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Migraine and cardiovascular disease

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ABSTRACT

Migraine, especially migraine with aura is an established risk factor for ischemic lesions of the brain. Recent evidence has also linked migraine with and without aura to a broader range of ischemic vascular disorders including angina, myocardial infarction, coronary revascularization, claudication and cardiovascular mortality. The topic is therefore of considerable interest. Accordingly, herein we review the association between migraine and cardiovascular disease. We start by briefly presenting diagnostic criteria for migraine and revising its pathophysiology. We follow by summarizing the evidence on the topic. We then briefly present the results of a recent meta-analysis. We close by highlighting results of a large epidemiological study conducted after the publication of the meta-analysis.

Key words: migraine, cardiovascular disease, stroke.

Migrânea e doenças cardiovasculares

RESUMO

A migrânea, especialmente a migrânea com aura, é fator de risco para lesões cerebrais. Evidência recente sugere que migrânea com e sem aura é associada com outras doenças cardiovasculares isquêmicas, incluindo a angina, o infarto do miocárdio, revascularização coronária, claudicação e morte súbita. Iniciamos discutindo o diagnóstico da migrânea e seus mecanismos fisiopatológicos. Após sumarizar a evidência, discutimos resultados de meta-análise recente. Por fim, ressaltamos resultados de um grande estudo populacional sobre o assunto.

Palavras-chave: migrânea, doença cardiovascular, acidente vascular cerebral.

The association between migraine and ischemic vascular events has been studied for many years[1,2]. Original studies controversially reported an association between migraine with aura (MA) and stroke. The relationship was stronger in young women, and was magnified by the use of hormonal contraception or by tabagism[1]. Controversial topics included whether migraine without aura (MO) was also a risk factor to stroke, if the association also happened in men, and whether migraine was associated with other forms of cardiovascular disease[3].

The field has advanced considerably in recent years, with the publication of evidence that MA is indeed an established risk factor for subclinical ischemic lesions of the brain[4], as well as for ischemic stroke, particularly among women of younger age[5,6]. The association has also been shown in men[7]. Furthermore, migraine seems also to be linked with other forms of cardiovascular disease (CVD), including myocardial infarct, angina and claudication), as well as with risk factors to CVD[8,9]. The topic has indeed gained considerable traction and robust evidence is now available. Accordingly, herein we review the association between migraine and CVD. We start by briefly presenting diagnostic criteria for migraine and revising its pathophysiology. We follow by summarizing the evidence on the topic. We then briefly present the results of a recent meta-analysis. We close by highlighting results of a large epidemiological study conducted after the publication of the meta-analysis.

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Migraine: a brief overview

Migraine is a prevalent disease that affects 12% of the adult population in the United States and is three times more common in women than in men[10,11]. Migraine is characterized by recurrent attacks of pain and associated symptoms, typically lasting from 4 to 72 hours[12-14]. It has features in common with episodic pain disorders (self-limited attacks of pain). It also has features in common with chronic pain disorders in that sufferers have an enduring predisposition to pain and subclinical neurophysiological markers. It is therefore best described as a chronic-episodic disorder[15]. Migraine is classified into five major categories, the two most important of which are Migraine without aura and Migraine with aura. Aura is the only distinguishing feature between both subtypes; pain and associated symptoms are identical.

Criteria for migraine without aura are met by various combinations of features[14]. At least two of the following pain features need to be present when pain is at the worst: [1] Throbbing in nature; [2] Unilateral or more severe in one side than in the other; [3] Aggravated by movements or physical activity; [4] Of moderate or severe intensity. Additionally, at least one of the following combination of associated symptoms is necessary: [1] Photophobia and phonophobia; [2] Nausea or vomiting. We emphasize that unilateral, pulsating headache meets the criteria but so it does bilateral, pressing headache if it is moderate or severe in intensity and aggravated by routine physical activity. With regard to associated features, a patient without nausea or vomiting but with both photophobia and phonophobia may fulfill the criteria[12].

