Migraine as a cardiovascular risk factor for women

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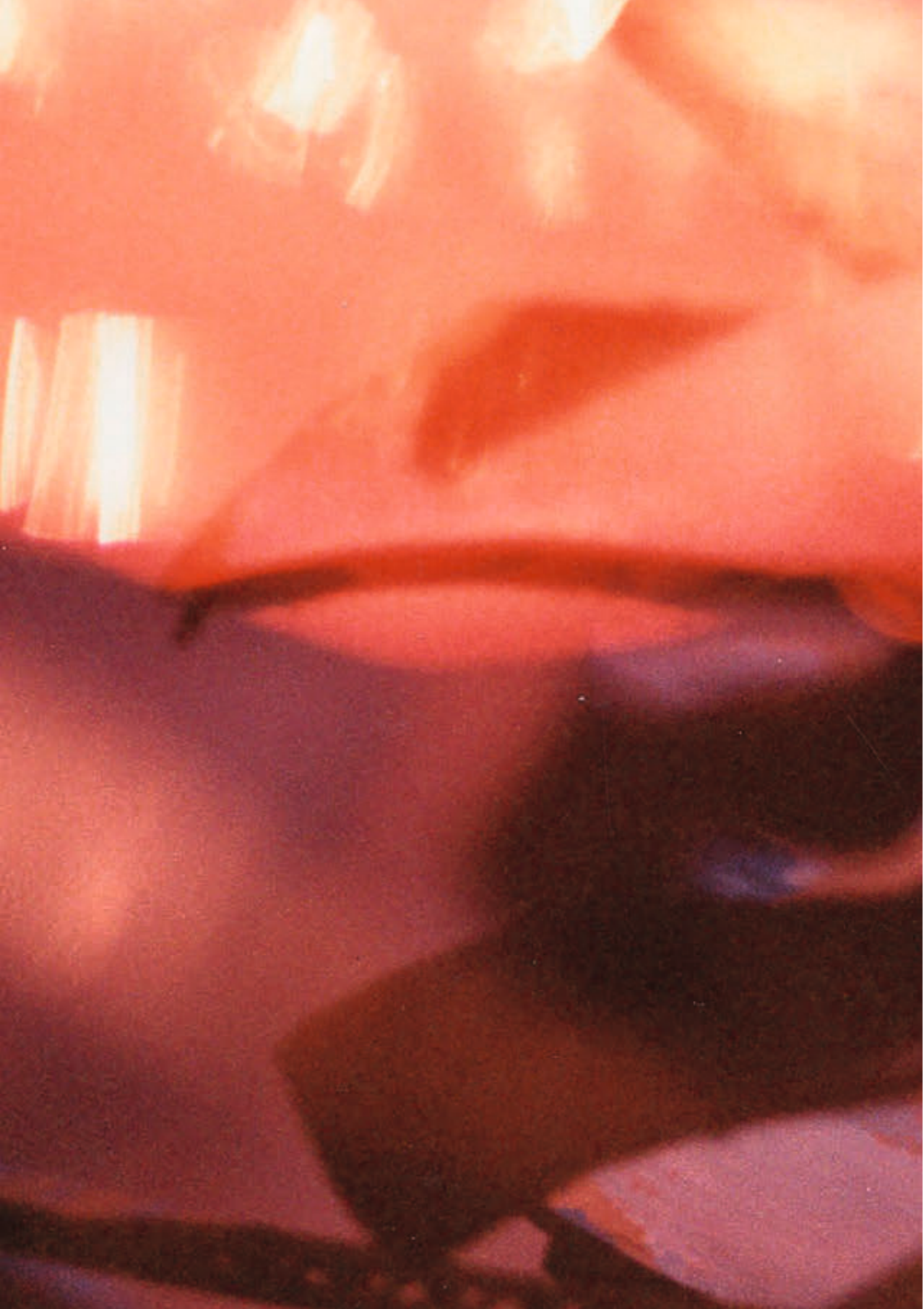

CHAPTER 9

Summary, conclusions and future perspectives

In this thesis, the role of migraine as a cardiovascular risk factor is investigated in different populations with a varying medical history, including stroke and polycystic ovary syndrome (PCOS). We focused primarily on women and sex-specific features, exploring both conventional and novel measures for vascular health. This thesis was written in the context of the CREW consortium. The aim of the CREW consortium, a cooperation of major medical centers in the Netherlands and commissioned by the Dutch Heart Institute, was to study female-specific cardiovascular pathophysiology. The CREW-MIST (Cardiovascular Riskprofile in Women – MIcrovascular STatus) project, which was part of this consortium, focused on migraine in relation to stroke in women. Female-specific factors such as sex hormone- and pregnancy-related disorders were included in our studies and we explored microvascular health through heart- and brain imaging and functional measurements of the vasculature.

SUMMARY

Chapter 1 introduces the clinical features and epidemiology of migraine and the association with cardiovascular disease including stroke. The possible mechanisms behind this association are explored, with a focus on the role of female-specific factors.

