Migraine as a cardiovascular risk factor for women

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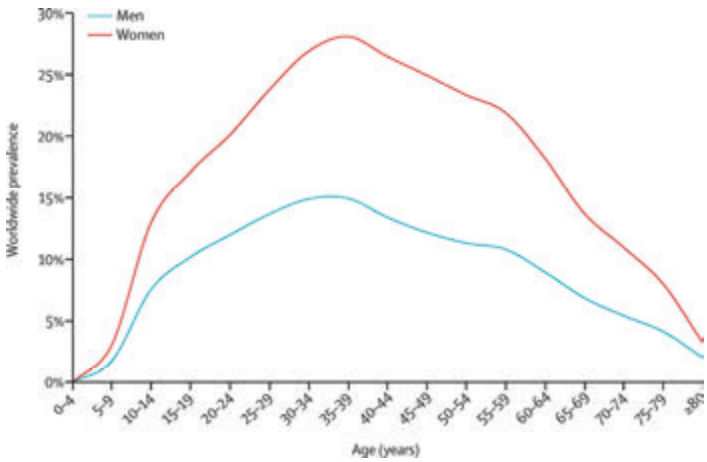
CHAPTER 1

General introduction and outline

MIGRAINE IN WOMEN

Migraine is a chronic disabling neurological disorder characterized by recurring severe headache attacks. The life time prevalence of migraine is 15% in the general population and globally more than 1 billion persons are affected.[1,2] Migraine occurs two to three times more often in women compared to men. Migraine prevalence fluctuates with age, with a peak occurring between age 30 and 40, when prevalence rises up to 15% in men and 27% in women (figure 1).[3] Migraine is the second largest cause of disability worldwide and is responsible for around 5.6% of total years lived in disability.[2] Because mainly a young working population is affected, migraine has a huge impact on individual and societal level.

Figure 1. migraine prevalence in different age groups, stratified by sex.



Source: Vetvik et al., 2017[3]

Migraine attacks are characterized by a severe pulsating one-sided headache that may last up to 72 hours, often accompanied by severe nausea and/or photo- and phonophobia.[4] Though any individual can experience a migraine attack once in a lifetime, the diagnosis migraine is made after 5 or more attacks.[4] One third of migraine patients experiences migraine auras preceding the headache phase. Migraine auras are transient, reversible positive neurological symptoms, most commonly visual but sometimes including aphasia, sensory or motor features.

Migraine headache pathophysiology is attributed to a yet incompletely understood mechanism originating in activation of the trigeminovascular system. This subsequently leads to the release of neuropeptides such as calcitonin gene-related peptide (CGRP) and substance P, which are associated with vasodilation, inflammation and pain. It is yet unclear what lowers the threshold for this cascade to be set in motion. Most likely, a combination of factors is involved in migraine susceptibility. Next to a genetic component and external (lifestyle) factors, fluctuations in sex hormone levels are associated with increased sensitivity to attacks.

The prevalence of migraine, but also the attack frequency and severity are influenced by fluctuations in levels of gonadal hormones, especially estrogen. In women, before puberty and after menopause, migraine is far less common than during the fertile years. In times of instable hormone levels, many women experience a surge in migraine activity. This is often observed around pregnancy, perimenopause and during the early follicular phase of the menstrual cycle, when estradiol levels drop quickly.[5] Approximately 55% of women with migraine suffer from menstrually related migraine (MRM).[6] Apart from being more frequent, perimenstrual migraine attacks are reported to be longer and more severe.[6,7] Evidence on altered absolute hormone levels in any stage of the menstrual cycle in women with migraine is conflicting.[8] The use of exogenous hormones, for example in the form of oral contraceptives (OC) by migraine patients is a matter of debate. Though several guidelines argue against the use of OC by women with migraine because of the increased cardiovascular risk, this advice seems to be based on very limited evidence.[9,10] Also, it is unknown whether low dose OC carry the same risk as high dose OC. There is some evidence for OC use as prophylactic migraine treatment in women with MRM. The estrogen withdrawal during the pill free interval may trigger headache in around 70% of women, which is why a shortened pill free interval regimen is suggested to be of benefit.[8]