The typical aura of migraine is characterized by focal neurological features that usually precede migrainous headache but may accompany it or occur in the absence of the headache[14]. Typical aura symptoms develop over ≥5 minutes and last no more than 60 minutes, and visual aura is overwhelmingly the most common. Typical visual aura is homonymous, often having a hemianopic distribution and expanding in the shape of a crescent with a bright, ragged edge, which scintillates. Scotoma, photopsia or phosphenes and other visual manifestations may occur. Sensory symptoms occur in about one-third of patients who have migraine with aura. Typical sensory aura consists of numbness (negative symptom) and tingling or paresthesia (positive symptoms). The distribution is often on the face and hand. Other types of aura are less frequent and require careful neurological assessment before diagnosis.

Overview of migraine's pathophysiology

Migraine is best understood as a primary disorder of the brain with peripheral consequences[16,17]. There is abundant evidence that migraine is a familial disorder with genetic foundation[18]. The first neurological event of migraine is a point of controversy and two non-mutually exclusive hypotheses exist[19,20]. Migraine may result from a dysfunction of an area of the brainstem that is involved in the modulation of pain, sensory processing and craniovascular afferents and have also been shown to control trigeminocervical nociceptive inputs[21]. According to this view, the pain is understood as a combination of altered perception (due to peripheral or central sensitization) of stimuli, as well as the activation of a feed-forward neurovascular dilator mechanism in the first division of the trigeminal nerve[22]. The brainstem activation would induce a pro-noniceptive state and also lead to deficits in the autonomic vascular control[20].

An alternative theory proposes that spreading depression of cortical activity (cortical spreading depression - CSD) is the first neurological event happening in migraine[23]. CSD would explain the migraine aura and would cause further activation of trigeminovascular afferents ultimately associated with inflammation at the level of the extra-cephalic blood vessels[24]. We highlight that CSD is a potent electrical wave that is followed by intense vasoconstriction and it may be linked to ischemic consequences into the migraineur brain.

Regardless of the exact site of initiation of migraine, neurological events that are fairly specific to migraine (CSD and activation of the trigeminal nucleous caudalis), non-specific dysmodulation in pain processing pathways, and vascular consequences seem to be of importance in migraine pathophysiology.

Migraine and cardiovascular disease

In this section we first present the evidence linking migraine with subclinical brain lesions that may be ischemic in nature. We follow by discussing the association of migraine and true ischemic lesions. We expand the discussion for non-neurological ischemic events and close by presenting evidence that migraine is indeed associated with several risk factors for CVD[9].

Migraine and subclinical brain lesions

Incidental deep brain lesions have long been reported as happening more frequently in migraineurs[25], although most studies lacked a contemporaneous control group. In a well designed population-based study from the Netherlands, Kruit and colleagues randomly selected approximately 150 individuals from each of 3 groups for neuroimaging (MA, MO and non-migraine controls)[4,26]. They excluded individuals with a history of stroke, TIA, or with abnormal neurological exam. This study included blinded evaluation of MRI by a neuro-radiologist and aura classification was performed under the supervision of expert headache diagnosticians without knowledge of the MRI

results. Overall, there were no differences in the prevalence of clinically relevant infarcts between migraineurs and controls. This may be explained by the exclusion of prior history of TIA and stroke (which would also exclude those with clinically relevant infarcts). However, those with MA had significant increase of sub-clinical infarcts in the cerebellar region of the posterior circulation. Risk was highest in MA with more than one headache attack per month (OR=15.8, 95% CI:1.8-140). In addition, women with migraine were about twice as likely to have deep white matter lesions as the non-migraineurs. These findings were independent of the presence of some traditional cardiovascular risk factors.

Migraine and stroke

The association between migraine and ischemic stroke is well demonstrated[27-29]. A meta-analysis of 11 case-control studies and three cohort studies published before 2004 showed that, relative to individuals without migraine, the risk of stroke was increased in migraineurs [pooled relative risk (RR)=2.16, 95% confidence interval (CI)=1.9-2.5]. This risk was higher for MA (RR 2.27; 95% CI: 1.61-3.19), but was also apparent in patients with migraine without aura (MO, RR, 1.83; 95% CI, 1.06-3.15)[27].

