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Hacking stroke in women: towards aetiology-driven precision prevention

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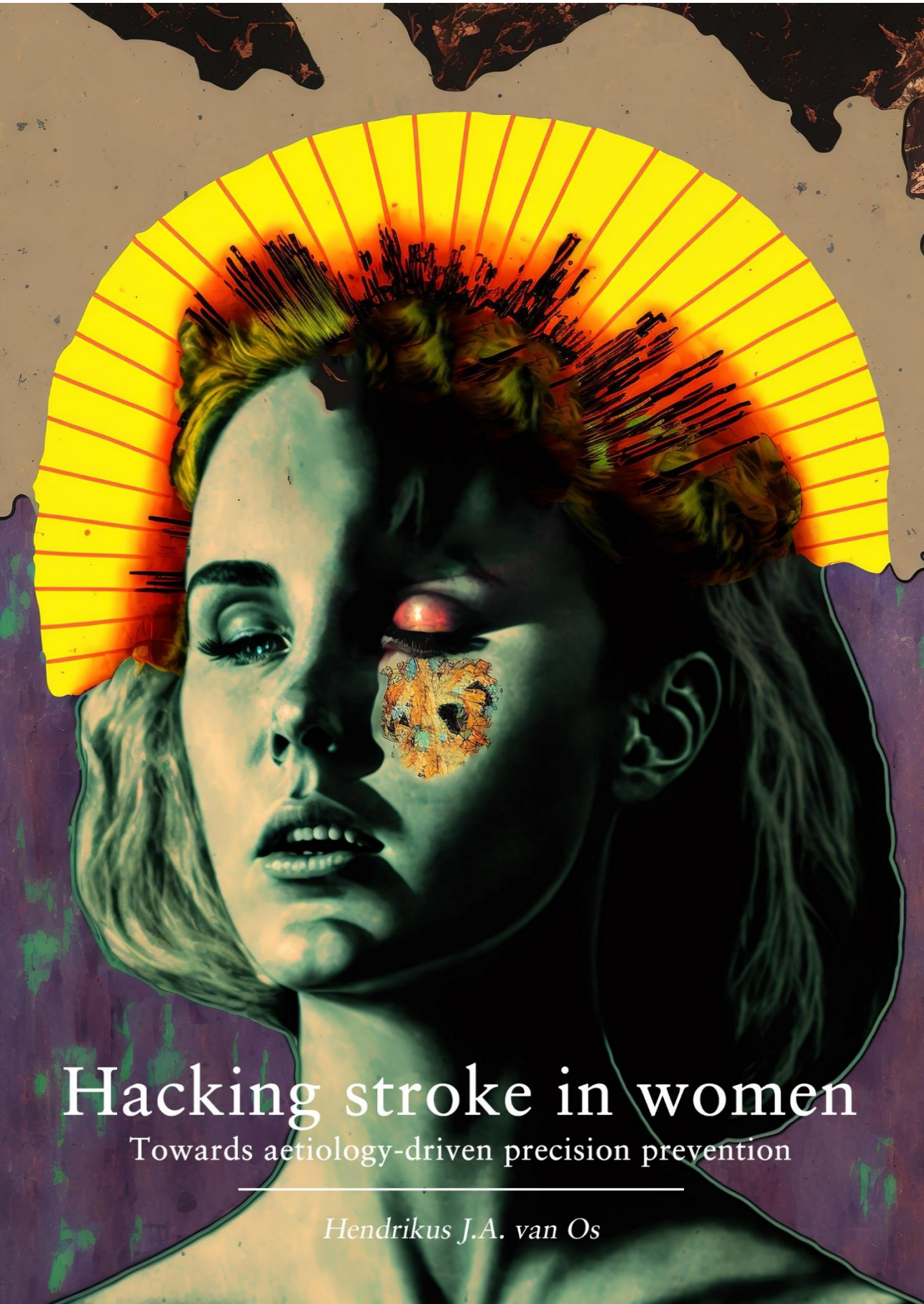

Hacking stroke in women

Towards aetiology-driven precision prevention

Hendrikus J.A. van Os

Hacking stroke in women

Towards aetiology-driven precision prevention

PROEFSCHRIFT

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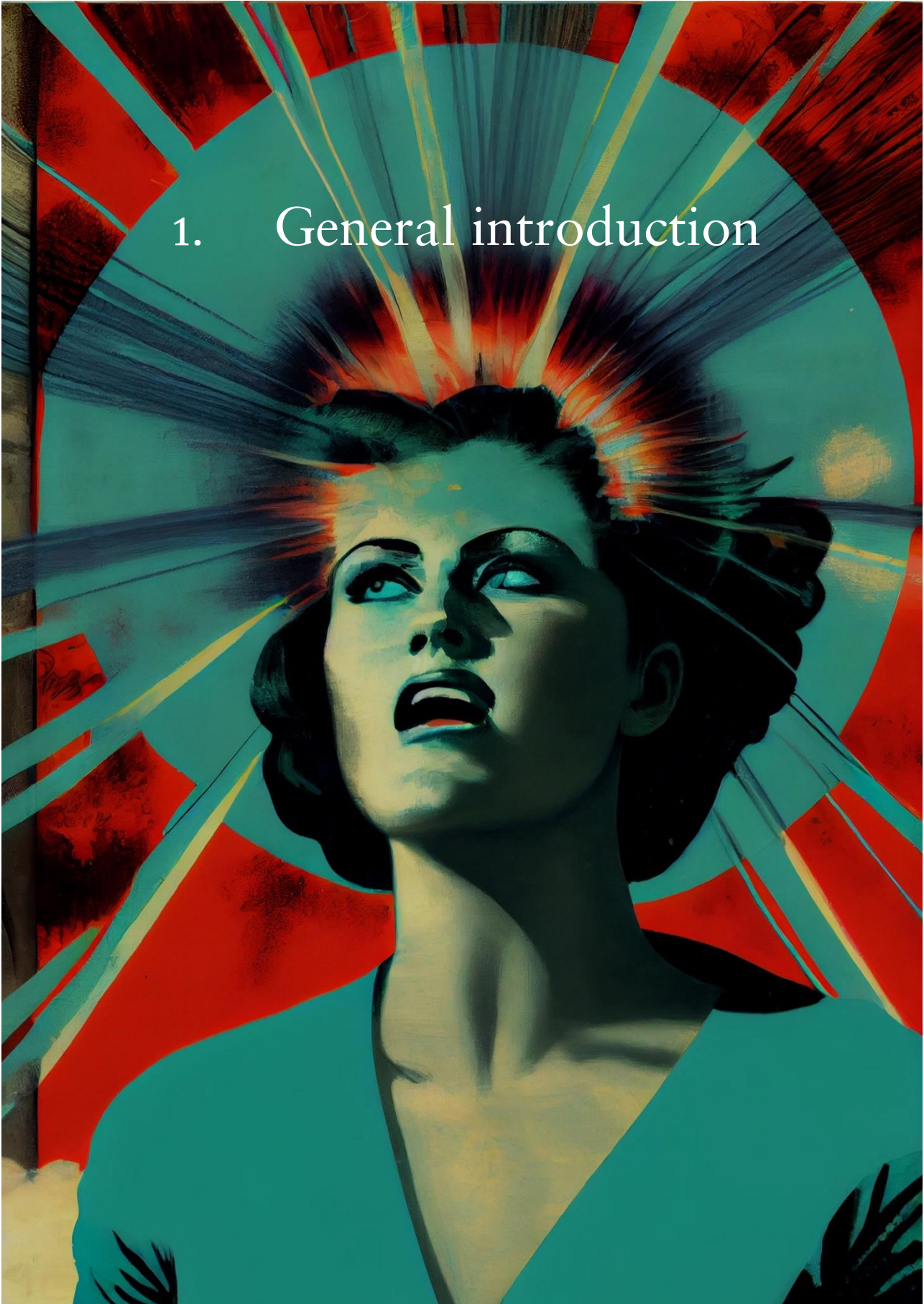
1. General introduction



Introduction

Stroke represents one of the leading causes of disability and death globally.[1] Causing about 2% of total healthcare expenditure, stroke represents a substantial burden on society.[2] The COVID-19 pandemic has emphasised the importance of resilience of healthcare systems, and a shift of focus from treatment to prevention is urgently needed to keep healthcare sustainable.[3,4] Therefore, prevention of stroke is key, but in clinical practice the prevention targets for cardiovascular (including stroke) risk management are often not reached.[5,6] Precision prevention is a derivative of precision medicine that aims to improve the effectiveness of preventive care, by tailoring health policies to the individual's clinical characteristics, lifestyle, genome and environment.[7,8] Perhaps one of the most poignant examples illustrating the need for precision prevention is sex differences in stroke pathophysiology.[9] Until now, women have been underrepresented in randomised clinical trials for stroke and other cardiovascular diseases.[10,11] This is particularly worrisome, because the treatment and prevention of stroke may warrant a sex-specific approach.[12] This thesis aims to provide the foundation for precision prevention of stroke in women by (i) increasing our knowledge on sex differences in the pathophysiology of stroke, and (ii) developing female-specific models for the prediction of the risk of stroke. This introductory chapter provides background information on stroke, sex differences in and female-specific risk factors of stroke, the need for the accurate prediction of risk of stroke in women, using routine healthcare data for prediction, the concept of statistical learning and its relationship with artificial intelligence, and ends with an overview of all following chapters.

Stroke

The global incidence of stroke is around 260 per 100,000 person years, and rises sharply with age.[13] Almost 70% of all strokes worldwide could be prevented, because they are attributable to modifiable risk factors such as smoking, hypertension, and obesity.[14] Stroke can be divided into two main categories: ischaemic and haemorrhagic.[15] Ischaemic stroke accounts for 80% of all strokes and results from a blockage or narrowing in the cerebral or cervical arteries. According to its location multiple phenotypes exist, and several classification systems are used to capture the heterogeneous aetiology of ischaemic stroke.[16] The TOAST (Trial of Org 10172 in Acute Stroke Treatment) classification is used most often, and has five categories: cardio-embolism, large-artery atherosclerosis, small-vessel occlusion, and stroke of other determined- and stroke of undetermined aetiology.[17] After a vessel occlusion, the ischaemic core within the brain tissue is generally surrounded by functionally impaired but structurally intact tissue. This tissue is called the penumbra, and is the result of a disturbance of energy metabolism.[18] One of the likely underlying mechanisms that causes the penumbra is spreading depolarisation,

which constitutes slowly spreading waves of neuroglial depolarisation, followed by a depression of brain activity.[19] The penumbra may be salvaged to some extent through quick brain reperfusion after ischaemic stroke.[18] The overall clinical outcome of ischaemic stroke patients has improved substantially thanks to new treatments such as intravenous thrombolysis and endovascular treatment. However, still only half of all patients is functionally independent 90 days after ischaemic stroke, and the three-month mortality is around 8%.[20]

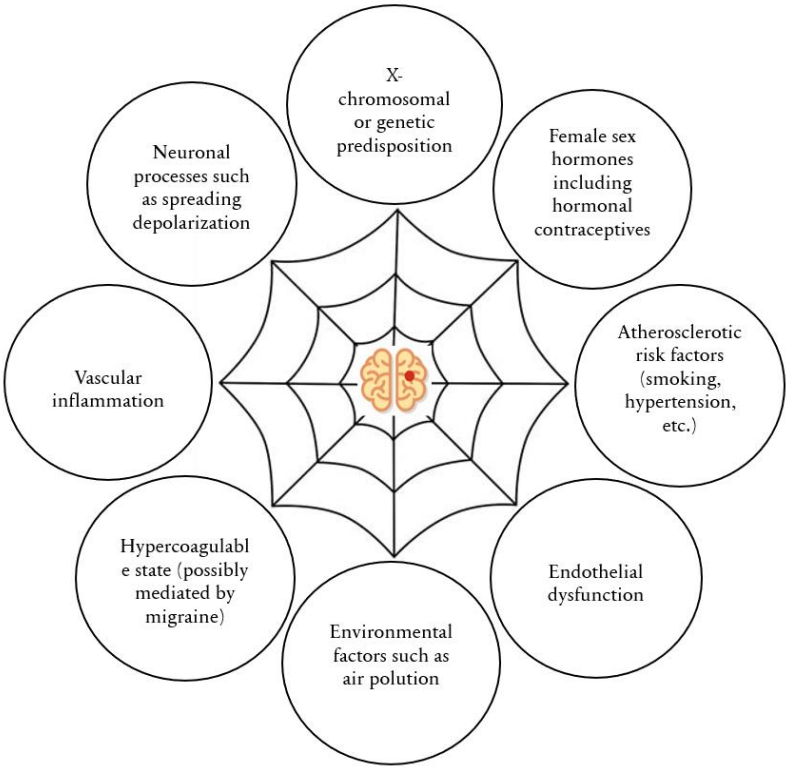
Haemorrhagic stroke represents around 15% of all strokes, and is subdivided into intracerebral and subarachnoid haemorrhage (SAH). Intracerebral haemorrhage is caused by bleeding into the brain tissue, and in case of SAH bleeding occurs into the subarachnoid space around the brain. SAH accounts for approximately 5% of strokes, and is most frequently caused by the rupture of a saccular aneurysm (aSAH).[21] In around 30% of aSAH patients delayed cerebral ischaemia occurs, which is defined as focal neurological impairment that cannot be attributed to other aetiologies after radiological and clinical assessment. Delayed cerebral ischaemia generally arises between day four and ten after aSAH onset, and is an important contributor to poor clinical outcome in aSAH patients.[22] The pathophysiology of delayed cerebral ischaemia is still largely unknown, but it is likely multifactorial.[23] In a pathological context – for example after aSAH – spreading depolarisation may be followed by spreading ischaemia.[24, 25]

Sex differences in stroke

The mortality rate of stroke is after adjustment for age similar in women and men, around 40 per 100,000 person years.[12] However, the functional outcome of stroke in the long term is worse in women compared with men, which is only in part explained by their longer life-expectancy and pre-existing comorbidities.[26] Although more research is needed to fully explain this sex difference, worse clinical outcome in women may be related to differences between women and men in the clinical presentation of stroke. Women may more often receive the incorrect diagnosis of a stroke mimic such as migraine with aura, which could lead to underdiagnosis and -treatment of stroke.[27] In stroke pathophysiology there also are important sex differences. Well known is the protective role of oestrogen, which in pre-menopausal women supresses the formation of atherosclerotic plaques and promotes tissue perfusion after stroke.[28] In general, sex differences are likely mediated by an interplay between sex chromosomal, neuronal, hormonal and environment factors, and traditional risk factors for stroke (Figure 1).[28] In addition, the effect of traditional cardiovascular risk factors on the risk of stroke appears to differ between women and men. For example, hypertension and smoking lead to a comparatively stronger increase of risk in women.[29, 30] Sex differences also exist in atherosclerotic processes, which is exemplified by men more often having macrovascular

extracranial atherosclerosis.[31] It is, however, unknown whether atherosclerosis in the intracranial vessels differs between men and women in, and whether sex differences in traditional cardiovascular risk factors lead to a different distribution in stroke subtypes between men and women.

