-significant (Table 4). In the entire cohort, only 70 stroke cases were recorded in twins  $\leq 50$  years of attained age, most stroke cases occurred in older twins ( $n = 1227$ ).

For migraine with aura, where the primary analysis showed a significant association with stroke, we performed

**Table 1** Baseline characteristics of the study population by migraine status

	Migraine with aura (n = 3553)	Non-aura migraineous headache (n = 5082)	No migraine (n = 44 769)
Mean age (SD)	42.5 (11.6)	44.9 (11.6)	45.6 (11.9)
Female sex	2811 (79.1)	3689 (72.6)	22 484 (50.2)
Obese (BMI > 30) <sup>a</sup>	299 (8.4)	428 (8.4)	3030 (6.8)
Smoking <sup>a</sup>			
Current	670 (18.9)	890 (17.5)	7955 (17.8)
Ever	1060 (29.8)	1620 (17.5)	14 025 (31.3)
Hypertension <sup>a</sup>	687 (19.3)	955 (18.8)	6399 (14.3)
Hyperlipidaemia <sup>a</sup>	277 (7.8)	408 (5.0)	3461 (7.7)
Diabetes <sup>a</sup> (type 1 or 2)	80 (2.3)	97 (1.9)	1120 (2.5)
Angina <sup>a</sup>	105 (3.0)	117 (2.3)	1042 (2.3)
Myocardial infarction <sup>a</sup>	38 (1.1)	44 (0.9)	540 (1.2)
Atrial fibrillation <sup>b</sup>	107 (3.0)	158 (3.1)	1927 (4.3)
Peripheral artery disease <sup>a</sup>	44 (1.2)	59 (1.2)	330 (0.7)

Data are given as mean (SD) or n (%) (n = 53 404). BMI = body mass index.

<sup>a</sup>Self-reported data.

<sup>b</sup>Data from National Patient Register.

**Table 2** Estimated hazard ratios with 95 % confidence intervals for total stroke, ischaemic stroke and haemorrhagic stroke related to migraine status

	Events (n)	Gender adjusted HR (95 % CI)	P	Multivariable adjusted <sup>a</sup> HR (95 % CI)	P
<b>Total stroke</b>					
No migraine headache	1126	1.00 (reference)		1.00 (reference)	
Any migraineous headache	171	1.07 (0.91–1.26)	0.39	1.04 (0.89–1.23)	0.59
Migraine with aura	70	1.27 (1.00–1.62)	0.05	1.20 (0.93–1.53)	0.15
Non-aura migraineous headache	101	0.97 (0.79–1.19)	0.78	0.96 (0.78–1.19)	0.72
<b>Ischaemic stroke<sup>b</sup></b>					
No migraine headache	920	1.00 (reference)		1.00 (reference)	
Any migraineous headache	135	1.02 (0.85–1.23)	0.82	0.99 (0.82–1.19)	0.93
Migraine with aura	58	1.28 (0.98–1.67)	0.08	1.19 (0.91–1.56)	0.20
Non-aura migraineous headache	77	0.89 (0.70–1.12)	0.33	0.88 (0.69–1.12)	0.29
<b>Haemorrhagic stroke<sup>b</sup></b>					
No migraine headache	215	1.00 (reference)		1.00 (reference)	
Any migraineous headache	41	1.22 (0.87–1.71)	0.26	1.22 (0.86–1.71)	0.26
Migraine with aura	14	1.18 (0.69–2.04)	0.54	1.16 (0.67–2.00)	0.59
Non-aura migraineous headache	27	1.23 (0.82–1.86)	0.32	1.24 (0.82–1.87)	0.31

Both models have attained age as underlying time scale.

<sup>a</sup>Adjusted for gender, current smoking, obesity, hypertension, hyperlipidaemia, diabetes, previous myocardial infarction, previous angina, atrial fibrillation and peripheral artery disease.

<sup>b</sup>Fourteen cases were diagnosed as both ischaemic and haemorrhagic stroke. These were included in both the ischaemic and haemorrhagic groups.

**Table 3** Estimated hazard ratios with 95% confidence intervals for stroke related to migraine status, by gender (n = 53 404)

	Events (n)	Females HR (95% CI)	P	Events (n)	Males HR (95% CI)	P
No migraine headache	393	1.00 (reference)		733	1.00 (reference)	
Migraine with aura <sup>a</sup>	50	1.33 (0.99–1.78)	0.06	20	1.16 (0.74–1.80)	0.52
Non-aura migraineous headache <sup>b</sup>	57	0.94 (0.71–1.25)	0.66	44	1.02 (0.75–1.38)	0.92
Any migraineous headache <sup>c</sup>	107	1.09 (0.88–1.35)	0.45	64	1.06 (0.82–1.36)	0.67

Underlying timescale was attained age.

<sup>a</sup>Interaction term between migraine with aura and gender, P = 0.60.