Chapter 2 presents a review of knowledge on migraine and the associated risk of cardiovascular disease at the time of the start of this thesis. It emphasizes how the increased risk for cardiovascular disease and in particularly stroke is most consistently described in women, especially those with migraine with aura. The role of cortical spreading depolarizations, genetics, sex hormones and vascular pathology including endothelial dysfunction are reviewed as underlying mechanisms for the assocation between migraine and cardiovascular disease. For clinical practice, it is advised that migraine with aura should be incorporated in cardiovascular risk assessments in women, even though the absolute risk remains low. Clinical advice for women with migraine remains limited to revising possible oral contraceptives use and lifestyle advise mainly aimed at quitting smoking.

Further exploration of the vascular component that may be altered in migraine patients is described in **chapter 3**, which presents a case-control study exploring cold extremities and sleep in men and women with migraine and healthy controls. This study focused on body temperature as a measure of dysfunctional autonomous vascular regulation that is a possible common pathophysiological mechanism linking migraine and cardiovascular disease. Women with migraine reported cold extremities more than twice as often as women without migraine, whereas such a difference was not found in men. This possibly indicates a vascular vulnerability in migraine patients that is sex-specific. No difference was found comparing the migraine subtypes with or without aura. Among the women with migraine, cold extremities were associated with higher attack frequencies, which was partly mediated by difficulty falling asleep. Further studies are needed to investigate whether cold extremities are associated with increased cardiovascular risk in migraine patients and could serve as a non-invasive marker for risk assessment in these patients.

Gonadal hormone levels likely play a role in the sex differences found in the increased cardiovascular risk in migraine patients. Previously, an altered pattern of estradiol levels and trigeminal nerve-mediated microvascular reactivity throughout the menstrual cycle in women with menstrually related migraine (MRM) was described by the Erasmus MC vascular pharmacology study group. These findings coincide with the results of our case-control study described in **chapter 4** that investigated the differences in pain perception in women with MRM at two different stages of the menstrual cycle, compared to women without migraine and postmenopausal women. Women without migraine reported higher pain sensation in the trigeminal dermatome at mid-luteal phase compared to the early follicular phase. Similar to the findings on estradiol levels and vascular reactivity, these cyclical changes were not found in women with MRM. Interestingly, differences in cyclicity of perceived pain were only detected in the trigeminal dermatome and not outside of this region. Our findings suggest that the fluctuation of trigeminal pain throughout the cycle is compromised in women with MRM; which may point to an altered trigeminovascular sensitivity that may aid in understanding pathophysiology and treatment response in these patients.

In **chapter 5** a cross-sectional study in women with PCOS is described, aimed at comparing microvascular function in women with and without migraine using novel non-invasive techniques. Measurements of dermal blood perfusion during local heating (local thermal hyperaemia; LTH) were used to assess regulation of the microvasculature. Measurements were performed with and without blockade of axon reflex induced neuropeptide release and nitric oxide availability, two important components of the vasoregulatory response to heating. The application of EMLA anesthetic cream resulted in less inhibition of axon reflex mediated vasodilation in women with migraine compared to women without migraine (86.7%, SD = 26.5 versus 67.9 %, SD = 24.2; p = 0.014). This finding suggests that vasoregulation in women with migraine is altered, however this difference was not found in the control conditions without blockade. The observed affected peripheral neuropeptide activity was not reflected by a conventional cardiovascular risk score (Framingham Risk Score; FRS) in these women, which may indicate that the altered vasoregulation in women with migraine is not associated with the conventional cardiovascular risk factor profile.

In **chapter 6** ischemic stroke characteristics and cardiovascular risk profile were assessed in women with a history of pregnancy-related complications associated with vascular disease (preeclampsia, HELLP syndrome and placental abruption). While no differences were found in ischemic stroke etiology, age at onset was 10 years younger and the risk for young stroke (onset <50 years) was increased almost five-fold in these women compared to women without a history of pregnancy complications. No differences in stroke characteristics were found when women with and without migraine were compared, however age at onset was 9 years younger in these patients. Our results suggest that both pregnancy-related disorders and migraine are associated with a risk for CVD at a younger age. This could imply that both disorders should be incorporated in cardiovascular risk assessment of women. Whether the combination of these factors leads to an even further increased cardiovascular disease risk needs further study.

Chapter 7 describes a nested case-control study with data from electronic health records and a subsequent systematic review and meta-analysis on the ischemic stroke risk in women with migraine using combined oral contraceptives (COC). In the case-control study, risk of stroke was substantially increased in women with migraine using COC compared to women with neither of these risk factors (aOR: 6.83; 95% CI: 3.95–11.68) The risk even further increased when the factor smoking was added (aOR: 30.24; 95% CI: 4.22–610). The systematic review including the results from our nested case control study showed a substantially increased ischemic stroke risk for women who both had migraine and used COC compared to women without migraine and COC use (pooled aOR: 4.95; 95%CI: 2.13–11.48). In a subanalysis in women with migraine using lower estrogen dose COC (<50 µg) ischemic stroke risk was still increased (pooled aOR: 3.14; 95%CI: 1.75–5.62). Evidence on the risk of ischemic stroke in women with migraine using COC remains limited and heterogenous. Further studies are needed to improve personalized decision making regarding COC prescription in women with migraine.