Figure 1. A visualisation of the web of interrelated pathophysiological mechanisms of sex differences in stroke pathophysiology



Female-specific risk factors of stroke

Female-specific risk factors likely also play an important role in the pathophysiology of stroke. Most of these risk factors occur exclusively in women, such as pregnancy related complications and the use of female sex hormone-based pharmacological agents.[29] There are also risk factors such as migraine which occur in both sexes, but increase the risk of stroke specifically in women and can therefore be regarded as female-specific risk factors.[32] Female-specific risk factors of stroke are clinically relevant due to both their high prevalence in the general population, and their substantial increasing effect on the risk of stroke. For example, preeclampsia

complicates around five percent of all pregnancies, and increases the risk of cardiovascular events significantly (relative risk [RR]: 1.9–2.5).[33, 34] Migraine is an even more frequently occurring condition, with a lifetime prevalence of about 33% in women versus 18% in men.[35] Recent, large cohort studies show a relative increase in the risk of stroke of around two-fold in women with versus those without migraine below the age of 50. This risk increase is most pronounced for – or even occurs exclusively in – patients with migraine with aura.[36, 37] The migraine–stroke relationship offers us important insights into female-specific mechanisms for stroke, and multiple hypotheses explain its underlying pathophysiology. First, increased endothelial dysfunction in patients with migraine might explain the increased risk of stroke, and the question rises whether this increase is primarily mediated by macrovascular atherosclerosis resulting from the endothelial dysfunction.[38] Second, another likely contributing mechanism closely linked with endothelial dysfunction is hypercoagulability, which has been found to occur during or even in between migraine attacks.[39] It is yet unclear whether primarily the intrinsic or extrinsic coagulation cascade is involved. Third, not only vascular or haematological mechanisms, but also neuronal processes may underly the increased risk of stroke in migraine patients. Spreading depolarisation – a likely mechanism that causes the ischaemic stroke penumbra, and delayed cerebral ischaemia after aSAH – is also the probable biological substrate of migraine aura.[40] Evidence from multiple mouse experiments suggests that the migraine brain is more susceptible to spreading depolarisations, and that spreading depolarisations may more often lead to spreading ischaemia.[41, 42] Therefore, patients with a history of migraine who suffer from aSAH might have an increased risk of delayed cerebral ischaemia compared with patients with aSAH without migraine.[24] Sex and age may be important effect modifiers of this potential association, because mouse experiments support that susceptibility to spreading depolarisations is increased in context of female sex hormones and at a relatively young age.[41, 43] Fourth, another frequently occurring risk factor specific to women is the combined oral contraceptive pill, which is used by about 20% of all women of fertile age and leads to a clinically relevant increase in the risk of ischaemic stroke (hazard ratio [HR]: 1.4–2.2).[44]

Interestingly, the combination of the exposure to the combined oral contraceptive pill, smoking, and migraine has been found to lead to a supra-additive effect on the risk of ischaemic stroke (odds ratio [OR]: 5.3–34).[45, 46] It should be noted that the incidence of ischaemic stroke in women of fertile age is very low (around 19 per 100.000 in the Netherlands).[47] However, female-specific risk factors such as migraine and preeclampsia exert a relative risk increase that is independent from traditional cardiovascular risk factors such a smoking and hypertension.[48, 49] This means that the absolute risk due to traditional cardiovascular risk factors will be multiplied in the presence of such female-specific risk factors, and that even at a

relatively young age a combination of female-specific and traditional cardiovascular risk factors may cause a high absolute cardiovascular risk. Young women could in such cases have an absolute ten-year risk of cardiovascular events of well over 2.5%, which is an indication for the consideration of preventive medication according to the European Society of Cardiology guideline published in 2021.[50]

The need for accurate prediction of the risk of stroke in women

In Europe, current guidelines include the use of the Systematic COronary Risk Evaluation (SCORE2) for the estimation of cardiovascular risk in the general population.[51] The SCORE2 prediction model only includes traditional cardiovascular risk factors: age, sex, total- and HDL-cholesterol, systolic blood pressure, and smoking. However, the question rises whether female-specific risk factors should be included for the assessment of the risk of cardiovascular events and stroke specifically. Including female-specific risk factors may lead to early identification of women at high risk of cardiovascular disease and stroke in particular, specifically of those who would not have been identified with current cardiovascular risk prediction models. Failing to identify these women in time would mean withholding preventive measures, resulting in undertreatment. This is an important health problem, given the high prevalence of many female-specific risk factors. A systematic review published in 2019 showed that only two (1%) of 160 sex-specific cardiovascular risk prediction models that were identified actually contained minimally one female-specific risk factor. These two models, and an additional one published a year later, showed that the inclusion of several female-specific risk factors in prediction models for cardiovascular risk led to marginal improvement of model discrimination.[52-54] However, these three studies did not include important female-specific risk factors such as migraine, and did not provide analyses specifically for the outcome of stroke. In addition, study populations predominantly consisted of women of postmenopausal age, whereas the effects of female-specific risk factors on the risk of stroke are generally more pronounced in premenopausal age. Therefore, there is a need for prediction research into female-specific and traditional risk factors for stroke, in a sufficiently large population to allow analyses in premenopausal women. Prediction models based on data from such cohorts would also enable early identification of women at increased risk of stroke and timely preventive interventions in these women – which is essential in preventing stroke and cardiovascular disease later in life.[55]

How could we translate more accurate prediction of the risk of stroke in women into clinical added value? Two major applications can be distinguished: (i) on the individual patient level and (ii) on the population level.[56] (i) Prediction models on the individual patient level offer individualised information about the risk of stroke which can be used directly in cardiovascular risk management decisions, supporting

the physician-patient dialogue and shared decision making. A good example for this is the web-based U-Prevent prediction tool, which also includes individualised preventive treatment benefit based on lifetime risk reduction.[57] Individual risk information has been proven to support shared decision making and may improve therapy adherence of preventive interventions for cardiovascular disease.[58] (ii) The application of prediction models on the population level could result in the identification of patient subgroups based on the distribution of absolute risk of stroke. This could, for example, aid the general practitioner (GP) to tailor preventive policies to subgroups of patients within population of a primary care practice center in whom a high risk of stroke is identified.

Routine healthcare 'big data': a relatively untapped source of value

The incidence of stroke in pre-menopausal women is low (around 7 per 10,000 person years, based on data presented in **chapter 14**). We, therefore, require a large sample size to assess the potential added value of female-specific risk factors with respect to the estimation of the risk of stroke. The advent of big data sources in healthcare may provide an answer.[59] The concept of 'big data' has been formalised using the following characteristics: very large volume, variety and velocity of availability of data.[60] In practice, this often means the collection or reuse of very large and heterogeneous datasets without a priori hypothesis. In case of prediction research, this could result in opportunities for the discovery of unknown predictor-outcome relationships or interactions among predictors that may lead to better prediction of disease risk.[61] Important sources of big data are large biobanks which have been set up in the last decades.[62] An important Dutch example is the Parelsnoer Institute biobank, which is a partnership between all eight University Medical Centers that started in 2009, and is based on prospectively collecting data and biomaterials in routine care processes.[63] The subsection of the Parelsnoer Institute database that focusses on stroke is called the Dutch String-of-Pearls Stroke Study. The clinical use of prediction models developed with biobank data is, however, limited to the representativeness of the healthcare organisations that form the data source. In addition, enriching models with predictors based on biomaterials is of little use if these biomaterials are not yet used in everyday clinical practice.[62, 64]

Another important – and relatively untapped – source of big data is pooled information from electronic health records (EHRs). EHR-derived patient cohorts offer a great opportunity for the development of clinical prediction models, since large quantities of routine health data are captured during the clinical workflow on a scale that is not feasible for traditional cohort research.[65] EHR-based studies are relatively inexpensive and require less time to complete, and the large variety of information that is recorded in the EHR allows for a more complete characterisation of populations.[66] However, the question remains to what extent clinically useful

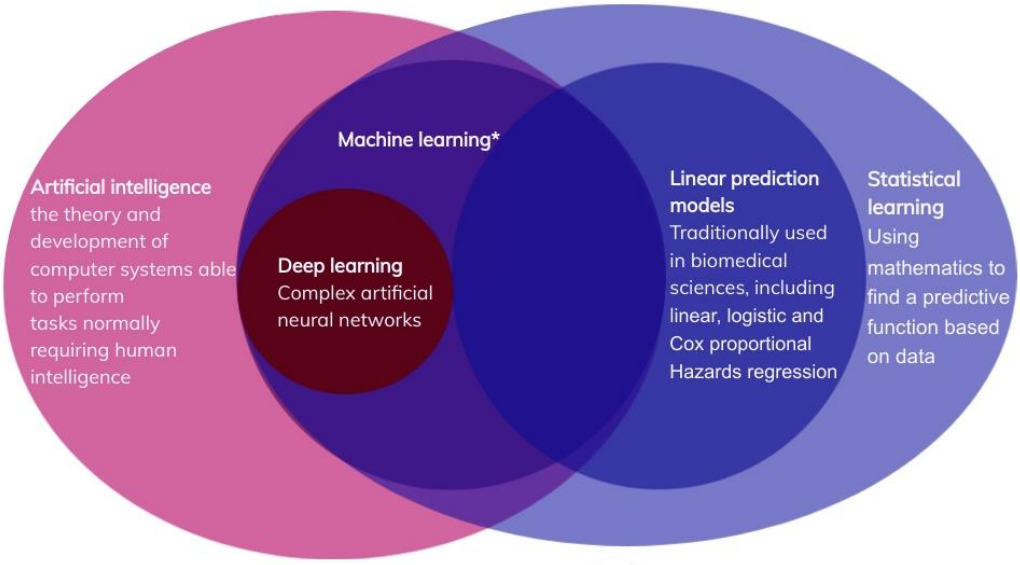
information can be retrieved among the enormous quantities of routine care data. After all, EHRs are not designed for research but to support the clinical workflow, generally within a limited timeframe. Therefore, besides the three 'V's of volume, variety and velocity, a fourth and perhaps most important 'V' of veracity (accuracy) has been added to the definition of big data.[67] For the development and implementation of prediction models based on EHR data, several methodological challenges have to be overcome, such as handling missing value, and measurement error in outcome and predictors.[66, 68]

Statistical learning, and the importance of demystifying artificial intelligence

Because of very large sample size and number of potentially relevant predictors of pooled routine data sources, novel methodologies may be required to extract all useful information. Methodologies within the artificial intelligence (AI) domain are widely regarded as a solution to this problem.[69] AI is an umbrella term that includes machine learning (Figure 2). In the Cambridge Dictionary, machine learning is defined as: 'the process of computers changing the way they carry out tasks by learning from new data, without a human being needed to give instructions in the form of a program'.[70] This definition, however, does not formally discern machine learning from statistical models that have been in use for several decades in biomedical sciences, such as logistic and Cox Proportional Hazards regression. After all, regression models also learn from new data using for example maximum likelihood estimation.[71] Creating an artificial distinction between machine learning and traditional statistical models may be dangerous, because the epidemiological principles of prediction model development and validation – such as generalisability and transportability – are applicable to all statistical models. These principles should also be applied to machine learning models to enable safe implementation in clinical practice.[72,73,74] Consequently, it may be advisable to use the overarching term statistical learning for both complex machine learning models and traditional statistical models, and to define a statistical learning spectrum using the dimensions of model complexity and interpretability (Figure 3). Interpretability in this context is the degree to which humans can understand the contribution of model parameters to the outcome of the model. On one end of this spectrum are human-guided models or decision rules that are simplest in model structure and therefore most interpretable.[75] On the other end of the spectrum there are fully data-driven models with a more complex internal structure, for example a large number of so-called hyperparameters, that are less interpretable but potentially better at capturing high-dimensional interactions in the data. One subgroup of models at this end of the spectrum is neural networks, especially those neural networks with a complex internal structure such as convoluted or recurrent neural networks. This subgroup