CARDIOVASCULAR DISEASE IN WOMEN

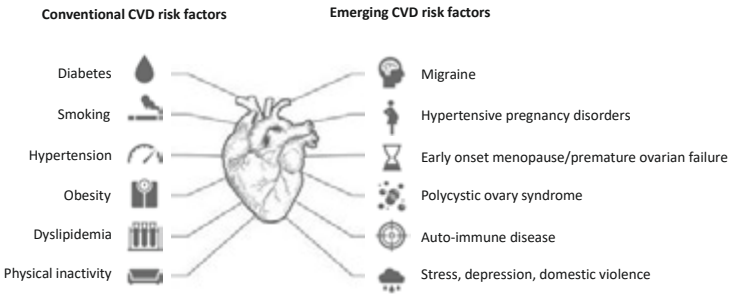
Cardiovascular disease is the most common cause of mortality in both men and women, accounting for one third of all deaths. An estimated 275 million women suffer from cardiovascular disease globally.[11] In the past few decades, a positive change has been made in the awareness of the impact of cardiovascular disease in women and the importance of acknowledging sex differences. However, there remain large steps to be made to close the gap in scientific knowledge and to improve recognition by patient and health professional.[11] Women with cardiovascular disease are still less likely to be treated correctly or to be treated at all.[12]

Sex differences in cardiovascular disease are present in etiology, risk factors and outcome. Cardiovascular disease etiology in women seems to involve a wider spectrum than atherosclerotic large vessel disease which is common etiology in men. In ischemic heart disease, an increased focus on female type pathophysiology has revealed a large role for microvascular, endothelial and vasomotor dysfunction as opposed to the obstructive atherogenic pathophysiology more often observed in men.[13,14] Instead of pathology in the large distal parts of the vasculature, female type vascular pathology more often presents in the distal, microvascular beds.[15,16]

The established traditional risk factors for cardiovascular disease such as diabetes, smoking and hypertension may have different influences depending on sex. For example, women with type 2 diabetes mellitus have a 50% higher risk of fatal coronary heart disease compared to men.[17] Moreover, besides the traditional risk factors, women are burdened by additional risk factors that are much more common for or even unique to their sex such as autoimmune disease,

obstetric complications or sex hormone disorders. Migraine is possibly a cardiovascular risk factor that is both more prevalent and induces a higher cardiovascular risk in women than in men.

■ **Figure 2.** Tradional and non-traditional cardiovascular risk factors in women



Adapted from Garcia et al., 2016[12]

REPRODUCTIVE DISORDERS AND CARDIOVASCULAR RISK

Reproductive disorders, such as preeclampsia and polycystic ovary syndrome (PCOS) are female-specific risk factors for cardiovascular disease. Preeclampsia is a syndrome presenting as gestational hypertension in combination with one or more new onset conditions which are proteinuria, organ dysfunction or placental dysfunction.[18] It occurs in 3-5% of all pregnancies and is the second cause of maternal mortality wordwide.[19] Preeclampsia is associated with an increased risk for cardiovascular disease. For women with a history of preeclampsia, the risk for stroke and myocardial infarction is twice as high, and the risk for hypertension is increased almost four times.[20] The risk of cardiovascular disease is even increased 7-8 times for women with the severe early-onset type preeclampsia.[20,21] Pregnancy is considered to be a stress test for cardiovascular disease later in life.[22] However, whether preeclampsia can be seen as a marker for future risk or as a part of the causal pathway, remains unclear. PCOS is the most common hormonal disorder in women of reproductive age, affecting 8-15% of women.[23,24] It presents as a combination of at least two criteria including oligo- or anovulation, hyperandrogenism and polycystic ovaries on ultrasonography. Women with PCOS have an increased risk for unfavourable cardiometabolic and cardiovascular profiles including increased obesity and dyslipidemia, insulin resistance, type 2 diabetes and hypertension.[25,26] However, the long term effect of these increased risk factors, as well as the role of increased testosterone in women with PCOS remains uncertain, as no evidence for increased atherosclerosis, CVD risk or mortality has been found.[27,28]