The increased risk for stroke in patients with migraine seems to be sex-dependent, however the underlying mechanisms remain unclear. **Chapter 8** presents a large prospective study based on the multicenter Dutch Parelsnoer Institute CVA database, in which we investigated sex differences and the role of migraine in cardiovascular risk profile and stroke characteristics. We concluded that migraine was not associated with sex differences in cardiovascular risk profile. It is important to note that only conventional, and not female-specific risk factors were taken into account in this analysis. In women as opposed to men, migraine was associated with an almost twofold increased risk for young stroke. In men, but not in women, migraine was associated with stroke from 'other determined etiology' according to the trial of ORG 10172 in acute stroke treatment (TOAST) classification and with a poorer outcome according to the mRS. This study suggests that there are sex differences in the pathophysiology underlying the association between migraine and ischemic stroke that are not related to conventional cardiovascular risk factors. This stresses the importance of sex-specific cardiovascular risk assessment and the need to study what factors give rise to sex differences in future research.

DISCUSSION

Although there is extensive literature describing the association between migraine and cardiovascular risk there are still many unknowns. Current knowledge gaps are: 1) which mechanisms may drive this association, 2) why the increased cardiovascular risk appears to be more prominent in women with migraine, 3) how migraine as a risk factor relates to other female-specific conditions associated with increased cardiovascular disease risk, such a pregnancy-related complications and sex hormone disorders and 4) which clinical recommendations might be given to women with migraine to reduce the risk of cardiovascular events. The studies described in this thesis aim to investigate these topics and provide a basis for further research.

1. POSSIBLE MECHANISMS FOR THE ASSOCIATION OF MIGRAINE WITH CARDIOVASCULAR DISEASE

1.1 VASCULAR VULNERABILITY

There is increasing evidence that the association between migraine and cardiovascular disease is not based on conventional risk factors resulting in atherosclerosis.[1,2] Our results in **chapter 8** support this view, as the prevalence of conventional cardiovascular risk factors was not increased in men or women with migraine in a population of ischemic stroke patients. In the study population of women with PCOS described in **chapter 5** we also found no increased cardiovascular risk scores according to the conventional Framingham Risk Score (FRS) in women with migraine. It is suggested that instead of these conventional cardiovascular factors, there are other mechanisms responsible for the migraine – cardiovascular disease association. Besides the factors summarized in **chapter 2**, including vascular comorbidities and a shared genetic predisposition, there is an increased interest in the role of the microvasculature. Therefore, we focused in several studies of this thesis on microvascular function and vulnerability. A possible cardiovascular pathophysiological mechanism that lies outside of the conventional scope is described **chapter 3**, in which we show that women with migraine more often suffer from cold extremities than women without migraine. Cold extremities indicate peripheral vascular autonomous dysregulation, which may indicate the presence of a systemic vascular vulnerability. Interestingly, the higher prevalence of cold extremities was only found in women, which may suggest that the altered vascular reactivity in migraine is (at least partly) sex-specific. This finding strengthens the idea that sex differences in cardiovascular risk for migraine patients may be based on a more 'female type' cardiovascular etiology; presenting as dysregulation of the microvasculature rather than large artery atherosclerosis.[3,4] In the field of cardiology, this female-specific pathophysiology is observed in the large percentage of women with angina pectoris and cardiac ischemia with no obstructive coronary artery disease (ANOCA and INOCA).[5] In these patients, coronary vasomotor dysfunction is the common etiology, which interestingly is associated with systemic dysfunction beyond the cardiac vasculature.[6,7]

The microvascular vulnerability possibly underlying the increased CVD risk in patients with migraine may be caused by endothelial dysfunction. Where the endothelium has vasoprotective properties when in healthy homeostasis, dysfunction leads to inflammation, increased vessel wall permeability, altered vascular tone, platelet activation and thrombogenicity.[8,9] Serum levels of several biomarkers for endothelial dysfunction are altered in patients with migraine, including endothelial precursor cells (EPCs), endothelial microparticles and secondary factors involved in inflammation and coagulation.[10,11] Levels of the vasoactive protein endothelin-1 (ET-1) rise in the early ictal phase in patients with migraine.[12] The ET-A and ET-B receptors have contrasting effects on the vasculature and the ratio of their expression varies greatly among vascular locations. The ET-A receptor has vasoconstrictive effects and is the predominant receptor in the trigeminovascular system. Besides its vasoactive role, ET-1 is associated with cortical spreading depolarization, induction of pain and sensitization, and the release of substances involved in migraine initiation such as nitric oxide (NO) and calcitonin gene-

related peptide (CGRP).[12,13] Increased ET-1 levels are also observed after ischemic stroke, both in patients with and without migraine.[13,14] Levels of NO synthase inhibitor ADMA are also increased in migraine patients, especially in the interictal period.[15] Interestingly, higher ADMA levels were also associated with white matter hyperintensities (WMH) in these patients, confirming the idea that the observations of subclinical damage on MRI are related to endothelial dysfunction.[16]