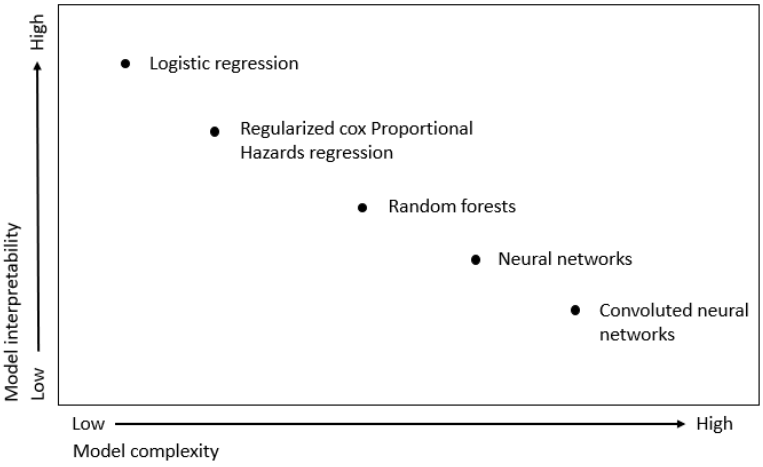
is also called deep learning, and has specific applications such as the direct analysis of raw image data. The machine learning subgroup of statistical models is less well demarcated.[75] I will therefore not use the term machine learning in this thesis, as it underpins a false dichotomy between machine learning and non-machine learning models. Instead, I discern between complex data driven and simple human-guided models, and I will assess the trade-off between model complexity and interpretability for these models.[76]

Figure 2. Mapping of the concepts of artificial intelligence, and machine learning and linear prediction models, that are included in the overarching term statistical learning



Machine learning has been defined in the text and includes statistical model families such as support vector machines, random forests, and neural networks.

Figure 3. Visualisation of the statistical learning spectrum



Increasing model complexity on the X-axis and decreasing model interpretability on the Y-axis. Different families of prediction models plotted on the spectrum.

The aims and outline of this thesis

The aim of this thesis is to create the foundation for precision prevention of stroke in women. For this purpose, the thesis consists of two complimentary parts: (i) through further elucidating the pathophysiological relationships between female-specific risk factors, traditional cardiovascular risk factors, and the risk of stroke, and (ii) by developing prediction models for early recognition of women at high risk of stroke, using data from EHR-derived, population-based cohorts.

Part I. Pathophysiology of stroke in women

In **chapter 2,** I tested the hypothesis that cerebrovascular atherosclerosis is the principal aetiology underlying the migraine–stroke association in a cohort of men and women with ischaemic stroke. In **chapter 3** I assessed the potential sex differences in intra- and extracranial cerebrovascular calcifications, in the same cohort which was used in chapter 2. In **chapter 4**, the potential risk factor interaction between intrinsic coagulation pathway constituents and a history of headache was investigated in a case-control study of women under 50 years, with ischaemic stroke as the outcome. In **chapter 5** I assessed the potential causal relationship between migraine and delayed cerebral ischaemia in a cohort of patients with aSAH, and in **chapter 6** I repeated this assessment in a subpopulation of aSAH patients under 50 years after extending the cohort used in chapter 5. In **chapter 7**,

the joint effect of migraine and combined oral contraceptive use on the risk of ischaemic stroke was assessed using data from a population-based cohort, and results were integrated with previous evidence using a systematic review and meta-analysis. In **chapter 8,** I described the design of the Dutch String-of-Pearls Stroke Study and in **chapter 9** I assessed potential sex differences in cardiovascular risk factors and stroke aetiology among ischaemic stroke patients with and without migraine using the String-of-Pearls Stroke Study cohort. In **chapter 10,** I investigated potential sex differences in the clinical presentation of acute stroke, and specifically whether women present more frequently with non-focal stroke symptoms. In **chapter 11** the pathophysiology of headache as a presenting symptom of ischaemic stroke was assessed in a subset of patients from same cohort that was used in chapters 2 and 3.

Part II. Prediction of stroke in women

In **chapter 12,** the methodological challenges and practical solutions of deriving and validating risk prediction models using primary care EHR data were presented using a case study, in which first-ever cardiovascular events based on Dutch primary care EHR data was predicted. In **chapter 13,** I compared the predictive performance of complex data-driven- and traditional regression models, which predicted functional outcome after ischaemic stroke. I used data from a cohort of patients who underwent endovascular treatment. In **chapter 14,** the potential added value of female-specific and psychosocial risk factors in addition to traditional cardiovascular risk factors for the prediction of the risk of stroke was assessed in a large, prospective Dutch population-based cohort of young women. In **chapter 15** I developed sex-specific prediction models for the risk of first-ever cardiovascular events in primary care patients aged 30–49 years using the same data source as chapter 14, and I assessed whether complex data-driven models may offer added value to predictive performance compared with traditional regression models. Concluding, in the general discussion in **chapter 16,** I will discuss the overarching challenges that were encountered in parts I and II of this thesis, and provide next steps for research and the implementation of my results in clinical practice.

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Part I.
Pathophysiology of stroke in women

2. Migraine and cerebrovascular atherosclerosis in patients with ischemic stroke

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Abstract

Background and purpose: Migraine is a well-established risk factor for ischemic stroke, but migraine is also related to other vascular diseases. This study aims to investigate the association between migraine and cerebrovascular atherosclerosis in patients with acute ischemic stroke.

Methods: We retrieved data on patients with ischemic stroke from the Dutch acute stroke study. Migraine history was assessed with a migraine screener and confirmed by telephone interview based on the ICHD criteria. We assessed intra- and extracranial atherosclerotic changes and quantified intracranial internal carotid artery (ICA) calcifications as measure of atherosclerotic burden on non-contrast CT and CT-angiography. We calculated risk ratios (RR) with adjustments for possible confounders (aRR) with multivariable Poisson regression analyses.

Results: We included 656 patients, aged 18 to 99 years, of whom 53 had a history of migraine (29 with aura). Patients with migraine did not have more frequent atherosclerotic changes in intracranial (51% versus 74%; aRR: 0.82; 95%CI: 0.64–1.05) or extracranial vessels (62% versus 79%; aRR: 0.93; 95%CI: 0.77–1.12) than patients without migraine and had comparable ICA calcification volumes (largest versus medium and smallest volume tertile, 23% versus 35%, aRR: 0.93; 95%CI: 0.57–1.52).

Conclusion: Migraine is not associated with excess atherosclerosis in large vessels in patients with acute ischemic stroke. Our findings suggest that the biological mechanisms by which migraine results in ischemic stroke are not related to macrovascular cerebral atherosclerosis.

Introduction

Migraine, especially with aura, is a risk factor for ischemic stroke.[1] Migraine patients also have an increased risk for cardiovascular disease in the systemic circulation such as myocardial infarction and peripheral artery disease.[2] The connection between migraine and cardiovascular disease is complex and probably multifactorial. One of the possible mediating mechanisms is enhanced atherosclerosis. The aim of our study was to investigate the association between migraine and cerebrovascular atherosclerosis in a large cohort of patients with acute ischemic stroke.

Methods

Patients

We included patients from the Dutch acute stroke study (DUST), a large prospective multicenter cohort study performed between May 2009 and August 2013.[3] Inclusion criteria for DUST were: age ≥18 years, onset of stroke symptoms <9 h and NIHSS ≥2 or ≥1 if intravenous thrombolysis with rtPA was indicated. Exclusion criteria were known renal failure and contrast agent allergy.[3] DUST was approved by the Medical Ethical Committee of the participating hospitals. Informed consent was obtained from all patients for use of the data. All patients underwent non-contrast CT (NCCT), CTA and CTP on admission with standardized scan protocols (Supplementary Methods). Radiologic parameters were assessed by trained neuroradiologists with good inter observer variability.[3] At baseline we collected data on cardiovascular risk factors and medical history. Stroke subtype was classified according to the TOAST criteria. The DUST research nurses recorded the MISS (Migraine In Stroke Screener), a five-item migraine screener that retrospectively assesses migraine history and was validated previously in a stroke cohort. MISS data were obtained when the patient entered the DUST study. The MISS has a very high negative predictive value (0.99), but a moderate positive predictive value especially for aura symptoms.[4] In case of one or more positive answers to the screener the participants were contacted by telephone by a migraine research nurse. This semi-structured telephone interview consisted of detailed questions on headache and aura characteristics, including ICHD-II migraine and aura criteria. Patients were excluded when there was suspicion of migraine based on the screener but the migraine diagnosis could not be confirmed by telephone because patients were lost to follow-up or refused participation.

We assessed patients with any sign of atherosclerosis in intra- and extracranial vessels of the anterior and posterior circulation on CTA. We measured intracranial internal carotid artery (ICA) calcification volume, using calcium as a measure for

atherosclerosis. Calcium volumes were measured from the petrous part to the top of the intracranial carotid arteries on NCCT using dedicated software (Supplementary Methods). We performed multivariable Poisson regression analyses (Supplementary Methods). Risk ratios (RR) and adjusted RR (aRR) with 95% confidence intervals (CI) were calculated.

Results

In total, 707 DUST participants (82%) filled in the screener. Fifty-one patients were lost to follow-up or refused to participate in the telephone interview and were excluded. Therefore, 656 patients were included in this study of whom 53 had a confirmed migraine diagnosis (29 with aura) by telephone interview and 603 had no history of migraine. The median of time since the last attack was 1 year (n=47) and 38% of patients reported to have active migraine. Median attack frequency was 2 times per month (n=22). The baseline characteristics are shown in Table 1.

Table 1. Clinical characteristics of the participants

Characteristics	Migraine (n=53)	No migraine (n=603)
Demographics		
Age, mean years (±SD)	59.9 ± 11.0	67.0 ± 13.4
Age under 50, n(%)	10 (19%)	76 (13%)
Women, n(%)	29 (55%)	223 (37%)
History, n(%)		
Hypertension	21 (40%)	289 (49%)
Diabetes mellitus	7 (13%)	92 (15%)
Hyperlipidemia	21 (40%)	200 (34%)
Previous stroke or TIA	14 (26%)	139 (23%)
Myocardial infarction	5 (10%)	77 (13%)
Atrial fibrillation	6 (11%)	70 (12%)
Peripheral artery disease	3 (6%)	24 (4%)
Smoking: current	23 (44%)	170 (30%)
Smoking: lifetime*	34 (65%)	372 (65%)
Alcohol use	27 (73%)	267 (62%)
Baseline NIHSS**, median	5	5

**Current smokers and smokers who stopped smoking >6 months ago; **NIHSS: NIH Stroke Scale*

Atherosclerosis in intracranial vessel segments was as frequent in migraine patients as in patients without migraine (Table 2). This was the same for extracranial vessels and was also true for both the anterior and posterior circulation. High intracranial ICA calcification volumes were as frequent in migraine patients as in patients without migraine. We found no differences in atherosclerotic changes in migraine patients with and without aura, although group sizes were small. Our results remained consistent after stratification for age and stroke etiology (Supplementary Table I and II).

Table 2. Prevalence of atherosclerotic changes according to presence or absence of migraine

Atherosclerotic changes	Migraine (n=53)	No migraine (n=603)	RR (95% CI)	aRR (95% CI)†
Intracranial circulation				
Any sign of atherosclerosis*	27 (51%)	445 (74%)	0.69 (0.53–0.90)	0.82 (0.64–1.05)
Any sign of stenosis	4 (8%)	80 (13%)	0.57 (0.22–1.49)	0.77 (0.29–2.02)
Tertile largest ICA calcification vol.**	12 (23%)	211 (35%)	0.65 (0.39–1.08)	0.93 (0.57–1.52)
Extracranial circulation				
Any sign of atherosclerosis*	33 (62%)	476 (79%)	0.79 (0.64–0.98)	0.93 (0.77–1.12)
Atherosclerosis anterior circulation	32 (60%)	465 (77%)	0.78 (0.63–0.98)	0.92 (0.76–1.13)
Atherosclerosis posterior circulation	12 (23%)	225 (37%)	0.61 (0.36–1.01)	0.86 (0.54–1.37)
Any sign of stenosis	18 (34%)	260 (43%)	0.79 (0.53–1.16)	0.97 (0.67–1.41)
Stenosis ≥70%	10 (19%)	139 (23%)	0.82 (0.46–1.46)	0.91 (0.51–1.62)

**Anterior and posterior circulation combined*

***Tertile largest versus tertiles medium and smallest volume of internal carotid artery calcifications*

†Age and sex adjusted

Discussion

Our findings argue against the hypothesis that migraine patients are at higher risk for ischemic stroke because of higher atherosclerotic load in the cerebral vasculature. If anything, our data suggest that the prevalence of atherosclerotic changes was lower in stroke patients with migraine. This confirms previous findings in the literature where the risk for ischemic stroke was apparent for migraine patients without vascular risk factors (except for use of oral contraceptives and

smoking) and low Framingham risk scores.[5] Strong points of our study include the large number of participants and the state-of-the-art imaging methods enabling detailed assessment of the radiological characteristics of atherosclerosis. All migraine diagnoses were confirmed by an extensive telephone interview according to the ICHD-II criteria which are comparable with the recent updated ICHD-III criteria.