More recently, two large longitudinal studies added to the evidence linking migraine and ischemic stroke (and are included in a more recent meta-analysis, summarized below). As a part of the Women's Health Study, data were prospectively gathered over more than 10 years[5]. Compared with controls, participants who reported MA (but not MO) had increased adjusted hazards ratios (HRs) of 1.53 (95% CI 1.02 to 2.31) for total stroke and 1.71 (95% CI 1.11 to 2.66) for ischemic stroke but no increased risk for hemorrhagic stroke. The increased risk for ischemic stroke was further magnified (HR 2.25; 95% CI 1.30 to 3.91) for the youngest age group in this cohort (45-54 years). The associations remained significant after adjusting for cardiovascular risk factors and was not apparent for non-migraine headache[5].

The second prospective study used data from the Atherosclerosis Risk in Communities Study and included over 12,000 men and women aged 55 and older[30]. Compared to participants without headaches, migraineurs (of both subtypes) had a 1.8-fold increased risk of ischemic stroke (relative risk 1.84; 95% CI, 0.89-3.82). The fact that the risk estimates did not reach statistical significance may be due to migraine classification, since the category of "other headache with aura" showed a significant increased risk of ischemic stroke (RR 2.91, 95% CI, 1.39-6.11). Similarly, in a stroke prevention study in young women study, those with MA had 1.5 greater odds of ischemic stroke, as compared to individuals without migraine (95% CI, 1.1 to 2.0).

Mechanisms to explain the association between migraine and brain lesions

As mentioned, in most studies, the association of CVD is either limited to MA or it is stronger in this group. The physiological substrate of aura is cortical spreading depression, a self-propagating wave of neu-

Table 1. Putative mechanisms of the relationship between migraine and cardiovascular disease.

Mechanisms of association	Putative mechanisms	Comments
Causal association (migraine causes CVD)	• Repetitive episodes of cortical spreading depression may predispose to ischemia, perfusion changes and chronic inflammation.	• Justifies migraine with aura as a stronger risk factor. • Justifies the relationship with stroke but not with coronary problems.
Shared predisposition (environmental and/ or biological factors predispose to both migaine and CVD)	• Migraineurs with aura are more likely to have poor cholesterol profile, elevated Framingham risk score for coronary heart disease, hypertension, and history of heart attack in the family. • A polymorphism of the C677T gene was seen in one study and codes high levels of homocysteine. Not confirmed by a second study	• Accordingly, migraineurs with aura are more likely to present one or multiple risk factors for CVD.
Common comorbidities	• Obesity is associated with increased headache frequency in both migraine with and without aura. • Limited evidence also suggests that metabolic syndrome predisposed to increased headache frequency. • Clinic-based studies suggest that PFO and other congenital heart problems are more common in migraine with aura.	• Likely magnifies the relationship between migraine with aura and cardiovascular disease, since frequency of attacks is associated with number of deep brain lesions. However, in some studies adjustments for body mass index were conducted.

ronal and glial depolarization[31,32]. CSD triggers a series of cellular and molecular events, eventually resulting in massive surges of extracellular potassium and intracellular calcium. CSD also alters the permeability of the blood-brain barrier via activation of matrix metalloproteinases (MMPs), a family of neutral metalloproteases[33].

The CSD-related MMP activation may underlie changes in vascular permeability in the central nervous system[34].

Accordingly, it may be speculated that ischemic lesions on the brain are a direct consequence of CSD, as well as an indirect consequence of poor CVD profile by migraineurs (Table 1).

Migraine and coronary heart disease

Although some studies yielded negative or conflicting results for the overall association of migraine and coronary heart disease[35], other studies reported a positive association and even electrocardiographic changes experienced by migraineurs[36-38].

Population studies support the relationship between migraine, specially MA, and coronary disease. In the Atherosclerosis Risk in Communities study[37], patients with headache were roughly twice as likely to have a history of angina, as compared to controls, with the risk most elevated in the headache group with aura.

In the Women's Health Study, MA but not MO approximately doubled the relative risk of major CVD (ischemic stroke, myocardial infarction, coronary revascularization procedures, angina, as well as death related to ischemic cardiovascular events)[5,39]. These associations remained significant after adjusting for many cardiovascular risk factors.

Finally, as part of the Physician's Health Study, men with migraine (with or without aura) were at increased risk for major CVD (HR=1.24, 95% CI: 1.06-1.46), a finding which was driven by a 42% increased risk of myocardial infarction[7].