Assessment of endothelial vasoregulation can be performed by a wide variety of functional tests, including (brachial artery) flow-mediated dilation (FMD), venous occlusion plethysmography and pulse wave velocity. In several systematic reviews, vasoregulation measured with these modalities was not clearly impaired in women with migraine. However, the heterogeneity and small sizes of the studies complicate interpretation of the results.[17,18] Many of the techniques assessing microvascular function are invasive or prone to inter- and intra-observer variability. Moreover, any of these functional measurements is challenged by having to control a variety of artefact-inducing circumstances, such as temperature, stress and breathing patterns to which the microvasculature inherently responds. The novel technique LTH (laser Doppler assessment of blood flow changes induced by local thermal hyperemia) that we used to assess microvascular reactivity in **chapter 5** is non-invasive, has good reproducibility and allows for controlling of interfering circumstances. Moreover, using blockades of axon reflex induced neuropeptide release and NO-dependent responses allows for further assessment of the role of the involved vasoactive components and endothelium. Our findings in a study population with PCOS show that neuropeptide release is inhibited less after blockade with anesthetic EMLA cream in women with migraine than in women without migraine. This suggests that an altered microvascular response, occurs in these women. No differences were found in overall responses without blockade or in after blockade of NO was established by application of LNMMA, which suggests the involved mechanisms are likely complicated and masked by compensatory effects. Further investigation of the mechanisms of microvascular function in both women and men with migraine is needed. Although the vasodilatory component of microvascular function may certainly play an important role in the migraine – CVD association, more attention is also needed for the pathogenic roles of inflammation, platelet activation and thrombosis and their interplay with the endothelium.

1.2 MIGRAINE SEVERITY, SUBTYPE AND CVD RISK

An important question to address to improve individual risk assessment for patients with migraine, is whether more frequent, more severe migraine or particular migraine subtypes are associated with a further increased underlying microvascular vulnerability and thus increased CVD risk.

There is conflicting evidence on whether patients with a higher migraine attack frequency have a higher CVD risk compared to those with a lower attack frequency.[19,20] Literature on the subject is limited to the assessment of migraine severity in terms of attack frequency and is mostly focused on women and the risk of ischemic stroke.[19] In patients with migraine with aura, a frequency of more than one migraine attack per month was associated with a further

increased risk of ischemic stroke compared to lower frequencies.[20,21] Interestingly, risk for angina and myocardial infarction was decreased in women with an attack frequency of more than once a month, while risk for ischemic stroke was increased in women with more than one attack per week.[20] In men, no evidence was found that migraine attack frequency was related to further increase of CVD risk.[22] In MRI studies, infarct like lesions in the posterior circulation were found more extensively in patients with higher migraine attack frequencies (≥1 per month).[23,24] However, progression of white matter hyperintensities was not associated with number or frequency of migraine attacks nor with activity (attacks in the past year) or use of migraine therapy.[25] Moreover, it is unknown whether white matter hyperintensities or infarct like lesions are associated with a higher CVD risk in migraine patients.

If increased CVD risk in migraine patients would be the consequence of repeated attacks, reducing the attack frequency would be a major therapeutic goal to minimize this risk. However, even if a robust association between migraine severity and CVD risk would be confirmed, it should not directly be concluded that it is a causal relation. It is possible and maybe even more likely that such an association represents a shared underlying pathology responsible for both (more severe) migraine and developing CVD. For example, in **chapter 7** of this thesis, we found that women with migraine who report cold extremities have a higher attack frequency than those who do not have cold extremities. This could indicate that a higher level of vascular vulnerability in these women is responsible for both cold extremities and more severe migraine. In this light, cold extremities may provide a useful clinical marker for vascular vulnerability and risk in migraine patients. However, migraine frequency was also indirectly affected by difficulty falling asleep as a result of experiencing cold extremities. Thus, it might not be purely the vascular vulnerability itself leading to migraine severity. To aid migraine patients to alleviate sleep difficulties caused by cold feet, the LUMC has recently launched a campaign promoting the use of warm socks.

It is evident that migraine with aura is associated with an increased cardiovascular risk, however for migraine without aura the evidence is less conclusive. There is evidence that CVD risk for migraine patients without aura may also be increased, although the risk seems to be significantly lower than the for migraine with aura.[26] The difference in stroke risk between these two subtypes could be caused by the underlying physiological substrate of a migraine aura; cortical spreading depolarizations (CSDs). These propagating waves of neurovascular uncoupling in the cortex are in turn associated with ischemia and thus would be a logical link to explain increased stroke in patients with migraine auras. However, this theory does not explain the increased cardiovascular risk for events occurring outside the vasculature of the brain. Moreover, there is evidence that CSDs also occur asymptomatically in migraine patients without aura.[27] In this thesis, we found no differences in reported cold extremities in patients with migraine with versus without aura.

1.3 MIGRAINE AND CVD RISK IN RELATION TO HORMONES

Sex hormones play an extensive role in both migraine and cardiovascular disease and it is likely that the association between the two is likewise affected by gonadal hormone levels. The role of sex hormones are also likely a part of the explanation behind the observed sex differences in CVD risk in patients with migraine.