Our study also has limitations. First, the study is performed in a stroke population with highly prevalent traditional risk factors such as older age, history of hypertension, diabetes and hyperlipidemia. Compared with these traditional risk factors, the contribution of the possible migraine-related atherosclerosis may be too small to be detected. Second, our study did not include a control group without stroke. One could hypothesize that migraine patients might show enhanced atherosclerosis at younger ages resulting in earlier strokes but with comparable atherosclerotic changes than patients without migraine at time of the stroke. However, although migraine patients were indeed younger at time of their stroke, our results were consistent in different age categories. Third, not all patients filled in the MISS and not all screen positives could be confirmed by telephone interview. Patients with possible migraine but without confirmation were excluded from the study to avoid misclassification bias. Therefore, the exact prevalence of migraine in our stroke population cannot be derived from our study. Also, patients who were moribund or severely aphasic were less likely to have filled in the screener. We cannot rule out that this affected the generalizability or the internal validity of the results.

Our study does not provide information on other possible mechanisms underlying the increased ischemic stroke risk in migraine patients. Endothelial dysfunction has been related to early development of atherosclerosis but also to activation of the coagulation pathway, enhanced inflammatory responses and impaired vascular reactivity.[6] Although we found no excess atherosclerosis in migraine patients, future studies should investigate the possible impact of endothelial dysfunction on stroke risk via other mechanisms.

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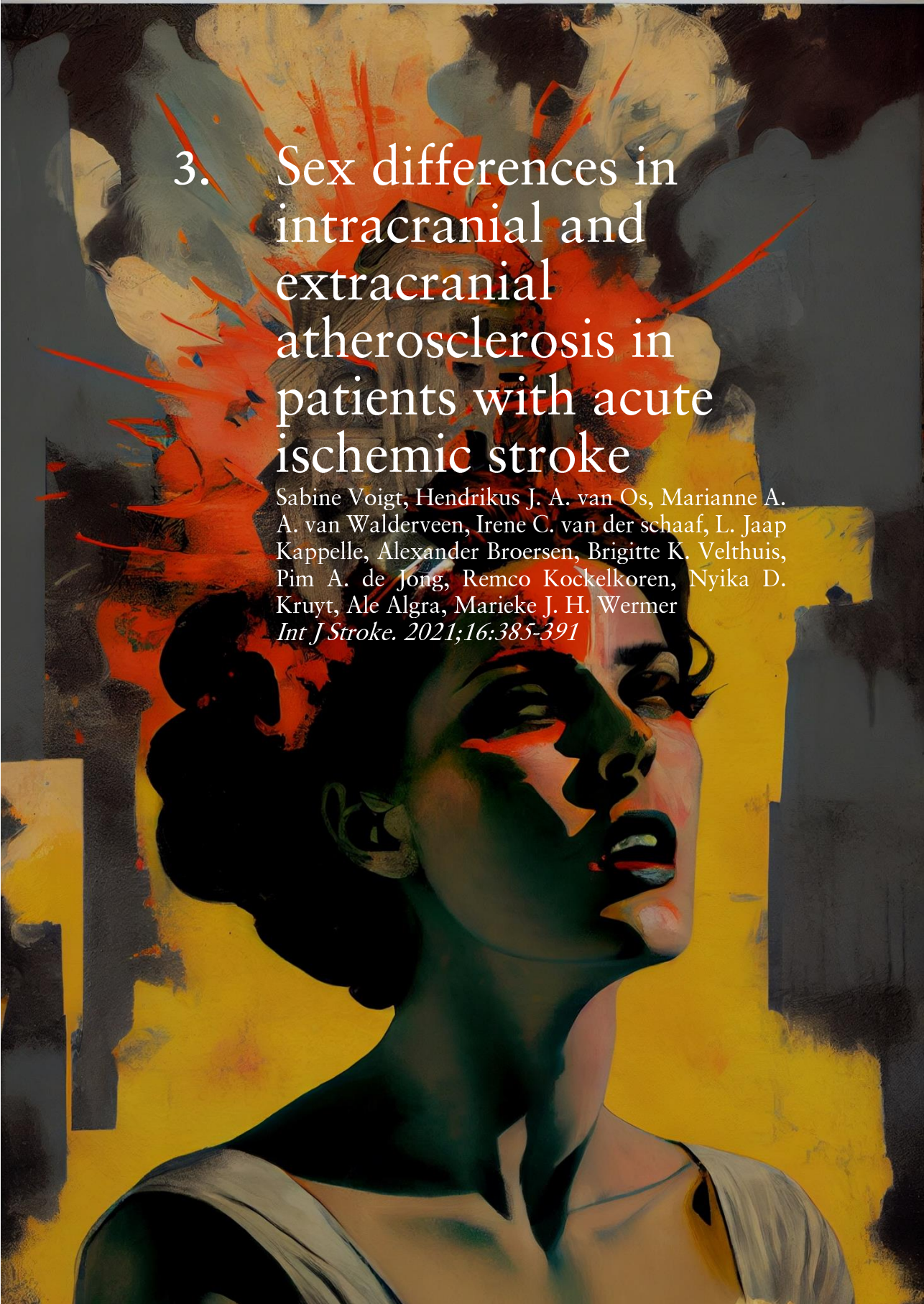

3. Sex differences in intracranial and extracranial atherosclerosis in patients with acute ischemic stroke

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Abstract

Background and purpose: To investigate sex differences with respect to presence and location of atherosclerosis in acute ischemic stroke patients.

Methods: Participants with acute ischemic stroke were included from the Dutch acute stroke study (DUST), a large prospective multicenter cohort study performed between May 2009 and August 2013. All patients received CT/CT-angiography within 9 hours of stroke onset. We assessed presence of atherosclerosis in the intra- and extracranial internal carotid (ICA) and vertebrobasilar arteries (VBA). In addition, we determined the burden of intracranial atherosclerosis by quantifying ICA and VBA calcifications, resulting in calcium volumes. Prevalence ratios (PR) between women and men were calculated with Poisson regression analysis and adjusted (aPR) for potential confounders (age, hypertension, hyperlipidemia, diabetes, smoking and alcohol use).

Results: We included 1397 patients with a mean age of 67 years, of whom 600 (43%) were women. Presence of atherosclerosis in intracranial vessel segments was found as frequently in women as in men (71% vs. 72%, aPR 0.95; 95% CI 0.89-1.01). In addition, intracranial calcification volume did not differ between women and men in both intracranial ICA (large burden 35% vs. 33%, aPR 0.93; 95% CI 0.73-1.19) and VBAs (large burden 26% vs. 40%, aPR 0.69; 95% CI 0.41-1.12). Extracranial atherosclerosis was less common in women than in men (74% vs. 81%, aPR 0.86; 95% CI 0.81-0.92).

Conclusion: In patients with acute ischemic stroke the prevalence of intracranial atherosclerosis does not differ between women and men, while extracranial atherosclerosis is less often present in women compared with men.

Introduction

Atherosclerosis is the most common cause of ischemic stroke worldwide and an important prognostic factor for recurrent vascular events.[1] Evidence is accumulating that development, distribution and severity of atherosclerosis may be dependent on sex.[2, 3] Several studies have shown that extracranial atherosclerosis is more common in men than in women with ischemic stroke.[4] Less is known about sex differences in intracranial atherosclerosis. Risk factors for intracranial internal carotid artery (ICA) calcification seem to differ between men and women, suggesting a difference in pathophysiological mechanisms.[2] Studies on sex differences in intracranial atherosclerosis have been mainly performed in Asian populations. One large Chinese stroke study with 1335 participants found no sex differences in presence of intracranial atherosclerosis.[5] In contrast, in another Chinese stroke study with 551 participants, men had a higher prevalence of intracranial atherosclerosis with an odds ratio of 2.3 (95%CI:1.48-3.26).[6] Studies on intracranial atherosclerosis in Caucasian stroke patients are scarce.

We investigated sex differences in presence, location and burden of intra- and extracranial atherosclerosis in a large population of Western-European acute ischemic stroke patients.

Methods

Participants

We included participants from the Dutch Acute Stroke Study (DUST), a large prospective multicenter cohort study performed between May 2009 and August 2013. The aim of DUST was to investigate the value of CT-angiography (CTA) and CT-perfusion (CTP) for predicting outcome after ischemic stroke. Inclusion criteria were age ≥18 years, onset of stroke symptoms <9 hours, and National Institute of Health Stroke Scale (NIHSS) ≥2 or ≥1 if intravenous thrombolysis was indicated. Exclusion criteria were known renal failure and contrast agent allergy. For the current study, participants from all 14 participating DUST centers were included.[9] We assessed the following characteristics on admission: demographic features, cardiovascular risk factors, a history of cardiovascular disease, baseline NIHSS and blood pressure on admission. Stroke etiology was classified according to the TOAST criteria. Data were prospectively retrieved from the medical record of the patient by the local investigators. All participants underwent Non-Contrast Computed Tomography (NCCT), CTA and CTP on admission with scan protocols standardized between centers.[10]

Standard protocol approvals, registrations and patient consents

DUST was approved by the Medical Ethics Committee of the University Medical Center Utrecht and local approval was obtained from all participating hospitals. CTA/CTP imaging on admission was performed as part of the routine clinical work-up of ischemic stroke patients. Patients or a legal representative gave written informed consent for use of the date, clinical follow-up and follow-up imaging. The medical ethics committee waived the need for informed consent for patients who died soon after admission before consent could be obtained.

Radiologic parameters

Scans were assessed by an observer with at least five years of experience in neurovascular imaging (from a pool of three observers). We assessed the presence of any sign of atherosclerosis (both non-calcified and calcified plaque on CTA) in intracranial and extracranial segments of the ICA or VBA. In addition, we determined the burden of calcified intracranial atherosclerosis by assessing intracranial ICA and vertebrobasilar artery (VBA) calcifications on thin slice (0.5 – 0.9 mm) NCCT, using calcium as measure for intracranial atherosclerosis since both parameters are strongly related.[11] Intracranial ICA calcifications were measured manually from the petrous bone to the top of the intracranial ICA, and VBA calcifications were assessed from the point where the vertebral arteries enter the dura until the tip of the basilar artery, at the origin of the posterior cerebral arteries. Calcium volumes were assessed using dedicated software (CalcScore V11.1 by Medis Specials bv).[12] Regions of interest were drawn to discern the intracranial ICA calcifications from the skull base using a threshold, which was set to the optimal threshold of 160 Hounsfield units (HU) by performing a small pilot study.[13] Since calcification volumes were non-normally distributed we divided ICA and VBA calcification volumes into tertiles. We then analyzed large (upper tertile) versus small (middle and lower two tertiles) burden of intracranial atherosclerosis. We only trichotomized calcification volumes for patients in whom VBA calcifications were present, as the majority of patients did not have any VBA calcifications. We followed the same procedure for ICA calcifications.

Intracranial ICA calcifications were also subdivided according to dominant intimal or dominant medial location. This was done using a previously validated score based on matched NCCT- and histological slides.[14] The score was constructed by assigned points to different calcification characteristics (circularity, thickness and morphology) which were weighted according to their relation to either medial or intimal calcification.[3] Extracranial vessel segments were divided into anterior (common and internal carotid arteries) and posterior (vertebral arteries). On CTA, we defined stenosis of the extracranial circulation as any sign of stenosis and stenosis of ≥70%, performed according to the NASCET criteria.

Statistical analysis

We performed (multivariable) Poisson regression analyses to identify possible relationships between sex and radiological characteristics of atherosclerosis.[15]

Adjustments were made for age, hypertension, hyperlipidemia, diabetes, smoking and alcohol use because we considered these factors to be potential confounders. We stratified for age (young stroke defined as stroke <50 years). Prevalence ratios (PR) and adjusted PR (aPR) with 95% confidence intervals (CI) were calculated. For all analyses we performed complete case analysis. All data were analyzed with SPSS (v25).

Results

In total, 1397 participants were included. Mean age was 67 ± 14 (SD) years, 600 (43%) were women, and median NIHSS was 6 (Table 1). The overall prevalence of any intracranial atherosclerosis was 72%. Presence of atherosclerosis in intracranial vessel segments was found as frequently in women as in men (71% vs. 72%, aPR: 0.95; 95% CI: 0.89–1.01) (Table 2). In 914 of the 1397 patients the thin-slice NCCT was retrievable and of sufficient quality for calcification volume measurements. The baseline characteristics of these excluded patients (whom did not have a retrievable NCCT) were similar to included patients (Supplementary Table 1). In 11 of these scans only assessment of ICA calcification volume was possible, as an artefact in the posterior fossa prohibited assessment of VBA calcification volume.

Intracranial ICA calcification volume did not differ between women and men in the ICA (large burden 35% vs. 33%, aPR: 0.93; 95% CI: 0.73–1.19) or the VBAs (large burden 26% vs. 40%, aPR: 0.69; 95% CI: 0.41–1.12). Intima calcifications in the intracranial circulation were less prevalent in women (25% vs. 36%, aPR 0.76; 95% CI 0.63–0.93), whereas for presence of media calcifications no clear sex differences were found after adjustments (54% vs. 42%, aPR: 1.09; 95% CI: 0.96–1.25). In the 180 participants younger than 50 years (50% women), the presence and volume of intracranial atherosclerosis was similar in men and women (Table 3).