STROKE IN WOMEN

Yearly, approximately 12 million people are affected by stroke worldwide.[29] Stroke is the second most common cause of mortality and accounts for 11.5% of all deaths.[29] Both age-adjusted incidence and mortality are lower in women compared to men between the age 45-75 years, but higher at the ages below and above this range. However, because of their longer life expectancy, this amounts to a larger absolute number of women than men experiencing stroke incidence and mortality.[30,31]

Stroke is an acute restriction of blood supply to part of the central nervous system, caused by either an arterial occlusion (ischemic stroke) or rupture (hemorrhagic stroke). The resulting deprivation of oxygen and nutrients can lead to irreversible tissue damage within minutes. Approximately 85% of all strokes is ischemic in nature. Ischemic stroke etiology subtypes are described according to the 'Trial of Org 10172 in Acute Stroke Treatment' (TOAST) criteria: large-artery atherosclerosis, cardioembolism, small-vessel occlusion, stroke of other determined etiology and stroke of undetermined etiology.

Similarly to cardiovascular disease in general, sex differences in stroke have been increasingly acknowledged over the past few decades. Women are at a higher risk of young stroke (at an age under 50 years) and stroke at an older age (above 75 years) compared to men. The latter may be due to the longer life expectancy for women and the loss of the protective mechanisms of estrogen after menopause.[32,33] Women more often suffer from stroke of cardio-embolic etiology whereas stroke in men more often has large vessel etiology.[34] Also, sex differences in hemostatic activation have been found in stroke patients, with increased levels of procoagulatory factors found in women.[35] Also, women with stroke deal with more debilitating consequences in outcome compared to men.[30] This may be due to the higher age at onset for women and the resulting lower pre-stroke ability.[30] Risk factor profiles are likely different between sexes, with men more often having a history of smoking and coronary artery disease and women more often atrial fibrillation and hypertension.[36] Risk factors unique to women, such as reproductive and hormonal disorders, may be accountable for sex differences as well.

MIGRAINE AND CARDIOVASCULAR DISEASE IN WOMEN

Migraine is an important risk factor for cardiovascular disease, including stroke.[37] Migraine with aura increases the risk of ischemic stroke twofold. A twofold increased risk for hemorrhagic stroke is also described for migraine with aura.[38,39] Compared to established risk factors, migraine with aura is more strongly associated with the risk for a major cardiovascular event than obesity or dyslipidemia.[40] Evidence that migraine without aura is a risk factor for stroke is less convincing.[41] Whereas some meta-analyses describe an increased risk of stroke of 1.2 for patients with migraine without aura, others do not find an increased risk at all.[42] Besides stroke, migraine is associated with an increased risk for myocardial infarction. Cardiovascular mortality was increased around 1.5 fold in women with migraine and 2.5 fold in patients with migraine with aura.[43] A young age (<45 years), smoking and the use of oral contraceptives

increase the risk of cardiovascular disease even further.[41] Although an increased cardiovascular risk has also been found in men with migraine, it is markedly more pronounced in young women.[41,44] Whereas the risk for a major CVD event was increased twofold in women it was only increased by a factor 1.2 in men.[45] Whether the lower prevalence of migraine in men has caused bias in these observations, is uncertain.[46] The matter remains unresolved as some of few studies comparing sexes find no difference between men and women at all.[47]