Both female and male sex hormones are under scrutiny for their influence on migraine and CVD. However, it is unlikely that the susceptibility for migraine and the related cardiovascular risk are dependent on the absolute level of a single hormone. Rather, fluctuations of hormone levels and possibly ratios of hormones are involved. A clear example of abrupt hormonal fluctuations effecting both migraine and the vasculature is pregnancy and the postpartum period, during which migraine activity often surges and the female vasculature is undergoing enormous changes, sometimes leading to pregnancy-related vascular disorders. Women with active migraine during pregnancy are more at risk of vascular complications including ischemic stroke and myocardial infarction.[28,29] Within two weeks after delivery, post-partum angiopathy may occur. This is a rare condition of multifocal vasoconstriction of cerebral arteries of unknown cause, that presents with severe headache and visual disturbances and can lead to ischemic stroke.[30] There is still much to uncover in the field of neuro-obstetrics about the intersection of such cerebrovascular complications of pregnancy with migraine and ischemic stroke, and the possible involvement of sex hormones.

Estradiol is an especially interesting hormone in relation to migraine and CVD because of its wide array of genomic and non-genomic influences and its different receptors in many tissues of the body. Estradiol receptors present in vascular endothelial cells and smooth muscle cells and are involved in the regulation of lipid metabolism, inflammation, fibrinolysis and thrombosis.[31] Likewise, estradiol stimulates vasodilation through nitric oxide synthesis in the endothelium, increases nerve excitability by stimulating norepinephrine (NE) release and influences pain sensitization through serotonergic and GABA-ergic pathways.[32,33] Moreover, increased estradiol levels are associated with enhanced cortical excitability and spreading depolarizations, which might increase susceptibility to cerebral ischemia.[34] In the trigeminovascular system, estradiol interacts in a not yet understood way with CGRP, possibly further enhancing hypersensitivity and vasodilation.[35] The complexity of the role of estrogens increases further, as the effects vary dependent on the interplay with healthy or dysfunctioning endothelium and whether it is exogenous or endogenous of origin.[36] It is through any of these roles that estrogen may influence the vascular status of patients with migraine. Although it is unlikely that only the level of this single hormone is responsible for the association between migraine and CVD by itself, it may influence the proposed vascular vulnerability underlying this association as well as its observed sex specificity.

The effect of gonadal hormones on migraine severity and risk of CVD makes it important to carefully consider the use of hormonal therapy in patients with migraine. This is especially important for post-menopausal women on hormone replacement therapy (HRT), for

transgender patients on gender affirming hormonal therapy and for women using oral contraceptives. Whereas endogenous female hormones seem to have a vasoprotective role, this does not seem to be the case for exogenous hormones.[31,36] The influence of exogenous hormones is investigated in **chapter 7**, where we summarize the evidence for an increased stroke risk in women with migraine using combined oral contraceptives. Risk of ischemic stroke in these women was increased substantially compared to women without these two risk factors (pooled aOR: 4.95; 95%CI: 2.13–11.48), even in a sub-analysis that focused on low dose estrogen COC (pooled aOR: 3.14; 95%CI: 1.75–5.62). The use of exogenous estrogen is associated with increased hypercoagulability due to platelet hyperactivity. Possibly, this increased hypercoagulability interacts with the endothelial dysfunction that is already present in patients with migraine and results in a supra-additive increase of cardiovascular risk.

In this thesis we also took a closer look at the influence of sex hormones on migraine pathophysiology. In **chapter 4**, we found that women with menstrually-related migraine (MRM) have an altered cyclical pattern of trigeminal pain perception compared to women without migraine and postmenopausal women. Pain outside of the trigeminal dermatome was not different in these women. These findings are in line with the absence of cyclicity in estradiol levels and vascular reactivity which was described in a previous study from the Erasmus migraine study group in the same population.[38] Further studies should further explore the vascular status and CVD endpoints in relation to sex hormone level cyclicity in migraine patients.

Women with polycystic ovary syndrome (PCOS) are interesting to study in the perspective of both cardiovascular disease and migraine because of their sex hormone level imbalance. This hormone imbalance may present as increased levels of androgens including testosterone. To dissect sex differences in the association between migraine and cardiovascular disease, it is of interest to discover whether women with a more androgenous hormone profile suffer less from migraine and are less at risk for 'female type' microvascular dysfunction. In **chapter 5** of this thesis we evaluated the microvascular response to local thermal hyperemia in women with PCOS with and without migraine. Our findings indicated an altered vasoreactivity after axon reflex blockade in women with PCOS and migraine as opposed to women with PCOS without migraine. Interestingly, another study found a slightly increased axon reflex peak phase after administration of estradiol, progesteron or a combination in women with PCOS.[39] Moreover, when testosterone levels are suppressed in women with PCOS, microvascular dilation is improved and this effect is mediated through the endothelin-1 ET-B receptor.[40] These findings support the idea that neuropeptide release is influenced by gonadal hormones and might be involved in vascular dysfunction in women with migraine.

2. SEX DIFFERENCES IN MIGRAINE AS A RISK FACTOR

Whether the increased cardiovascular risk is exclusive to women with migraine or whether men share this risk partly or even equally is uncertain. Even though the main body of research concerning migraine as a cardiovascular risk factor addresses women, there is some evidence

that men with migraine are also at risk.[22,41,42] However, most of the existing data on the migraine – CVD association come from the studies including only women such as the Women's Healthy Study, and only very few studies investigated sex differences in migraine as a CVD risk factor.[42] In cohorts including both men and women, stratification by sex is often lacking and statistical power is often still poorer for men as they have a lower migraine prevalence. It might be that sex differences that are currently observed in the risk for cardiovascular disease in patients with migraine are based on underpowered evidence. In order to provide clarity, the focus of future research on the risks of migraine should shift more towards men.