<sup>b</sup>Interaction term between non-aura migraineous headache and gender, P = 0.63.

<sup>c</sup>Interaction term between any migraineous headache and gender, P = 0.87.

**Table 4** Estimated hazard ratios with 95% confidence intervals for stroke, by attained age 50 years or younger, or above 50 years (*n* = 53 404)

	Events ( <i>n</i> )	Attained age ≤50, gender adjusted HR (95% CI)	<i>P</i>	Events ( <i>n</i> )	Attained age >50, gender adjusted HR (95% CI)	<i>P</i>
No migraine headache	58	1.00 (reference)		1068	1.00 (reference)	
Migraine with aura <sup>a</sup>	9	1.85 (0.92–3.73)	0.09	61	1.22 (0.94–1.59)	0.13
Non-aura migraineous headache <sup>b</sup>	3	0.46 (0.14–1.45)	0.18	98	0.99 (0.80–1.22)	0.91
Any migraineous headache <sup>c</sup>	12	1.06 (0.57–1.98)	0.45	159	1.07 (0.91–1.27)	0.40

Underlying time scale was attained age.

<sup>a</sup>Interaction term between migraine with aura and attained age, *P* = 0.26.

<sup>b</sup>Interaction term between non-aura migraineous headache and attained age, *P* = 0.20.

<sup>c</sup>Interaction term between any migraineous headache and attained age, *P* = 0.98.

within-pair analysis to assess whether the association might be confounded by familial factors. This analysis was based on 2142 twin pairs discordant for migraine with aura and showed a HR for stroke of 1.09 (95% CI 0.81–1.46). Thus, the HR was attenuated compared to the primary analysis, although confidence intervals were wide.

## Discussion

In this large population-based twin study of >50 000 individuals, we did not find an overall association between migraine and a risk of stroke. For migraine with aura, there was a 27% increased stroke risk, potentially influenced by familial factors. This is the first population-based study using a symptom-based algorithm for identifying migraine, investigating the association with stroke and also controlling for familial factors. Our results agree with previous literature and indicate that only the subtype migraine with aura is associated with an increased risk of stroke.

Several previous prospective cohort studies evaluated the association between migraine and stroke, with varying results. The recent Nurses' Health Study including females only (Kurth *et al.*, 2016), data from the Physicians Health Study including males only (Buring *et al.*, 1995), and four studies including both genders (Merikangas *et al.*, 1997; Hall *et al.*, 2004; Velentgas *et al.*, 2004; Peng *et al.*, 2017) showed a significantly increased risk for stroke associated with any migraine. Other prospective studies showed an association in individuals with migraine with aura but not in individuals without aura (Stang *et al.*, 2005; Kurth *et al.*, 2006), or no increased risk for stroke related to migraine (Kurth *et al.*, 2007; Monteith *et al.*, 2015). In the Merikangas study (1997) and the Kurth *et al.* study (2016), migraine was identified through self-reported 'physician-diagnosed migraine' (Merikangas *et al.*, 1997; Kurth *et al.*, 2016), and in the Velentgas study, migraine information was obtained from patient registers or insurance claims (Velentgas *et al.*, 2004). As many patients with milder migraine never seek medical attention for their headaches, migraine patients with higher

attack frequency and more severe attacks might be over-represented in these studies, while individuals with milder migraine remain unidentified. It has been suggested that the risk of stroke is related to active migraine (i.e. migraine attacks within the last 12 months) (Donaghy *et al.*, 2002a; Kurth *et al.*, 2006) and increases with attack frequency (Chang *et al.*, 1999; Kurth *et al.*, 2009). Our methodology of identifying migraine based on symptoms rather than physician-diagnosed migraine might thus in part explain why we observe a somewhat weaker association between migraine and stroke compared to some of the previous prospective studies.

Previous studies have consistently shown an increased risk for primarily ischaemic stroke related to migraine with aura, and in the meta-analysis from Schurks *et al.* (2009), migraine with aura had a 2-fold increased risk for stroke, while migraine without aura was not significantly associated with stroke (Kurth *et al.*, 2005; Stang *et al.*, 2005; Schurks *et al.*, 2009; Peng *et al.*, 2017). In line with these findings, our data showed an association between migraine with aura and stroke but no association for non-aura migraineous headache. However, the magnitude of the association was weak, indicating that although an association between migraine with aura and ischaemic stroke exists, the absolute attributable risk is probably very low. Regarding haemorrhagic stroke, we observed no association, but we observed too few haemorrhagic endpoints to make any firm conclusion.