UNDERLYING MECHANISMS FOR THE ASSOCIATION BETWEEN MIGRAINE AND CARDIOVASCULAR DISEASE IN WOMEN

MIGRAINE AND STROKE

The pathophysiological mechanisms behind the association between migraine and stroke are incompletely understood and likely multifactorial.[45] Extensive MRI studies have shown that migraine patients (and again women in particular) have an increased risk of white matter lesions.[48] These lesions are a subclinical sign probably caused by small vessel damage. There is of yet no conclusive evidence that these lesions lead to cognitive or cerebellar symptoms or that increased frequency of headache attacks leads to more white matter lesions or faster lesion progression.[49] In contrast, increased white matter lesions were found even in patients who no longer suffered from active migraine.[50] This observation seems to indicate that there is a common pathophysiological aspect that leads to both migraine and stroke, rather than migraine attacks causing progressive brain lesions. Interestingly, the lesions are more prominent in patients with migraine with aura compared to migraine without aura.[51] Similarly, the association with stroke and other cardiovascular disease is higher in migraine patients with aura than in those without aura.[52] The occurrence of migraine auras has been linked to cortical spreading depolarizations (CSD). CSDs are slowly propagating waves of membrane depolarization, moving from the visual cortex towards the frontal cortex. Similar spreading depolarization is observed in ischemic areas during stroke. Whether and how cortical phenomena and deep tissue subclinical damage in migraine patients are related remains unclear. There are several conditions that imply the co-morbidity of migraine and stroke, including migrainous infarction, persistent foramen ovale and carotid dissection, however these do not account for the majority of cases.[39,53] There is genetic evidence linking stroke and migraine in several hereditary disorders such as spreading familial hemiplegic migraine (FHM), cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), hereditary cerebral hemorrhage with amyloidosis – Dutch type (HCHWA-D) and retinal vasculopathy with cerebral leukoencephalopathy and systemic manifestations (RVCL-S).[54–58] In genome-wide assocation (GWAS) studies, a common locus was found implicated to migraine and four other cardiovascular disorders (coronary artery disease, cervical artery dissection, fibromuscular dysplasia and hypertension). The SNP thought to be responsible was revealed to have a regulatory effect on expression of the EDN1 gene, which codes for the protein endothelin 1 (ET-1).[59] Higher levels of ET-1 have been found in migraine patients, especially in the interictal period. Moreover ET-1 has been found to trigger CSDs in

rats, providing an interesting link between the substrate of the migraine aura and the vascular mechanims of migraine.[60] However, it is difficult to comprehend how these genetic findings can be translated to the clinical context. For example, the effect on coronary artery disease was contradictory to the effect on migraine, hypertension and cervical artery dissection.

MIGRAINE AND CARDIOVASCULAR DISEASE

Together, the observations above suggest that migraine is linked to stroke because of local vascular phenomena. However, migraine is associated with vascular disease outside the brain as well, which calls for a broader explanation.[61] One such explanation is a possible increased presence of established cardiovascular risk factors such as hypertension and hypercholesterolemia in migraine patients.[62] However, it is unlikely that a single traditional cardiovascular risk factor will be the sole driving force behind the migraine – cardiovascular disease association. Moreover, the association between migraine and stroke is most prominent in women with a lower Framingham Risk Score, which suggests that there are other factors involved besides the asessed conventional vascular risk factors.[63] Although migraine is associated with an increase of vascular markers such a prothrombin, von Willebrand factors and endothelin, there are no signs of enhanced atherosclerosis.[64,65] In women with migraine with symptoms of angina, lower scores for coronary artery stenosis are found on angiography.[66,67] It is hypothesized that a systemic vascular vulnerability predominantly present in the proximal microvasculature underlies the association and overlap between migraine and cardiovascular events.[39,68,69] Existence of comorbidities involving disturbed peripheral vasoregulation such as Raynaud's syndrome in migraine patients seem to support this view. Women with migraine often report cold extremities which could suggest impaired vascular regulation. However, it has never been investigated whether cold extremities actually more often occur in women with migraine. Among the proposed mechanisms behind the vascular vulnerability are increased platelet aggregation and prothrombotic state, vasospasm and endothelial dysfunction.[68] Endothelial dysfunction occurs when the endothelial vascular lining loses its ability to balance blood vessel tone and blood fluidity. It is an early, and sometimes still reversible, step in the pathological process towards atherosclerosis. An increased pro-inflammatory and procoagulatory state of the endothelium is combined with reduced vasodilatory properties, particulary by a decreased release of nitric oxide (NO). Several parameters for endothelial dysfunction have shown to be associated with migraine, including reduced flow-mediated dilation (FMD) in the brachial artery and increased serum levels of endothelial microparticles and endothelial precursor cells (EPC).[70,71] However, evidence is contradictory and based on a heterogeneity of biomarkers and techniques. Several new and uninvasive techniques exist which can be used to determine endothelial response in the microvasculature after provocation. The EndoPAT (peripheral artery tonometry) technique measures plethysmographic changes in the finger after occlusive hyperemia. Another technique uses laser Doppler imaging to measure skin blood flow changes after local thermal hyperemia (LTH), induced by dermal application of warm water. This method has excellent reproducibility and can be combined with application of chemical blockades to allow for distinction of NO-dependent and axon reflex-related components.