In **chapter 8** we assessed sex differences in stroke characteristics in patients with migraine. Slight sex differences in age at onset, etiology and stroke outcome were found, however no differences were observed in cardiovascular risk factors. It is important to emphasize that only information on conventional cardiovascular risk factors was available in this study, whereas we believe that the association between migraine and CVD is likely influenced by other factors. Men with migraine had a higher risk of poor stroke outcome compared to men without migraine, whereas no differences were found in women. Interestingly, previous studies on stroke outcome in patients with migraine only included women, in whom a poorer stroke outcome was mostly found. More studies including patients from both sexes are needed to confirm our findings of a poorer stroke outcome in men with migraine.

Interestingly, there were differences in stroke etiology in men with migraine compared to men without migraine, whereas no such differences were found in women. The TOAST classification stroke subtype 'other determined etiology' was more common in men with migraine compared to men without migraine; which includes non-atherosclerotic vasculopathies, hypercoagulable states, vasculitis, microangiopathies and hematological disorders. This suggests that men with migraine have an underlying vascular pathology that is usually more often associated as 'female type', than men without migraine. Possibly, this could be related to the evidence that men with migraine have a more feminine sex hormone profile with higher estradiol levels, lower testosterone levels and more often present with clinical androgen deficiency symptoms compared to men without migraine.[43–45] Moreover, it has been shown that gender affirming hormonal therapy in male to female transsexuals (MFTs) increase circulating NO levels and NO dependent vasodilation and leads to a similar rate of migraine as in genetic females.[46,47]

Future research should focus on the non-conventional and female-specific risk factors and their possible interaction with sex hormone profiles as well as further investigate the stroke causes that fall under the 'other' and 'undetermined' categories of the TOAST classification in more detail.

In this same population of ischemic stroke patients, only in women, migraine was associated with a younger age at stroke onset. This was confirmed in the group of women with a history of pregnancy-related complications described in **chapter 6**, where not only the hypertensive disorders of pregnancy, but also migraine was associated with a younger age at stroke onset.

Another sex disparity in migraine as a risk factor for CVD was described in this thesis in **chapter 3**. The increased prevalence of cold extremities in migraine patients was exclusively found in women. If cold extremities are considered as a marker for vascular vulnerability, this seems to indicate a higher cardiovascular risk for women.

In this thesis, several findings point towards sex differences in the cardiovascular profile of migraine patients. However, the same limitation occurred in the studies of this thesis as in much of the other migraine literature; the under-inclusion of men. It is important to investigate possible sex differences further, to be able to understand the pathophysiological mechanisms. For instance, there could be common underlying mechanisms shared by men and women with migraine, which are more apparent in women due to their sex hormone profile. The importance of including more men in migraine-oriented research to be able to provide them with substantiated clinical advice regarding their risk of CVD should not be underestimated.

3. MIGRAINE IN COMBINATION WITH FEMALE-SPECIFIC RISK FACTORS

Allthough more research is needed to investigate whether migraine is a female-specific cardiovascular risk factor, current evidence clearly indicates that women with migraine have an increased risk of CVD. Therefore, it is interesting to investigate how migraine acts as part of the female-specific cardiovascular profile in terms of pathophysiology and interaction with other female-specific co-morbidities. With a combination of female risk factors, an additive or even a supra-additive risk of CVD could arise. Reproductive disorders, such as preeclampsia and polycystic ovary syndrome are examples of female specific risk factors for cardiovascular disease with interesting associations with migraine that we have investigated in this thesis.

Women with pregnancy-related complications associated with vascular disease (preeclampsia, HELLP syndrome and placental abruption) have a higher risk of young stroke (onset <50 years) and have an on average 10 years earlier stroke onset compared to women without these complications (**chapter 6**). This new finding is in line with the results of a systematic review that found that hypertensive disorders of pregnancy increase stroke risk and are associated with an earlier onset of type 2 diabetes mellitus and hypertension.[48,49] Although it is possible that these common conventional risk factors play a role, the pathophysiology of preeclampsia itself is under scrutiny for its possible long term effect on the vasculature after pregnancy, for example on coronary artery calcification and endothelial dysfunction.[50–52] We found no differences in ischemic stroke characteristics in women with and without migraine within this group, although this may have been a result of underpowered analyses. A lack of data on female-specific risk factors and the need to include very large groups is a common problem in studies aiming to investigate multiple risk factors simultaneously. The association of preeclampsia and migraine is interesting because of possible overlap in vascular pathophysiology. A history of migraine is associated with an increased risk of hypertensive disorders of pregnancy.[53] Not only do these disorders share similar, though slightly differing clinical characteristics