Mechanisms to explain the association between migraine and coronary disease

As mentioned, events linked to migraine pathophysiology unlikely explain the association of migraine with coronary disease. Nonetheless, specific disorders have been linked to migraine and CVD and may partially account for the relationships among them, although many studies adjusted for these covariates. Some of them are discussed below.

Obesity is a well established risk factor for CVD. In migraineurs, obesity has been associated with more frequent and severe headache attacks and with new onset of chronic migraine[40-42] but it is unrelated to migraine aura[43].

Among the putative mechanisms to explain the obesity/migraine relationship, metabolic syndrome (or the syndrome of insulin resistance) has been suggested[44]. Metabolic syndrome has been associated with chronic pain overall. Women with fibromyalgia are 5 times more likely than healthy controls to have metabolic syndrome[45]. Total and low-density lipoprotein cholesterol have also been significantly associated with fibromyalgia among women[45]. Additionally, migraineurs seem to have significantly higher levels of glucose and of insulin at fasting and after glucose loading.

Dyslipidemia, another component of the metabolic syndrome, has also been associated with migraine. In the Genetic Epidemiology of Migraine study, compared to controls, migraineurs with aura were more likely to have an unfavorable cholesterol profile[46]. Risk for elevated Framinghan score for coronary heart disease, as well as reduced HDL levels, were doubled for MA. Nonetheless, findings of the Women Health's Study showed that migraine was only weakly associated with elevated total cholesterol (OR=1.09, 95% CI: 1.01-1.18)[47]. Finally, a pro-inflammatory state has also been suggested in migraine. In the Women Health's Study, migraine was weakly associated with elevated levels of C-reactive protein (OR=1.13, 95% CI=1.05, 1.22), although the magnitude of the effect is insufficient to support a strong biological link[47].

The number of circulating endothelial progenitor cells (EPC) seem also to be of importance, since diminished EPC counts are associated with higher cardiovascular risk[48]. A recent study investigated whether abnormalities in EPC levels and functions are present in migraine patients[49]. The mean numbers of EPC colony-forming units were significantly reduced in MA, compared to other headaches. In addition, EPCs from migraine patients showed reduced migratory capacity and increased cellular senescence compared with EPCs from individuals with tension-type headache or without headaches.

Finally, MA has been associated with polymorphism in the methyltetrahydrofolate reductase (MTHFR) gene C677T, which also codes moderately increased homocysteine levels[50]. However, several small studies and recent findings from the Women's Health Study do not support such a link[51]. Accordingly, the importance of MTHFR in explaining the link between migraine and CVD remains uncertain (Table 1).

Taken together, findings suggest that migraineurs are more likely than non migraineurs to have an unfavorable health risk profile. This may add to the risk imposed by repetitive episodes of CSD and explain the increased likelihood for coronary events. .

Summarizing the evidence

Since the available evidence on the topic increased considerably over the past years, a recently published me-

Table 2. Association between migraine and CVD events, heterogeneity, and publication bias (based on[52]).

Migraine category	CVD event	Relative risk (95% CI)*
Any	**Ischemic stroke**	
All studies (case-control and cohort)		1.73 (1.31-2.29)
Case-control studies		1.96 (1.39-2.76)
Cohort studies		1.47 (0.95-2.27)
Women		2.08 (1.13-3.84)
Men		1.37 (0.89-2.11)
Women and men <45 years		2.65 (1.41-4.97)
Women <45 years		3.65 (2.21-6.04)
Women ≥45 years		1.22 (0.88-1.68)
Women currently using OCs		7.02 (1.51-32.68)
Women currently not using OCs		2.27 (0.69-7.47)
Smokers		9.03 (4.22-19.34)
Non-smokers		1.56 (0.41-5.85)
Migraine with aura	**Ischemic stroke**	
All studies		2.16 (1.53-3.03)
Smokers		1.5 (1.1-2.3)
Women currently using OCs		No RR given
Women currently using OCs and smoking		10.0 (1.4-73.7)
Migraine without aura	**Ischemic stroke**	1.23 (0.90-1.69)
Any	**TIA**	2.45 (1.94-3.09)
Any	**Hemorrhagic stroke**	1.18 (0.87-1.60)
Any	**Any stroke**	1.49 (1.31-1.70)
Any	**Myocardial infarction**	
All studies		1.18 (0.99-1.40)
Women		1.27 (0.88-1.81)
Men		1.28 (0.93-1.75)
Migraine with aura	**Myocardial infarction**	2.08 (1.30-3.31)
Migraine without aura	**Myocardial infarction**	1.22 (0.73-2.05)
Any	**Angina**	
All studies		1.31 (1.16-1.45)
Women		1.42 (1.17-1.73)
Men		1.45 (0.85-2.47)
Migraine with aura	**Angina**	1.71 (1.16-2.53)
Migraine without aura	**Angina**	1.12 (0.75-1.66)
Any	**CVD death**	
All studies		1.03 (0.79-1.34)
Women		1.60 (1.06-2.42)
Men		1.07 (0.80-1.43)
Migraine with aura	**CVD death**	2.33 (1.21-4.51)
Migraine without aura	**CVD death**	1.06 (0.46-2.45)