Why the cardiovascular risk for migraine patients is more pronounced in women remains unknown. The sex-specificity of migraine and the associated increased cardiovascular risk is likely indicating pathophysiological dissimilarities between men and women. Possibly, the proposed systemic vascular vulnerability is sex-specific. Also, gonadal hormone levels may account for these sex differences. Moreover, there may be a role for female-specific cardiovascular risk factors, such as pregnancy-related complications, hormonal disorders such as PCOS and the use of exogenous hormones including oral contraceptives. Besides the existence of risk factors that are unique to women, it is likely that conventional risk factors, such as smoking and hypertension, act differently in the female context.[32] The risk for cardiovascular disease in migraine patients is increased more than multiplicative by smoking, oral contraceptive use, young age and female sex.[53] Whether female-specific risk factors, including PE and PCOS, have a further supra-additive effect on cardiovascular risk in migraine patients is currently unknown.

THESIS OUTLINE

Although insights in sex differences in cardiovascular disease have increased over the last years, the role of migraine is still largely unknown. In this thesis I aim to add to this knowledge by further unravelling the role of migraine in cardiovascular disease in women.

Chapter 2 provides an overview of the knowledge at the time of the start of this thesis on (pathophysiological) mechanisms behind the association between migraine and cardiovascular disease in women. Also, this chapter summarizes the current clinical recommendations for young women with migraine, including recommendations on oral contraceptive use.

In **Chapter 3** I use the extensive Leiden University Medical Center Migraine Neuro Analysis programme (LUMINA) database to investigate whether women with migraine more often suffer from cold extremities than men, as a possible indication of a sex-specific systemic vascular dysregulation.

In **Chapter 4** I focus on the female-specific type of migraine that is related to the menstrual cycle. More specifically, I investigate whether pain sensation across the menstrual cycle is different in women suffering from menstrually related migraine (MRM) compared to women without migraine and postmenopausal women.

Chapter 5 describes a cross-sectional study aimed to determine and compare microvascular function in women suffering from the endocrine disorder PCOS with and without migraine with two techniques for the assessment of endothelial dysfunction: 1) laser Doppler assessment of blood flow changes induced by local thermal hyperemia (LTH) and 2) EndoPAT plethysmography to assess vascular reactivity after occlusion-derived hyperemia.

Chapter 6 describes the association between a history of pregnancy-related disorders (preeclampsia, HELLP syndrome and placental abruption), migraine and the occurrence of ischemic stroke in a large Dutch acute stroke cohort.

Chapter 7 presents a case control study and meta-analysis based on the current literature on the effect of combined oral contraceptives use on stroke risk in women with migraine.

In **Chapter 8**, sex-related differences in cardiovascular risk profile, stroke cause and outcome in ischemic stroke patients with and without migraine are investigated in a large prospective dataset of the collaborating university hospitals involved in the "Dutch Parelsnoer Institute Cerebrovascular Accident PSI-CVA Initiative".

Finally in **Chapter 9** I discuss the implications of my findings as well as possible directions for future research.

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