of headache with visual disturbances, both are associated with pathological changes in the vasculature including altered vasoreactivity and platelet activity and a resulting increased risk of CVD.[53] Similar to migraine, MRI studies show progressive white matter lesions in women with a history of hypertensive pregnancy disorders.[54,55] A higher rate of endothelial dysfunction has been demonstrated by several modalities.[50] Endothelin-1 (ET-1) is shown to be an important player in the clinical manifestations of hypertension, proteinuria and vasospasm observed in preeclampsia and thus could be part of the vascular vulnerability seen in both disorders.[56] Similarly, CGRP levels are altered in pregnancy and are lower in women with preeclampsia.[57] However, in contrast to migraine, preeclampsia is associated with atherosclerotic type vascular risk and, depending on subtype (early or late onset) its pathogenesis may involve defective placentation and genetic maternal factors varying per individual.[58] These differences show that understanding how the pathophysiology of migraine and preeclampsia interacts is complicated. It is hypothesized that hypertensive disorders of pregnancy do not play a causative role in vascular disease but rather act as a stress test for underlying vascular dysfunction which is brought to light by pregnancy. It could be argued that the similar vascular vulnerability that is observed in migraine patients occurs in women prone to hypertensive disorders of pregnancy as well. Further exploration of the possible supra-additive risk for CVD of migraine and preeclampsia could prove valuable for clinical management in these women.

In **chapter 5** we focused on cohort of women with the common hormone disorder PCOS. PCOS is associated with an increased CVD risk factor profile and a hyperandrogenous sex hormone profile. There is of yet only limited and contradicting evidence of a positive association between PCOS and migraine.[59,60] Although our findings describe a different vasodilatory reaction in women with PCOS with migraine, we did not include a control group to appraise differences in women without PCOS. Future research should investigate the epidemiology of migraine in women with PCOS and their associated CVD risk.

A recurrent theme with important clinical implications for female-specific vascular risk management is the use of exogenous hormones; in the form of hormone replacement therapy, gender affirming hormone therapy or combined oral contraceptives (COC). In the case-control study and systematic review presented in **chapter 7** we find confirmation that the use of COC is an additional risk factor for stroke in women with migraine, even in case of low dose estrogen COC. The risk in these women was further increased by smoking, which reinforces the importance to address smoking in women with migraine using COC as a serious modifiable risk factor.

Other female-specific CVD risk factors that have a possible association with migraine but that have remained outside the scope of this thesis are early onset menopause, depression, auto-immune disease and social factors such as domestic violence.[61–63] Whether certain combinations of these factors increase the CVD risk of women with migraine even further, remains to be investigated. For future research it is important to include pregnancy- and hormone related disorders and gender related psychosocial factors in our analysis of sex specific differences in cardiovascular risk for patients with migraine.

4. CLINICAL RECOMMENDATIONS

As we described in **chapter 2**, current clinical recommendations concerning cardiovascular risk reduction for patients with migraine are limited.

Our case control study and meta-analysis in **chapter 7** on the effect of combined oral contraceptives (COC) use in combination with migraine found a substantially increased risk for ischemic stroke in women even for low dose estrogen COC. However, the studies included in the meta-analysis were heterogeneous, few in number and did not distinguish between migraine with and without aura. Despite the limited extent, the literature concerning increased CVD risk for women with migraine has led to some clinical recommendations. The World Health Organization (WHO) and American Congress of Obstetricians and Gynecologists (ACOG) strongly recommends against the use of COCs by women with migraine with aura, classifying the use as an unacceptable health risk.[64,65] For migraine without aura, the WHO also advises against COC use, but only for women with migraine older than 35 years. For younger women, it is advised to make a careful assessment about starting or continuing COC use, weighing benefits against possible harms. The consensus statement by the European Headache Federation (EHF) and the European Society of Contraception and Reproductive Health (ESC) also provides separate recommendations for migraine with and without aura.[66] For migraine with aura COC use is contraindicated, whereas for migraine without aura, substitution by progesterone-only alternatives is advised. For women with migraine with or without aura it is advised to take additional cardiovascular risk factors into consideration. Our case control study showed a supra-additive effect of smoking on ischemic stroke risk in women with migraine using COC. Clinical advice for now should at least focus on the importance of quitting smoking in young women with migraine (with aura) and COC use. Personalized decision making is essential in these cases, as for many women with migraine, the benefits of using COCs (including decreased migraine severity) may outweigh the relatively small absolute risk of cardiovascular complications.

Currently, there is not enough evidence to support preventative pharmacotherapeutic measures for young women with migraine, such as starting antihypertensive or antiplatelet therapy. Although no such recommendations exist, it would be sensible to screen women with migraine, especially those with aura, for cardiovascular risk factors, including hypertension and pregnancy-related complications. Likewise, screening for migraine as cardiovascular risk factor should be part of follow up assessments in women with a history of pregnancy-related complications such as preeclampsia and cardiovascular events. In the Erasmus Medical Center in Rotterdam, this screening is now implemented as part of the follow up care for patients with hypertensive disorders of pregnancy. Moreover, ischemic stroke and migraine should be incorporated in primary care cardiovascular risk management. Because of the detrimental effect on sleep and concurrently increased migraine attack frequency, it might be advisable for women with migraine to combat cold feet by wearing warm socks when going to bed. For that reason, the LUMC headache research group has set up a warm sock campaign for patients with migraine.