Extracranial atherosclerosis

In extracranial vessels, women with stroke less often had any sign of atherosclerosis (74% vs. 81%, aPR: 0.86; 95% CI: 0.81–0.92) and less often a significant stenosis ≥70% than men (17% vs. 27%, aPR: 0.60; 95% CI: 0.47–0.76) (Table 2).

Table 1. Clinical characteristics of the participants

Characteristics	Women (n=600, 43%)	Men (n=797, 57%)
Demographics		
Age, mean years (±SD)	69 (15.4)	66 (13.0)
History, n (%)		
Hypertension	331 (56%)	397 (50%)
Diabetes mellitus	93 (16%)	121 (15%)
Hyperlipidemia	181 (31%)	276 (36%)
Previous stroke or TIA	155 (26%)	187 (24%)
Myocardial infarction	41 (7%)	129 (17%)
Atrial fibrillation	69 (12%)	109 (14%)
Peripheral artery disease	27 (5%)	55 (7%)
Smoking:		
Current	134 (25%)	249 (34%)
Lifetime*	148 (27%)	265 (36%)
Alcohol use	183 (31%)	347 (44%)
Baseline NIHSS**, median	6	6
Blood pressure on admission		
Systolic BP >160 mm Hg	226 (38%)	296 (37%)
Diastolic BP >90 mm Hg	158 (26%)	276 (35%)
Stroke etiology	n=380	n=561
Large vessel disease	171 (45%)	249 (45%)
Cardiac embolic source	99 (26%)	136 (24%)
Small vessel disease/lacunar infarct	80 (21%)	103 (18%)
Dissection	10 (3%)	40 (7%)
Other	20 (5%)	33 (6%)

**Current smokers and smokers who stopped smoking >6 months ago*
***Baseline NIHSS: NIH Stroke Scale on admission*

Table 2. Atherosclerotic characteristics in women and men

Atherosclerotic characteristics	Women (n=600)	Men (n=797)	PR (95% CI)	aPR (95% CI)**
Intracranial circulation (ICA, VBA, MCA, ACA and PCA)				
Any sign of atherosclerosis (n=1369)	416 (71%)	565 (72%)	0.98 (0.91–1.04)	0.95 (0.89–1.01)
Large vs. small burden ICA calcification volume (n=873)*	126 (35%)	166 (33%)	1.07 (0.84–1.34)	0.93 (0.73–1.19)
Large vs. small burden VBA calcification volume (n=250)*	27 (26%)	58 (40%)	0.66 (0.41–1.04)	0.69 (0.41–1.12)
Any sign of stenosis (n=1182)	69 (12%)	120 (15%)	0.76 (0.57–1.00)	0.68 (0.50–0.93)
Intima ICA calcification (n=1132)	123 (25%)	228 (36%)	0.71 (0.59–0.85)	0.76 (0.63–0.93)
Media ICA calcification (n=1132)	262 (54%)	269 (42%)	1.28 (1.13–1.45)	1.09 (0.96–1.25)
Extracranial circulation				
Any sign of atherosclerosis (n=1371)	433 (74%)	631 (81%)	0.91 (0.86–0.97)	0.86 (0.81–0.92)
Atherosclerosis anterior circulation (n=1371)	426 (72%)	617 (79%)	0.92 (0.86–0.98)	0.87 (0.82–0.93)
Atherosclerosis posterior circulation (n=1360)	202 (34%)	309 (40%)	0.85 (0.74–0.98)	0.77 (0.66–0.89)
Any sign of stenosis (n=1396)	244 (41%)	378 (47%)	0.86 (0.76–0.97)	0.78 (0.68–0.89)
Stenosis ≥ 70% (n=1396)	100 (17%)	213 (27%)	0.63 (0.51–0.77)	0.60 (0.47–0.76)

VBA = vertebrobasilar arteries; ICA = intracranial carotid artery; PR = Prevalence Ratio
**Tertiles are based on the patients with presence of ICA (n=873) or VBA (n=250) calcifications, respectively. We analyzed large (upper tertile) versus small (middle and lower two tertiles) burden of intracranial atherosclerosis*
***Adjusted for age, hypertension, hyperlipidemia, diabetes, smoking and alcohol use.*

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Table 3. Any sign of atherosclerotic changes according to sex difference, stratified for age

Subgroups	Atherosclerotic characteristics	Women (n=598)	Men (n=795)	PR (95% CI)	aPR (95% CI)*
Age group <50 (n=180)		n=90	n=90		
Intracranial circulation	Any sign intracranial atherosclerosis	17 (20%)	14 (16%)	1.23 (0.66–2.39)	0.97 (0.52–1.83)
	Intima calcification	9 (12%)	11 (16%)	0.76 (0.34–1.73)	0.67 (0.30–1.49)
	Media calcification	9 (12%)	8 (12%)	1.05 (0.43–2.56)	1.04 (0.44–2.49)
Extracranial circulation	Any sign extracranial atherosclerosis	23 (27%)	21 (24%)	1.13 (0.68–1.89)	0.94 (0.55–1.60)
	Stenosis ≥70%	13 (15%)	17 (19%)	0.77 (0.40–1.50)	0.78 (0.40–1.51)
Age group ≥50 (n=1213)		n=508	n=705		
Intracranial circulation	Any sign intracranial atherosclerosis	398 (79%)	550 (80%)	0.99 (0.94–1.05)	0.99 (0.93–1.05)
	Intima calcification	114 (28%)	217 (38%)	0.73 (0.60–0.88)	0.85 (0.69–1.03)
	Media calcification	253 (61%)	261 (46%)	1.34 (1.19–1.51)	1.12 (0.98–1.28)
Extracranial circulation	Any sign extracranial atherosclerosis	410 (82%)	609 (88%)	0.93 (0.89–0.98)	0.90 (0.85–0.95)
	Stenosis ≥70%	31 (6%)	54 (8%)	0.96 (0.90–1.02)	0.96 (0.90–1.02)

**Adjusted for age, hypertension, hyperlipidemia, diabetes, smoking and alcohol use.*

Discussion

In our study the prevalence and extent of atherosclerotic changes of the intracranial circulation in patients admitted for stroke was comparable in men and women whereas women less often had signs of extracranial atherosclerosis than men. The prevalence of intracranial ICA calcifications in our population was 72%. A study of 406 Dutch patients (mean age of 62 years) suspected of TIA or minor stroke reported a prevalence of intracranial ICA calcifications of 65%.[8] In this study a significantly higher threshold (500 HU) was used for detection of calcifications.[8] The prevalence of intracranial ICA calcifications in the Rotterdam population based study (N=2495, mean age 70) was 82%.[17] Possibly, the lower threshold for differentiation of calcifications (130 HU) as well as the higher mean age could explain the difference between the Rotterdam study and DUST.[17] Our threshold of 160 Hounsfield units was based on optimal distinction between intracranial ICA calcifications and skull base in data from all different vendors; calcification volume data did not differ notably between centers. In a previous Chinese study the prevalence of intracranial atherosclerosis was 63% in a population of ischemic stroke patients.[6] This lower prevalence could be due to ethnical differences.[7]

It has been previously reported that extracranial circulation atherosclerosis is more prevalent in men than in women.[4] Common understanding is that this is due to lack of protective effect of estrogen or increased exposure to vascular risk factors.[18] In contrast to the sex differences in the extracranial circulation in our study, intracranial atherosclerosis prevalence was similar in men and women. Risk factors for intracranial ICA calcification seem to differ between men and women, suggesting a difference in pathophysiological mechanisms.[2] Excessive alcohol intake and smoking have been associated with intracranial ICA calcifications in men, whereas hypertension and diabetes were found to be strong risk factors in women.[2] This may indicate that either the protective effect of estrogen does not affect intracranial arteries as much as extracranial vessels, or that the effect of vascular risk factors on extracranial versus intracranial vessels differ between men and women. In a post-hoc analyses we did not find clear sex differences in vascular risk factors between patients with and without atherosclerosis but the numbers in the subgroups were very small (Supplementary Table 2). Although the overall intracranial atherosclerosis presence was similar for both sexes, women less frequently had intima calcifications compared with men. The prevalence of media calcifications on the other hand was higher in women, although this difference was no longer statistically significant after adjustment for confounders. The intimal layer consists of endothelial cells that proliferate in the process of atherosclerosis and grow into the arterial lumen forming plaques that narrow the lumen and can rupture. The medial layer consists of smooth muscle cells and elastic fibers which regulate blood flow and arterial pressure.[19] The sex differences in intima calcifications could suggest a different pathophysiology of intracranial atherosclerosis in men and women. Possibly, a different vascular pathology than atherosclerosis, for example arterial stiffness, influences intracranial calcification.[20]

Our study has methodological limitations. First, intracranial ICA calcification volume could not be assessed in one-third of participants. The main reason for this was that due to technical reasons the thin slice NCCT could not be retrieved from two of the DUST centers. We considered these missing to be random. In addition, in a small number of participants NCCT scans could not be evaluated due to presence of artefacts. Furthermore, due to a multicenter design, the scans were performed in different hospitals possibly leading to inconsistency. Second, the sample size of our subgroup analysis of our young stroke patients was small. Therefore, these results should be interpreted with caution and differences between sexes cannot be ruled out because of limited power. Due to the small sample size of young stroke patients, we were not able to investigate pre- and post-menopause differences. Third, as our study was cross-sectional, we were not able to draw conclusions on sex differences in atherosclerosis development over time. In our cross-sectional setting we found no differences in presence of atherosclerosis between young men and women with stroke. Fourth, we excluded patients with severe renal disease who have a high burden of systemic atherosclerosis as renal dysfunction is a contraindication for CTA/CTP. Fifth, lack of ethnical diversity in our cohort causes a difficulty to generalize outside of western European populations. Lastly, in our study we focused on biological sex differences between men and women. Cardiovascular risk factors are probably also influenced by gender but in the DUST study no information on gender aspects was available. Strong points are our large prospective cohort of Western European ischemic stroke patients who were all scanned within the first 9 hours of stroke onset. In addition, we were able to use state of the art tools for volumetric assessment of the burden of intracranial atherosclerosis.

Future research should focus on pathophysiological mechanisms in sex differences behind development of intracranial and extracranial atherosclerosis preferably in longitudinal studies and in young populations. Sex differences might be most pronounced in this population due to the effects of sex hormones. This could further help understand differences in development of atherosclerosis between men and women, and may eventually lead to a more sex specific management and prevention of ischemic stroke.

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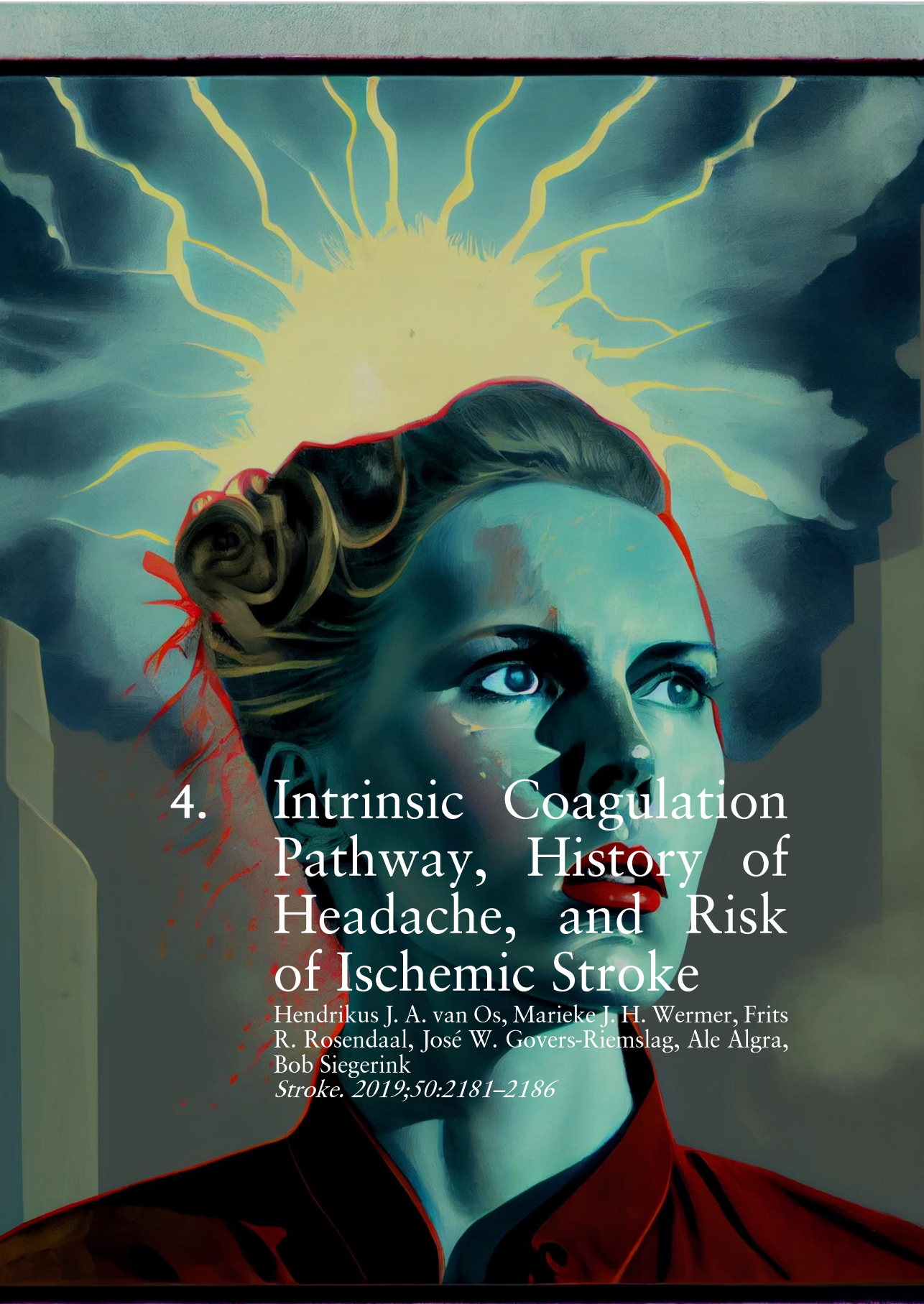

4. Intrinsic Coagulation Pathway, History of Headache, and Risk of Ischemic Stroke

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Abstract

Background and purpose: Hypercoagulable states in migraine patients may play a role in the pathophysiology underlying the association between migraine and ischemic stroke. This study aims to provide more insight into the potential association of headache, ischemic stroke and the intrinsic coagulation pathway.