Although few studies reported results for males and females separately, current evidence indicates a weaker association in males than in females (Tzourio *et al.*, 1993; Haapaniemi *et al.*, 1997; Kurth *et al.*, 2007; Schurks *et al.*, 2009) which are in line with our results, although the interaction with gender was non-significant. The association also seems to be stronger in younger age groups. For example, Kurth *et al.* 2016 reported data from the Nurses' health study, supporting an association between any migraine and stroke (HR 1.50). Merikangas *et al.* (1997) showed a decreasing stroke risk with older age of onset for stroke, and several studies reported no increased risk for stroke related to migraine in older populations (Mosek

*et al.*, 2001; Kurth *et al.*, 2005; Monteith *et al.*, 2015), which also our results indicate.

Our within-pair analysis showed an attenuation of the association between migraine with aura and stroke, suggesting that familial factors may contribute to the association. However, there was a substantial drop in sample size and therefore we need to interpret these results with caution. Nevertheless, genetic markers associated with stroke have also been implicated in migraine (Malik *et al.*, 2015) and based on mouse models of familial hemiplegic migraine, the hypothesis has been raised that migraine may be associated with a hyperexcitability phenotype leading to an increased susceptibility to ischaemia (Eikermann-Haerter *et al.*, 2012).

Another hypothesis regarding the mechanism behind the increased stroke risk in migraineurs is that individuals with migraine have a less favourable risk factor profile (Scher *et al.*, 2005). However, results are conflicting; some previous studies observed highest risk for stroke related to migraine in individuals with the lowest Framingham risk scores or without cardiovascular risk factors (MacClellan *et al.*, 2007; Kurth *et al.*, 2008), while others observed that cardiovascular risk factors such as obesity, smoking and hypertension were more common in migraineurs (Kurth *et al.*, 2016). We found a similar distribution of many cardiovascular risk factors between the groups, but twins with migraine had a tendency to be more obese and to have hypertension and peripheral artery disease than non-migraineurs, whereas atrial fibrillation was less common in migraineurs. Both obesity and peripheral artery disease have been associated with migraine, including chronic migraine (Bigal *et al.*, 2010; Ornello *et al.*, 2015). Whether cardiovascular risk factors indeed are overrepresented in migraine patients is still unclear, but they should be properly screened for cardiovascular risk factors and treated appropriately.

Another proposed mechanism potentially explaining the association between migraine and stroke is increased prevalence of patent foramen ovale and cervical artery dissection in migraine patients; both are considered common risk factors for stroke in younger age groups (Mawet *et al.*, 2015). Unfortunately, we could not examine this hypothesis, as we did not have data on patent foramen ovale or specific aetiology in stroke cases, i.e. if they were lacunar or embolic.

The strengths of our study include the use of a large population-based cohort and the prospective design. Another advantage is the twin-design that allows controlling for familial factors. Further, migraine diagnosis was not self-assessed, but instead identified using a validated questionnaire based on characteristic migraine symptoms and ICHD criteria. Stroke was identified from national patient registries, reducing the risk of misclassification compared to self-report that was used in previous studies as a screening tool for identifying events. Previous validation of patient register stroke diagnoses showed a very high (99%) accuracy (Ludvigsson *et al.*, 2011) but we had no access to medical records to verify the diagnosis, and in a few cases,

there was a double-diagnosis of both an ischaemic and haemorrhagic event. These might have been primary ischaemic strokes with haemorrhagic transformation, but we were not able to verify whether this was the case.

A limitation of the study is the fairly short follow-up time. Mean age at the end of study was 57 years of age, far preceding the average age at stroke onset in the general population, and therefore lessening our chances to detect an association. On the other hand, it is probably in younger and middle-aged individuals that migraine would contribute the most to the stroke risk, as compared to later in life when traditional risk factors such as large artery atherosclerosis or atrial fibrillation are more common. In our study we also lacked data on the frequency of migraine attacks and whether migraine was active at the entry of the study, variables that have shown particularly strong association with stroke (Kurth *et al.*, 2006; MacClellan *et al.*, 2007). Considering the age range for entering the study (20–65 years), and the fact that most individuals with migraine have their first migraine attack before 40 years of age (Bigal and Lipton, 2006), some individuals in the non-migraine population might have developed migraine attacks during the observation period, contributing to an attenuated risk estimate for stroke. Although validation showed a high accuracy of the questionnaire, we cannot exclude that some misclassification of migraine occurred, for example overdiagnosis of migraine with aura, also leading to attenuation of the stroke risk estimate. Another limitation is that we were not able to identify twins with migraine aura without headache. However, this is a rare event, and the prevalence of any migraine and migraine with aura in our cohort is consistent with previous estimated prevalence of migraine in the general population (Lipton *et al.*, 2001).

## Conclusion

In this large prospective, population-based study, overall migraine headache was not associated with an increased risk for stroke but there was a modestly increased risk, potentially influenced by familial factors, in patients with migraine with aura. Our results support previous data, that the increased risk for stroke is only apparent in the subset of individuals with migraine with aura, and provide valuable information of clinical relevance to the large population of individuals suffering from migraine headaches.

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