*From random effects model; † 4 study cohorts from 1 paper; ‡ 2 study cohorts from 1 paper.

ta-analyses sought to assess the current evidence on the association between migraine and various CVD events, including stroke subtypes, angina, myocardial infarction (MI), and CVD death[52] (Table 2).

Studies were heterogeneous with regard to the characteristics of investigated subjects and definition of cardiovascular events. Nine studies investigated the association between any migraine and ischemic stroke. The pooled RR (95% CI) was 1.73 (1.31-2.29). This association appeared only among MA (pooled RR=2.16; 95% CI 1.53-3.03), but not MO (RR 1.23 95% CI 0.90-1.69). In addition age <45 years, smoking and oral contraceptive use further increased the risk. Nine studies investigated the association between migraine and MI, and five between migraine and CVD death. The pooled RR were 1.18 (0.99-1.40) for MI and 1.03 (0.79-1.34) for CVD death. Only one study

investigating the association between women with migraine with aura and both MI and CVD death, which suggests a two-fold increased risk (Table 1).

Conclusions of the meta-analysis were: "Current data suggest that migraine is associated with a two-fold increased risk of ischemic stroke, which is only apparent among migraineurs with aura. Risk was magnified for younger migraineurs, smokers, and women using oral contraceptives. We did not find an overall association between any migraine and MI and CVD death. Too few studies are available to reliably evaluate the impact of modifying factors on the association between migraine and both MI and CVD death."

The American migraine prevalence and prevention study

A recent study not included in the meta-analyses adds to the evidence in the topic. As part of the American Migraine Prevalence and Prevention study, 120,000 US households representative of the US population have been followed for 5 years[11,53,54]. Headaches were accurately and meticulously characterized. CVD events were assessed using the same well validated CVD instruments from the Women's Health Study[39], in order to: [1] Profile cardiovascular risk factors for CVD in migraineurs and controls. [2] Ascertain cardiovascular events in individuals with migraine vs. controls. [3] Assess the relationship of MA and MO and CVD in both men and women across a broad range of ages.

In univariate analyses, we found that for migraine overall and for MA, rates were higher for heart attack, stroke, and claudication. For MO, rates were higher for heart attack and claudication, but not for stroke. Rates were highest in MA than in MO. Figure 1 displays the odds of reporting any of the possible CV events captured in our study, in MA and MO, relative to controls. As displayed, the magnitude of the association is higher for MA, but also significant for MO for men and white race, although not for the other categories.

Overall, migraineurs were also more likely than controls to have a medical diagnosis of diabetes (12.6% vs. 9.4%, OR=1.4, 95% CI=1.2-1.6), hypertension (33.1% vs.