Methods: We included patients from the RATIO study, a Dutch population-based case-control study including young women (age<50) with ischemic stroke and healthy controls. We defined a headache group based on a questionnaire on headache history. Intrinsic coagulation proteins were measured through both antigen levels (FXII, FXI, prekallikrein, HK) and protein activation, determined by measuring activated protein complex with C1esterase-inhibitor (FXIIa-C1-INH, FXIa-C1-INH, Kallikrein-C1-INH) or antitrypsin-inhibitor (FXIa-AT-INH). We calculated adjusted odds ratios (aOR), and performed an interaction analysis assessing the increase in stroke risk associated with high levels of intrinsic coagulation and history of headache.

Results: We included 113 ischemic stroke cases and 598 healthy controls. In total, 134 (19%) patients had a history of headache, of whom 38 were cases and 96 controls. The combination of headache and high intrinsic coagulation protein levels (all but FXII-antigen level and both FXIa-inhibitors) was associated with an increase in ischemic stroke risk higher than was expected based on their individual effects (aOR FXI antigen level alone: 1.7, 95%CI: 1.0–2.9, aOR headache alone: 2.0, 95%CI: 1.1–3.7, combination: 5.2, 95%CI: 2.3–11.6)

Conclusion: Headache and high intrinsic coagulation protein levels may biologically interact, increasing risk for ischemic stroke.

Introduction

Headache is a common symptom in the general population. Among women, migraine is one of the most common headache subtypes.[1] Migraine with aura (MA) is a cardiovascular risk factor and increases the risk of ischemic stroke approximately two-fold. This risk increase is most pronounced in young women, and is thought to be multicausal.[2-5] A likely contributing pathophysiological mechanism is hypercoagulability during or even between migraine attacks.[6-8] Several studies have shown platelet hyperactivity in migraine patients.[9-12] Additionally, multiple pro-thrombotic genetic polymorphisms have consistently been linked with migraine.[7, 13-17] Traditional thrombogenic factors such as von Willebrand factor (vWF), antiphospholipids (aPL) and prothrombin factor 1.2 were found to be elevated in migraine patients, though results were conflicting.[6, 18, 19] The proteins of the intrinsic coagulation pathway have not yet been assessed in headache patients in general and migraine patients in particular. The intrinsic coagulation proteins are linked to bradykinin formation (from the precursor High Molecular Weight Kininogen [HK]) and other related biological systems, which may play a role in the hemodynamic changes and vascular tone modifications observed during migraine attacks.[20-23] In acute ischemic stroke FXI plays a role in blood coagulation,[24] and high levels of activation of intrinsic coagulation proteins were found to increase stroke risk.[25-27]

This study aims to provide more insight into the connection between headache, ischemic stroke, and the intrinsic coagulation pathway in women. First, we will assess differences in intrinsic coagulation proteins between healthy controls with and without a history of headache, in a population of young women in whom we expect a high prevalence of migraine. Second, we will assess the interaction effect between history of headache and high levels of intrinsic coagulation proteins (activation and antigen levels) with respect to ischemic stroke risk.

Methods

Patients

We included patients from the Risk of Arterial Thrombosis In relation to Oral contraceptives (RATIO) study, a large multicenter population-based case-control study which included patients after the acute phase of their qualifying events that occurred between 1990 and 1995. The design of RATIO has been described previously.[25, 28-30] The aim of the RATIO study was to evaluate the risk of arterial thrombosis (both ischemic stroke and myocardial infarction) due to oral contraceptives of different generations. Inclusion criteria were age 18 to 50 years, no history of arterial thrombosis and confirmation of ischemic stroke by either

computed tomography or magnetic resonance imaging. Exclusion criteria were overt cardioembolic source of ischemic stroke, transient ischemic attack that lasted less than 24 hours, cerebral sinus venous thrombosis, carotid artery dissection, aphasia or cognitive impairment that prevented completion of the study questionnaire, or not speaking Dutch. Healthy controls were approached by random digit dialing and were frequency matched according to age, area of residence, and year of event. For the present study, we selected all ischemic stroke patients and all controls, based on whom we performed a complete case analysis with respect to both headache and intrinsic coagulation data. The RATIO study was approved by the ethics committees of the participating hospitals. All participants gave informed consent. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Patient characteristics

Baseline data were collected via a standardized questionnaire on patient characteristics and self-reported cardiovascular risk factors, i.e. hypertension, diabetes mellitus, hypercholesterolemia, ethnicity, familial medical history, use of oral contraceptives, use of alcohol, and smoking habits. The RATIO study also included a short headache questionnaire with the following questions: 1. 'Did you suffer from headache prior to stroke (or prior to [index year] for controls)?' 2. 'Did you ever visit your general practitioner (GP) for headache?' 3. 'Did you ever visit a neurologist for the headache?' 4. 'Did the neurologist arrive at a diagnosis?' 5. 'Did the neurologist prescribe medication for the headache?' Since no specific migraine related questions were present, we constructed a proxy variable based on the questions on headache history. Participants were divided into a 'no headache' group (negative answer to questions 1 or 2), and a 'headache' group including possible migraine (positive answer to questions 1 and 2). Questionnaires elicited information from the time period preceding the year of ischemic stroke in cases, and the corresponding index year in controls

Intrinsic coagulation proteins

The measurement of the intrinsic coagulation proteins was performed around three months after ischemic stroke, and has been described in detail elsewhere.[25] In short, intrinsic coagulation activation was measured through protein-inhibitor complexes (FXIIa-C1-INH, FXIa-C1-INH, FXIa-AT-INH, KAL-C1-INH), and expressed as a proportion of fully activated normal pooled plasma. Antigen levels were measured by ELISA, and expressed as percentage of antigen levels in normal pooled plasma. In other publications of the RATIO study, high levels of intrinsic coagulation proteins were defined as coagulation activation or antigen levels higher than the 90th percentile cut-off point of the control group.[25, 29] Because of the restricted sample

size of our study population with respect to the total RATIO population, we applied the 75th percentile cut-off point for the definition of high levels of intrinsic coagulation protein antigen and activation.

Statistical analysis

Presence of individual high intrinsic coagulation levels and number of levels were assessed in healthy controls; ORs and corresponding 95% confidence intervals were estimated via logistic regression. We performed an analysis of additive interaction in a standard case-control comparison for all eight intrinsic coagulation protein and activation levels. We used logistic regression to estimate ORs and corresponding 95% confidence intervals as measures of relative risk for high level of the coagulation protein alone (-/+), for headache alone (+/-), and for both (+/+) in comparison with the reference category with neither (-/-) risk factor. All ORs from logistic regression models were adjusted for matching variables (age, region, and year of event), confounding was further minimized by adjusting all ORs for potential and known sources of confounding (hypercholesterolemia, alcohol use, contraceptive pill use, and smoking).

Results

The RATIO study included 203 cases with ischemic stroke and 925 controls. During the recruitment of the second phase of the study, 50 additional ischemic stroke cases were included. In total, 711 participants (60%) had complete intrinsic coagulation and headache data and were included in our study. Of these 711 participants 113 (16%) were ischemic stroke cases. The predefined headache group consisted of 134 participants (19%). (Figure)

Baseline characteristics of participants of this study showed that – as expected and earlier reported – traditional risk factors were more prevalent in ischemic stroke cases than controls, especially hypertension, contraceptive pill use and smoking.[25] (Table 1) Baseline characteristics of these 711 participants were similar to the characteristics of the total RATIO population. (Supplemental Table I)

Figure. Flowchart of participants included in this study

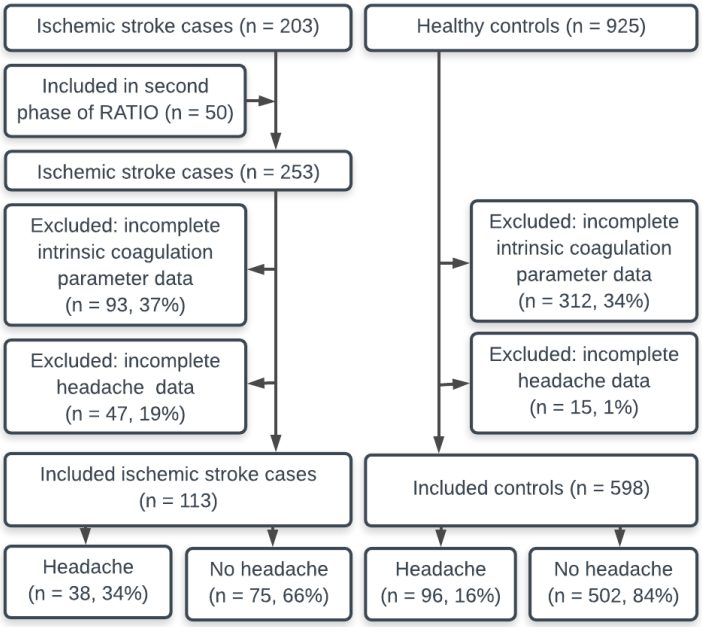

Table 1. Baseline characteristics of all participants

Baseline characteristics	Cases (n=113)	Controls (n=598)
Mean age (± SD)	40.5 (7.4)	38.9 (7.9)
Caucasian, n (%)	107 (96%)	569 (95%)
History, n (%)		
Hypertension	33 (29%)	38 (6%)
Diabetes mellitus	5 (4%)	10 (2%)
Hypercholesterolemia	7 (6%)	19 (3%)
Contraceptive pill use	54 (48%)	196 (33%)
Smoking	65 (58%)	252 (42%)
Alcohol use	67 (59%)	423 (71%)
History of headache, n (%)	38 (34%)	96 (16%)

Table 2. High levels of intrinsic coagulation proteins in healthy controls with and without a history of headache

Intrinsic coagulation protein†	Headache (n=96)	No headache (n=502)	OR (95% CI)*	aOR (95% CI)**
FXII antigen level	18 (19%)	134 (27%)	0.62 (0.36–1.08)	0.61 (0.35–1.07)
FXI antigen level	21 (22%)	130 (26%)	0.76 (0.44–1.30)	0.73 (0.42–1.36)
Prekallikrein antigen level	19 (20%)	131 (26%)	0.69 (0.40–1.19)	0.60 (0.34–1.05)
HK antigen level	24 (25%)	132 (26%)	0.96 (0.57–1.57)	0.83 (0.49–1.42)
FXIIa-C1-INH	24 (25%)	126 (25%)	0.88 (0.52–1.49)	0.76 (0.44–1.32)
FXIa-C1-INH	17 (18%)	132 (26%)	0.67 (0.37–1.20)	0.69 (0.38–1.24)
FXIa-AT-INH	19 (20%)	130 (26%)	0.80 (0.46–1.41)	0.82 (0.47–1.45)
KAL-C1-INH	14 (15%)	142 (28%)	0.47 (0.26–0.86)	0.47 (0.25–0.86)

**OR adjusted for matching variables (age, region, and year of event)'*

***OR adjusted for matching variables, hypercholesterolemia, contraceptive pill use, alcohol use and smoking*

Table 3. Ischemic stroke risk: interaction analysis of high intrinsic coagulation protein levels and activation, and headache