There is also limited evidence for recommendations about the use of triptans or the new generation CGRP (receptor) inhibitors in migraine patients with prior CVD. Based on their pharmacological vasoconstrictive effects, the American Academy of Neurology and the Dutch National Health Care Institute (ZIN) consider triptans to be contraindicated in patients with a history of ischemic vascular disease.[67] The Nederlandse Vereniging voor Neurologie states that there is no solid evidence to support contraindication of triptan use after a cardiovascular event. Theoretically, CGRP (receptor) inhibitors could increase risk of vasoconstriction and ischemia, however, no confirmation from long term clinical trials yet exists.[68,69] Erenumab, one of the large CGRP monoclonal antibodies, was associated with adverse events of hypertension, which would be a highly undesirable side effect for women with migraine.[70] In contrast, the small molecule CGRP receptor antagonists called gepants do not seem to cause vasoconstriction and are therefore considered safe for patients with a history of vascular events.[71] It is speculated that women in particular are more prone to be at risk for the cardiovascular complications of CGRP (receptor) blockade. In women, levels of CGRP are higher and female sex hormones further amplify the vasodilatory effects.[57] Moreover, CGRP induced vasodilation of coronary arteries is much more prominent in the most distal portions, which in women is more often the part involved in ischemic pathophysiology.[72] Further research is needed to assess the safety of triptans and CGRP (receptor) inhibitors and their interaction with other female-specific risk factors in migraine patients. There is currently no evidence that suggests that decreasing migraine attack frequency, for example through the use of prophylactic treatment, reduces future CVD risk.[73]

The absolute risk for cardiovascular disease for young women remains low. However, migraine with aura and possibly also without aura should be included as an important risk factor in clinical risk assessment. It is important for health care providers to be aware of migraine as a risk factor for cardiovascular disease and to properly inform their patients.

FUTURE PERSPECTIVES

This thesis was written during a time of growing awareness of the differences in medical science and clinical practice for women. Sex differences in cardiovascular health are being increasingly acknowledged over the past few decades. The field of cardiology has been at the forefront of this movement, with more recognition for heart disease in women as a result. However, women remain significantly underrepresented in clinical trials on cardiovascular disease.[74] Even in fields such as experimental migraine science, the majority of preclinical studies investigating migraine involves male animals.[75] For both research concerning cardiovascular disease and migraine, there remains a vast lack of comparisons between sexes. The first and most important future perspective is to continue to bring the standards of medical science and care for women to the same level as it is for men, which can only be attained by continued prioritization of appraisal of sex differences in future research and education. Whereas for cardiovascular science, this means shifting the focus towards women, for migraine science, it means including more men.

It is necessary to increase awareness among medical professionals about sex differences in cardiovascular disease. Stroke may present itself very differently in women. For example, headache as a symptom of stroke occurs much more often in women than in men.[76] It is important to educate health professionals about the risk of misdiagnosing stroke in patients with a history migraine as another attack, thereby withholding proper clinical care for these patients. Similarly, it is important to educate women themselves about cardiovascular disease, whether they have migraine or not, so that they are able to recognise symptoms, seek proper care and optimize their lifestyles to minimise risk. In this new view of assessing cardiovascular disease, it is important to include migraine as a cardiovascular risk factor, especially in the presence of other (female-specific) risk factors.

An important topic for further research on sex differences is better recognition of cardiovascular risk for women by improving prediction-models used in primary healthcare. Although there is a large amount of cardiovascular risk prediction models for women in the general population, these rarely include female specific predictors.[77] Further exploration of the interaction between migraine and other (female-specific) risk factors, including pregnancy-related complications and sex hormone disorders could provide vital information for cardiovascular risk assessment. Big data and machine learning are emerging methods that can help to interpret vast amounts of data. Our nested case control study on COC use in patients with migraine is an example of routine data collected from different sources and analysed to improve our understanding of risks and additive risks. In the future, the foundation of (personalized) clinical recommendations could advance significantly when collecting, sharing and combining routine data from clinical settings is improved.

Research on the unconventional (female type) vascular disease calls for different techniques to assess the microvasculature and endothelial function, especially in relation to migraine status. Although some of them are used in this thesis, there is still much to learn. Further use of the local thermal hyperaemia (LTH) technique as a non-invasive tool to assess vascular health in migraine patients is promising. A first step could be to compare microvascular function measured with this new technique in women and men with migraine to controls and to investigate possible sex differences. Moreover, MRI studies exploring the heart-brain axis could enable identification of markers for microvascular damage in patients with migraine, focussing on sex differences and differences in migraine subtype.

The foundations of these aims and perspectives have been addressed by the CardiovasculaR hEalthy ageing in Women (CREW) project, which was recently finished and further investigated several new modalities of cardiovascular health, possible sex-specific risk factors and pathophysiology. This research project was a great example of the potential in bringing together experts of different fields, including neurology, cardiology, gynaecology, radiology and epidemiology. Increased interdisciplinary collaboration, such as seen in the novel fields of neuro-obstetrics and gynecardiology, could greatly advance medical care and research. Continued funding of projects similar to CREW, appraising sex differences in cardiovascular

health and the role of migraine is essential. In the best case, elucidating the association between migraine and cardiovascular disease could improve understanding of the complex pathophysiology of migraine and sex disparities in cardiovascular disease and deliver therapeutic targets to minimise the risk for both men and women.

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