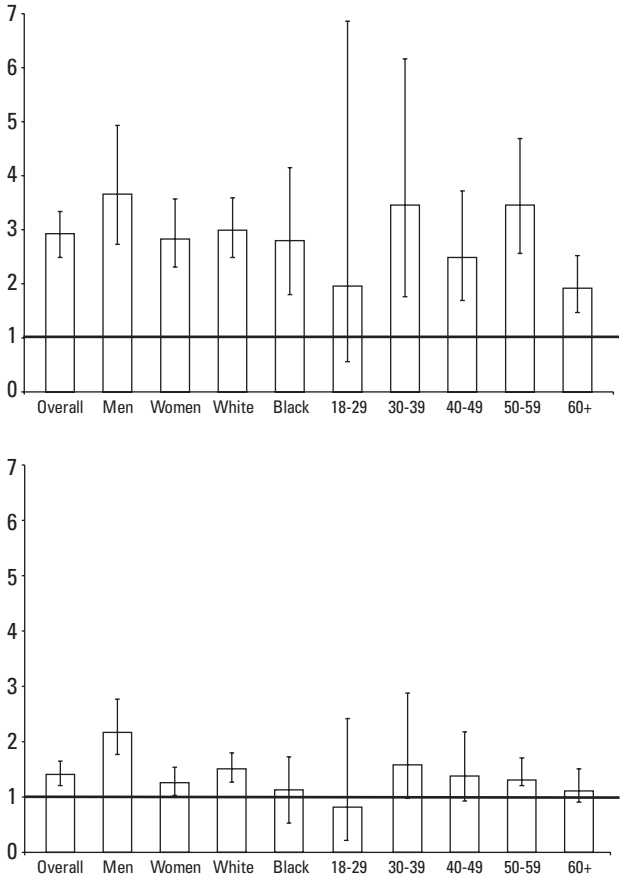

Fig 1. Odds ratio of reporting any cardiovascular event in individuals with migraine with aura (top graphic) and migraine without aura (bottom graphic) (based on[56]). Bars represent the odds ration and whiskers represent the confidence intervals.

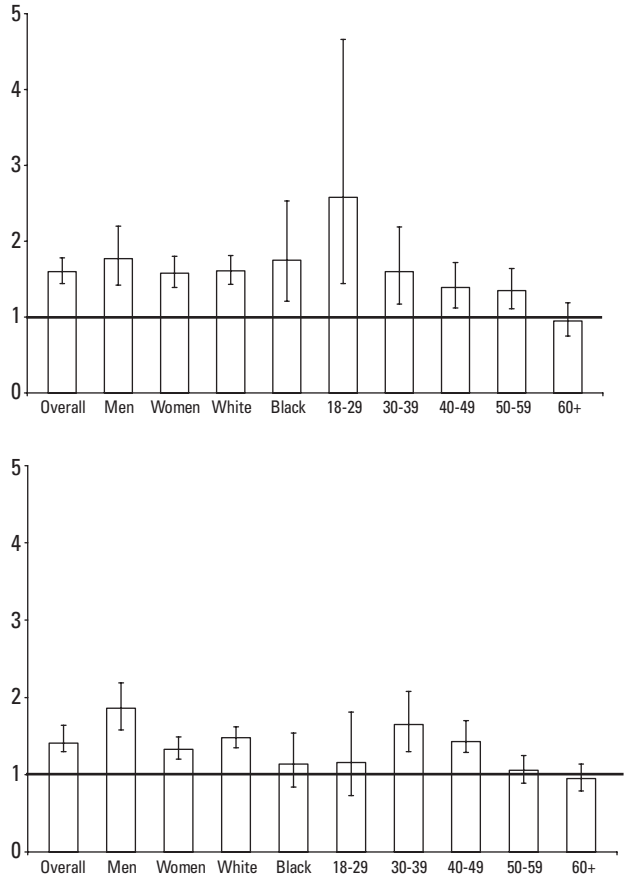

Fig 2. Odds ratio of reporting at least two risk factors for cardiovascular events in individuals with migraine with aura (top graphic) and migraine without aura (bottom graphic) (based on[56]). Bars represent the odds ration and whiskers represent the confidence intervals.