Intrinsic coagulation	>P75†	Headache	Controls, n (%)	Cases, n (%)	OR* (95% CI)	aOR** (95% CI)
FXII antigen level	-	-	368 (62%)	62 (55%)	1 (ref)	1 (ref)
	+	-	134 (22%)	13 (12%)	0.6 (0.3–1.1)	0.5 (0.2–0.9)
	-	+	78 (13%)	30 (27%)	2.0 (1.2–3.3)	1.9 (1.1–3.3)
	+	+	18 (3%)	8 (7%)	2.1 (0.8–5.3)	1.6 (0.6–4.3)
FXI antigen level	-	-	391 (65%)	45 (40%)	1 (ref)	1 (ref)
	+	-	111 (19%)	30 (27%)	1.8 (1.1–3.1)	1.7 (1.0–2.9)
	-	+	78 (13%)	21 (19%)	2.0 (1.1–3.7)	2.0 (1.1–3.7)
	+	+	18 (3%)	17 (15%)	5.7 (2.7–12.1)	5.2 (2.3–11.6)
Prekallikrein antigen level	-	-	371 (62%)	58 (51%)	1 (ref)	1 (ref)
	+	-	131 (22%)	17 (15%)	0.8 (0.4–1.4)	0.7 (0.4–1.3)
	-	+	77 (13%)	20 (18%)	1.4 (0.8–2.5)	1.4 (0.7–2.5)
	+	+	19 (3%)	18 (16%)	5.1 (2.4–10.6)	4.6 (2.1–10.1)
HK antigen level	-	-	370 (62%)	57 (50%)	1 (ref)	1 (ref)
	+	-	132 (22%)	18 (16%)	0.8 (0.5–1.5)	0.8 (0.5–1.5)
	-	+	72 (12%)	20 (18%)	1.6 (0.9–2.9)	1.5 (0.8–2.7)
	+	+	24 (4%)	18 (16%)	3.9 (1.9–7.9)	4.2 (2.0–8.9)
FXIIa-C1-INH	-	-	372 (62%)	53 (47%)	1 (ref)	1 (ref)
	+	-	130 (22%)	22 (20%)	0.9 (0.5–1.6)	0.9 (0.5–1.7)
	-	+	72 (12%)	24 (21%)	2.0 (1.1–3.5)	1.7 (1.0–3.1)
	+	+	24 (4%)	14 (12%)	2.8 (1.3–6.0)	3.6 (1.6–7.8)
FXIa-C1-INH	-	-	372 (62%)	49 (43%)	1 (ref)	1 (ref)
	+	-	130 (22%)	26 (23%)	2.2 (1.3–3.8)	2.2 (1.3–3.9)
	-	+	79 (13%)	29 (26%)	2.5 (1.5–4.4)	2.5 (1.4–4.3)
	+	+	17 (3%)	9 (8%)	4.5 (1.8–11.4)	4.4 (1.7–11.6)
FXIa-AT-INH	-	-	372 (62%)	47 (42%)	1 (ref)	1 (ref)
	+	-	130 (22%)	28 (25%)	2.2 (1.3–3.8)	2.1 (1.2–3.6)
	-	+	77 (13%)	32 (28%)	2.7 (1.6–4.6)	2.5 (1.5–4.4)
	+	+	19 (3%)	6 (5%)	4.0 (1.4–11.1)	4.2 (1.5–12.1)
KAL-C1-INH	-	-	360 (60%)	43 (38%)	1 (ref)	1 (ref)
	+	-	142 (24%)	32 (28%)	2.3 (1.3–3.8)	2.2 (1.3–3.8)
	-	+	82 (14%)	27 (24%)	2.3 (1.3–4.1)	2.3 (1.3–4.1)
	+	+	14 (2%)	11 (10%)	8.2 (3.3–20.5)	7.4 (2.9–19.1)

†Antigen or inhibiting factor level above 75th percentile
**OR adjusted for matching variables (age, region, and year of event)*
***OR adjusted for matching variables, hypercholesterolemia, alcohol use, contraceptive pill use, and smoking*

Second, we confirmed the association between the history of headache and ischemic stroke risk. Thirty eight stroke patients (34%) reported history of headache versus 96 women in the control group (16%), resulting in an aOR of 2.2 (95% CI: 1.4–3.6). (Supplemental Table II) Similar to history of headache, high levels of multiple intrinsic coagulation proteins were associated with an up to two-fold risk of ischemic stroke, which is in line with previous analyses of these data: FXI antigen (aOR 1.7, 95% CI: 1.0–2.9), FXIa-C1-INH (aOR: 2.2, 95% CI: 1.3–3.9), FXIa-AT-INH (aOR: 2.1, 95% CI: 1.2–3.6), and KAL-C1-INH (aOR: 2.2, 95% CI: 1.3–3.8). Interestingly, high FXII antigen levels were associated with a decrease in ischemic stroke risk (aOR: 0.5, 95% CI: 0.2–0.9), (Table 3) while previous analyses that applied the 90th percentile cut-off showed no association (aOR:1.0, 95% CI: 0.4–2.5).[29] The combination of both a history of headache and high intrinsic coagulation protein levels resulted in a clearly supra-additive stroke risk in five of eight intrinsic coagulation protein levels. This association was most pronounced for KAL-C1-INH (aOR protein alone: 2.2, 95% CI: 1.3–3.8, headache alone: 2.3, 95% CI: 1.3–4.1, combination: 7.4, 95% CI: 2.9–19.1), and FXI antigen level (aOR protein: 1.7, 95% CI: 1.0–2.9, aOR headache alone: 2.0, 95%CI: 1.1–3.7, combination: 5.2, 95% CI: 2.3–11.6. (Table 3) After additional adjustment for hypertension and diabetes the results of the interaction analysis remained essentially the same.

Discussion

In healthy controls we found that participants with a history of headache less often had high levels of KAL-C1-INH than those without a history of headache. For the combination of both risk factors (headache history and high intrinsic coagulation protein levels) we found an increase in ischemic stroke risk higher than could be expected based on individual effects of both factors. Other intrinsic coagulation protein antigen or activation levels were not associated with history of headache in healthy controls.

Our study shows synergistic effects of increased levels of the majority of all intrinsic coagulation proteins and positive headache history in increasing risk for ischemic stroke. These associations were most pronounced for KAL-C1-INH and FXI antigen, and may indicate a biological interaction between pathophysiological mechanisms underlying headache and the intrinsic hypercoagulability. These analyses further showed that the sole effect of the increased intrinsic coagulation levels and activation was largely in line with previous publications of the RATIO study.[25, 29] (Table 3) Especially high KAL-C1-INH and FXI antigen levels were strong risk factors for ischemic stroke, also in line with previous publications. FXII antigen showed a lower association with stroke risk than in previous publications,

possibly because we applied the 75th instead of the 90th percentile to define high levels of intrinsic coagulation proteins. Additionally, these analyses are restricted to those RATIO participants in whom headache data were complete. However, baseline variables of our subset were similar to those of the total RATIO population (see Supplemental Table I).[28, 29]

The increased ischemic stroke risk for patients with a history of headache and high intrinsic coagulation protein levels may be the result of a high migraine prevalence in the headache group. However, because we had no reliable data on migraine history this hypothesis remains speculative. Migraine, especially migraine with aura, has been found to be associated with endothelial dysfunction.[8, 31] Endothelial dysfunction causes a pro-thrombotic and pro-inflammatory state and impaired vascular reactivity, factors that could lead to clot initiation.[32, 33] Presence of high intrinsic coagulation antigen levels and activation could further lower the threshold for ischemic stroke in migraine patients by increased clot stability under flow, a process in which biological interaction with endothelial dysfunction mediated mechanisms could play a role.[34] Further, migraine has primarily been associated with platelet hyperactivity.[9-12] Activation of FXI by FXII can be bypassed in the coagulation cascade by feedback activation through thrombin as part of platelet-dependent arterial thrombosis.[35] Platelets contain a FXI receptor glycoprotein IBα, which stimulates this feedback activation in animal studies[36] and FXI-thrombin contributes to distal platelet activation and procoagulant microaggregate formation.[37] This may explain the relatively strong association of FXI activation and antigen levels compared with those of FXII.

Several methodological issues have to be considered. First and most important, because no migraine-specific questions were included in the headache questionnaire direct identification of patients with a history of migraine was not possible. History of headache can only to some extent be used as a proxy for migraine. Although sensitive (i.e. two-thirds of migraine patients visit the GP for their migraine specifically), the proxy has a low specificity.[38] Our study focusses on young women with a one-year migraine prevalence around 25%, making it safe to assume a substantial number of patients with headache in our study actually have migraine.[39] However, as exact prevalence and individual data on migraine are lacking, we cannot distinguish between migraine and non-migraine headache in our conclusions. An extensive literature search did not result in any studies investigating the association between tension or cluster headache and intrinsic or extrinsic coagulation parameters. Although we have no reason to suspect that such associations exist, we cannot rule out the possibility. For migraine the association with increased extrinsic coagulation parameters is well established. However, the hypothesis that migraine is the causative factor for any observed association

between history of headache and intrinsic coagulation proteins could not be assessed sufficiently with our data. The overall prevalence of history of headache in our population (19%) is lower than the average self-reported life-time prevalence of headache in the population (around 60%).[1] However, our definition of headache is more strict than self-reported headache, as it required a GP visit specifically for headache. A Dutch population study found that only 16% of patients with tension-type headache and around 25-50% of patients with migraine visit their GP specifically for headache complaints, explaining the headache prevalence of 19% in our controls.[40] This more restrictive definition likely results in a higher occurrence of moderate to severe headache phenotypes in our headache group including migraine. Second, as blood was collected after the event in the ischemic stroke group, reverse causation may have occurred. For this reason, we focused on the association between headache and intrinsic coagulation parameters only in the control group. In the interaction analysis however, we took the effect of intrinsic coagulation parameters on ischemic stroke risk into account, and also included ischemic stroke cases. Blood sampling in the RATIO study took place minimally one year and often 2-3 or more years after the event. Hence, we can rule out the possibility that our results directly reflect the transient effects of the acute phase of ischemic stroke, which lasts days to weeks. The absence of association between increased activation of the intrinsic coagulation proteins and myocardial infarction risk within the RATIO study suggests that a general post-hoc effect can also be ruled out. However, non-transient (or chronic) effects can still be the cause of reverse causation and can only be completely ruled out when blood samples are taken prior to the event.[25] Third, this study has no data on ischemic stroke sub-classification such as the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria.[41] Fourth, this study consists of young women only. Fourth, this study consists of young women only. This may decrease the generalizability of our results to men and to the elderly, although there are no plausible reasons why these associations would be qualitatively different in others. Fifth, we did not have direct data on anticoagulant use at time of blood drawing. We however could derive suspected oral anticoagulant use from endogenous thrombin potential data. The results of our analyses did not change when we excluded patients who were suspected to use oral anticoagulants at the time of blood drawing (data not shown). Finally, some analyses are based on a low number of participants, especially in the interaction analyses. This is reflected in the wide confidence intervals. So even when some results are 'statistically significant' in the traditional sense of $p < 0.05$, the imprecision of these estimates should be taken into account when interpreting our results. However, given the rare nature of ischemic stroke in young women, the number of included cases could be considered relatively large. Strong points of this study further include the detailed assessment of intrinsic coagulation parameters.

Our findings suggest that a biological interaction between history of headache and of intrinsic coagulation protein antigen levels and activation exists. We speculate that this interaction is caused by migraine although we were not able to investigate this in our study. Therefore, future studies in both men and women with detailed assessment of migraine are needed to assess the relationship of migraine and the intrinsic coagulation system. Especially investigation of the migraine with aura subset of migraine patients may be of interest, since in these patients the association with (micro)vascular abnormalities is better established. Additionally, good assessment of ischemic stroke subtype in such population could further elucidate the role of intrinsic coagulation proteins in the migraine-stroke relation.

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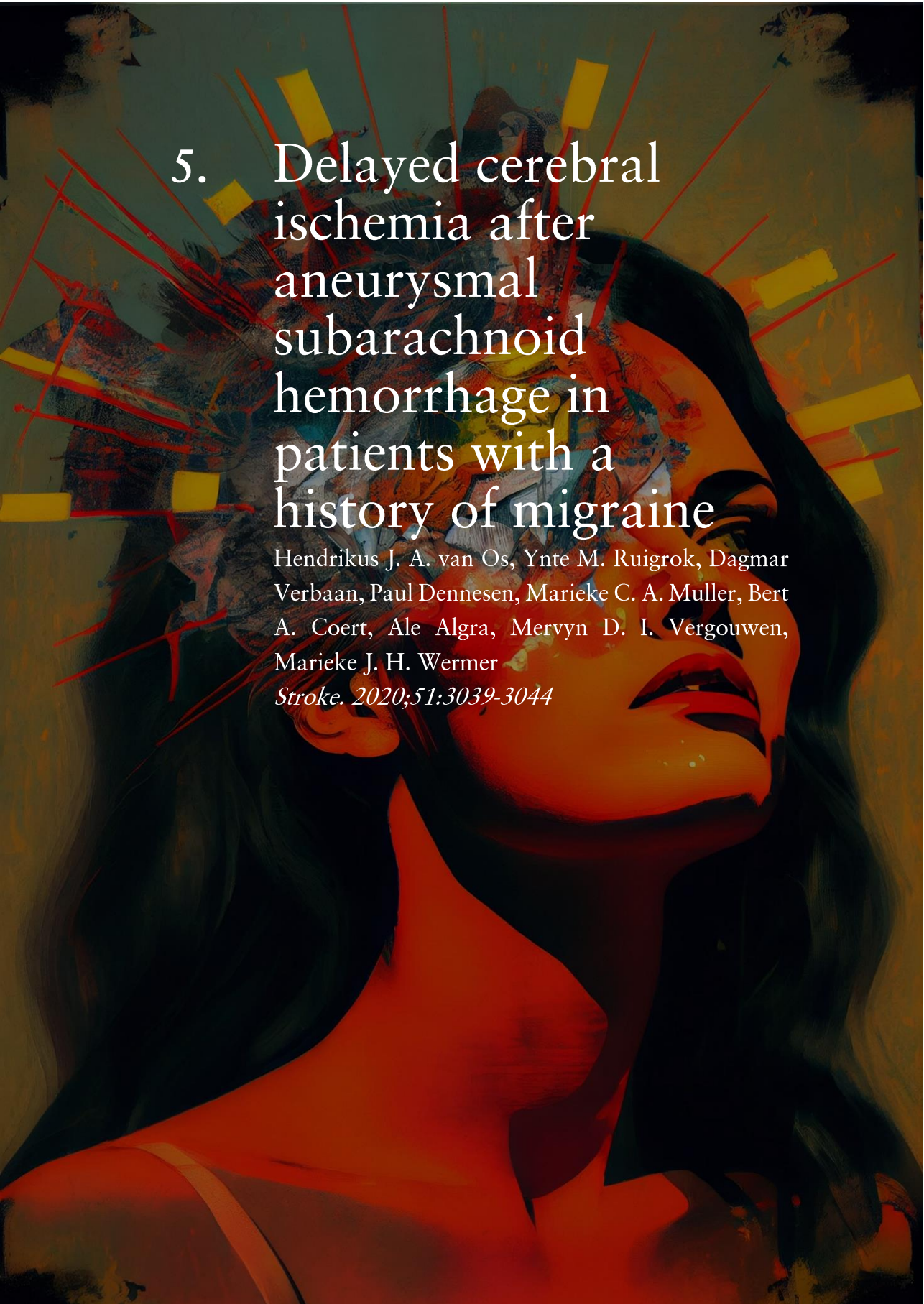

5. Delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage in patients with a history of migraine

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Abstract

Background and purpose: Delayed cerebral ischemia (DCI) is a major contributor to the high morbidity in patients with aneurysmal subarachnoid hemorrhage (aSAH). Spreading depolarizations may play a role in DCI pathophysiology. Since migraine patients are probably more susceptible to spreading depolarizations, we investigated whether aSAH patients with migraine are at increased risk for DCI.