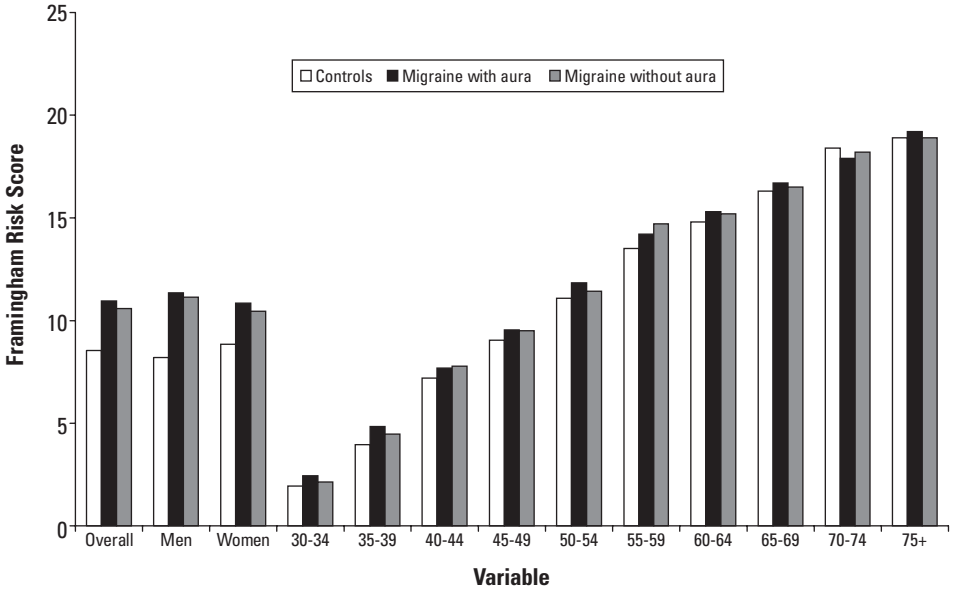

Fig 3. Mean Framingham scores of participants as a function of their headache status and of demographics (based on[56]). Stratification is by age in years.

27.5%, OR=1.4, 95% CI=1.3-1.6), and high cholesterol (32.7% vs. 25.6%, OR=1.4, 95% CI=1.3-1.5). Although they were significantly more likely to smoke, differences are small, and the significance likely reflects our large sample size.

MA was significantly associated with all risk factors. MO was significantly associated with diabetes, hypertension and high cholesterol, but not with smoking. Although the magnitude of the association was higher for MA than for MO, the differences were not as broad as seen for CVD (Fig 2).

Figure 3 displays the Framingham scores for migraine overall, MA and MO, as well as by gender and age. Overall, risk scores were significantly higher for all migraineurs (mean=10.7, SD=5.4), MA (11.0; 5.4) and MO (10.6; 5.4) as compared to controls (8.5; 6.1) ($p<0.001$ for all comparisons with controls). Scores were significantly higher in migraineurs of both genders (overall and for MO and MA). Scores were numerically higher for all age groups younger than 70 years. Scores were significantly higher for migraineurs in all age ranges from 30-59 years old.

Multivariate analyses

Because migraine was associated with both CVD and risk factors for CVD, and since some medications used to treat migraine are vasoconstrictive, in our multivariate models we tested main effects after adjusting for gender, age, disability, triptan use, as well as for the CVD risk factors assessed in our study (diabetes, hypertension, smoking, and high cholesterol). Overall migraine remained significantly associated with myocardial infarction (OR=2.2, 95% CI=1.7-2.8), stroke (OR=1.5, 95% CI=1.2-2.1), and claudication (OR=2.69, 95% CI=1.98-3.23). MA was significantly associated with the three outcomes. MO remained associated with myocardial infarct and claudication but not stroke.

Conclusions

It seems that the association between migraine and ischemic vascular events is demonstrated beyond reasonable doubt. What is yet to be defined are the subgroups at increased risk and how to prevent this increased risk. Also, it is undefined if migraine is per se a modifiable risk factor for CVD (in other words, does migraine treatment influence CVD outcomes?).

Longitudinal studies assessing the predictors of the relationship between migraine and CVD should be conducted. Future studies should assess the importance of headache frequency and severity, as well as frequency of auras.

It is important to emphasize that the increased risk of CVD imposed by migraine is small and that most patients are at no or little increased risk of CVD. Accordingly, most patients with migraine should be reassured instead of being frightened.

Nonetheless, it seems that studies have convincingly shown the association. Based on the findings, clinicians should have heightened vigilance for modifiable cardiovascular risk factors in migraineurs, such as hypertension, hyperlipidemia, and particularly smoking, that has been associated with magnifying risk for ischemic stroke among patients with MA. In particular, women with MA who take oral contraceptives, should strictly avoid

smoking and alternative contraceptive methods should be considered on an individual basis. Ultimately, as described above, it will be important to determine whether MA is itself a modifiable risk factor for CVD. Additionally, studies should investigate the possibility that preventive medications for migraine or antiplatelet therapy might reduce the risk of CVD in patients with overall migraine or MA[55].

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