Methods: We included aSAH patients from three hospitals in the Netherlands. We assessed life-time migraine history with a short screener. DCI was defined as neurological deterioration lasting >1 hour not attributable to other causes by diagnostic work-up. Adjustments were made for possible confounders in multivariable Cox regression analyses and adjusted hazard ratios (aHR) were calculated. We assessed the interaction effects of age and sex.

Results: We included 582 aSAH patients (mean age 57 years, 71% women) of whom 108 (19%) had a history of migraine (57 with aura). Patients with migraine were not at increased risk of developing DCI compared to patients without migraine (22% versus 24%, aHR: 0.89; 95% CI: 0.56–1.43). Additionally, no increased risk was found in migraine patients with possible aura (aHR: 0.74; 95% CI: 0.39–1.43), in women (aHR: 0.88; 95% CI: 0.53–1.45, $p_{interaction}$=0.859), or in young patients <50 years (aHR: 1.59; 95% CI: 0.72–3.49), although numbers in these subgroups were limited. We found an interaction between migraine and age with an increased risk of DCI among young migraine patients ($p_{interaction}$=0.075).

Conclusion: Patients with migraine are in general not at increased risk of DCI. Future studies should focus in particular on young SAH patients, in whom there might be an association between migraine history and development of DCI.

Introduction

Subarachnoid hemorrhage from a ruptured aneurysm (aSAH) results in death within three months of around one third of all patients, and more than half of all survivors make an incomplete recovery.[1] A major contributor to the high morbidity in patients who survive is delayed cerebral ischemia (DCI). DCI occurs in around 30% of SAH patients, mostly between day 4 and 10 after hemorrhage onset.[2] The mechanisms underlying DCI are still largely unknown. Several animal experiments suggest that spreading depolarisations (SDs) play a role in development of DCI, possibly induced by products of hemolysis.[3-6] SDs are the underlying mechanism of a migraine aura and are characterized by slowly spreading waves of intense neuroglial depolarizations followed by silencing of brain activity.[7, 8] Hemodynamically, SDs start with a short hyperemia which is followed by a prolonged period of oligemia.[9] In one study repetitively induced SDs resulted in neuronal death in the juvenile SAH rat brain, suggesting that spreading oligemia following SDs can in certain circumstances progress to tissue ischemia.[10] Additionally, valproate - which is an SD inhibitor - prevented SD related delayed brain injury in rats after experimental SAH.[11] In a small pilot study of aSAH patients with the aneurysms treated by clipping, SDs have been recorded directly with electrocorticography, and SD patterns seemed to be related to DCI development.[12, 13] Migraine with aura (MA) increases the risk of ischemic and hemorrhagic stroke approximately two-fold, especially in women.[14-16] This increased risk of ischemic stroke may be partly mediated by increased susceptibility to SDs.[7] One case-control study suggested that women with migraine might have an increased risk of developing DCI after aSAH compared with women without migraine. However, sample size was however limited and only women were included.[5]

In this study we investigated in a large prospectively collected cohort of aSAH patients whether patients with migraine are at increased risk of developing DCI compared with patients without migraine.

Methods

Patients

We included patients from two University hospitals (the University Medical Center Utrecht [UMCU] and the Amsterdam University Medical Center, University of Amsterdam [Amsterdam UMC]) and one large teaching hospital (Haaglanden Medical Center [HMC). In the UMCU, we included consecutive patients admitted for aSAH in the period from 2008 to 2018. In the Amsterdam UMC and UMCU, we included patients of the control arm of the ultra-early tranexamic acid after subarachnoid hemorrhage (ULTRA) study. The ULTRA study is a multicenter

prospective randomized open-label trial that investigates the effect of tranexamic acid on occurrence of rebleeds after SAH.[17] The ULTRA participants in our study did not receive the study medication and were included between 2011 and 2018. In the HMC, we consecutively included patients admitted for aSAH from 2014 to 2016. In all centers the following baseline characteristics were collected during admission: modified Rankin Scale (mRS) score before admission, age, sex, cardiovascular risk factors, history of cardiovascular disease, Glasgow Coma Score (GCS) at admission, location of aneurysm, and aneurysm treatment modality. Outcome was assessed via mRS score at discharge and after three (UMCU and HMC) or six months (Amsterdam UMC).

Standard protocol approvals, registrations, and patient consents

In the UMCU, data for this study were collected within the context of the String of Pearls study. This study was approved by the Medical Ethical Committee, and informed consent was obtained from all patients for use of the data. In the Amsterdam UMC and the HMC data were collected in the context of the NIASH registration. Medical ethical approval was not required for this registration.

Migraine questionnaire

In all three participating centers research nurses recorded a migraine screener.[18] From this screener the following questions were used for this study: 1. 'Did you ever or do you still have migraine attacks?' 2. 'Did you ever suffer from attacks of severe headache that lasted several hours to days during which you had very low tolerance of light and noise?' 3. 'Did you ever experience periods that lasted between 5 to 60 minutes during which your sight was diminished or blurry at one side with possible flashes or glitters in the visual field, followed by headache?' A history of migraine was considered to be present when answers to both question 1 and 2 were positive. If answers to all three questions were positive, patients were classified as having migraine with possible aura. The migraine screener has been validated previously in a stroke population. For the combination of questions we used in our study, the positive predictive value for migraine was 0.78, and the negative predictive value was 0.97. For migraine with aura, the negative predictive value was 0.97 and the positive predictive value was 0.38.[18]

Assessment of delayed cerebral ischemia

DCI was defined as the occurrence of focal neurological impairment (such as hemiparesis, aphasia, apraxia, hemianopia, or neglect) or a decrease of at least 2 points on the Glasgow Coma Scale. The symptoms had to last for at least 1 hour,

were not present immediately after aneurysm occlusion, and could not be attributed to other causes after clinical assessment, CT or MRI scanning of the brain, and appropriate laboratory studies. DCI was assessed during hospitalization.[19]

Sample size calculation

To calculate the sample size needed we choose an alpha of 5% and a power of 80%. We expected DCI to occur in around 30% of unexposed patients.[2] Migraine prevalence was found to be around 17% in patients with aneurysmal SAH,[20] and one third of migraine patients were expected to have migraine with aura.[21] For our calculation we used the odds ratio from a previous observational study investigating the risk of developing DCI in migraine patients versus those without (OR: 2.68).[5] Based on these parameters a total sample size of 228 patients was needed to detect an association with overall migraine, and 551 to detect an association with migraine with aura.[22]

Statistical analysis

Because the development of DCI is time dependent we performed a survival analysis to investigate whether migraine (with and without possible aura combined or with possible aura only) is associated with occurrence of DCI. Adjustments were made for possible confounders (age, sex, GCS at admission) in a multivariable Cox regression analysis, and hazard ratios (HR) and adjusted HR (aHR) with 95% confidence intervals (CI) were calculated. Since migraine is more often active in young patients and in women, we stratified for age < 50 years and sex and we included the interaction terms age*migraine and sex*migraine in the analyses.[21] Statistical testing for interactions was done using an a-priori α=0.10. In addition, we constructed a Kaplan-Meier curve showing DCI-free survival of patients with and without a history of migraine. We calculated adjusted relative risks (aRR) for outcome with Poisson regression.

Results

In total, 879 patients were eligible for the study. Of these patients, 582 had complete data on both migraine and DCI and were included. Baseline characteristics of excluded patients were comparable with those of included patients (data not shown). Mean age of the included patients was 57 ± 13 (SD) years and 415 (71%) were women (Table 1). A history of migraine was reported in 108 (19%) patients, and 57 (10%) patients had migraine with possible aura. Patients with migraine were more often female. Clinical outcome at three months was available for 294 of 382 patients (77%) from the UMCU and HMC, and clinical outcome at six months for 185 of 200 patients (93%) from the Amsterdam UMC.

Delayed cerebral ischemia

Patients with a history of migraine were not at increased risk for developing DCI compared to patients without migraine (22% versus 24%, aHR: 0.88; 95% CI:0.53–1.45). In addition, no increased DCI risk was found in migraine patients with possible aura compared to SAH patients without migraine (20% versus 24%, aHR: 0.74; 95% CI: 0.39–1.43). After stratification for sex, we did not find an association between migraine and DCI development in women (aHR: 0.88; 95% CI: 0.53–1.45), and interaction between migraine and sex was not statistically significant ($p_{interaction} = 0.859$).

Table 1. Baseline characteristics of the participants

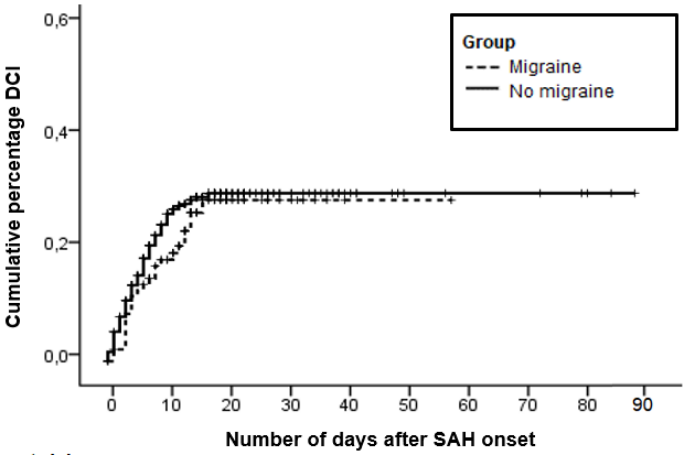
Characteristics	Migraine (n=108)	Migraine with aura (n=57)	No migraine (n=474)
Demographics			
Age, *mean years ± SD*	56 ± 12	58 ± 13	58 ± 13
Women, *n (%)*	90 (83%)	49 (86%)	325 (69%)
History, *n (%)*			
Hypertension	42 (40%)	22 (39%)	185 (40%)
Diabetes mellitus	4 (4%)	3 (5%)	20 (4%)
Hyperlipidemia	20 (19%)	14 (25%)	87 (19%)
Cardiovascular disease*	10 (9%)	6 (11%)	56 (12%)
SAH	4 (4%)	2 (4%)	13 (2%)
SAH in family history	2 (4%)	2 (6%)	5 (3%)
Intracranial hemorrhage	1 (1%)	0 (0%)	3 (1%)
Smoking: current**	54 (52%)	12 (20%)	217 (48%)
Smoking: past**	20 (19%)	30 (51%)	100 (22%)
Alcohol use**	51 (49%)	30 (55%)	277 (62%)
Medication on admission, *n (%)***			
Oral anticoagulation use	1 (2%)	1 (3%)	12 (5%)
Oral contraceptive use	7 (14%)	3 (10%)	17 (11%)
Platelet aggregation inhibitor use	9 (15%)	6 (16%)	29 (12%)
GCS at admission *(IQ range)*	15 (13 - 15)	15 (13-15)	15 (13-15)
GCS at admission < 13, *n (%)*	17 (18%)	7 (13%)	102 (23%)

**History of ischemic stroke, myocardial infarction and/or peripheral artery disease*
***Current smoking: within 6 months before admission; past smoking: quit smoking more than 6 months before admission; alcohol use: any use of alcohol*
****Medication at admission was assessed in the UMCU and the HMC only*

After stratification for age, we also did not find an association between migraine and DCI development in patients <50 years (aHR: 1.59; 95% CI: 0.72–3.49). However, the point estimate of the association changed from 0.70 in patients ≥50 to 1.59 in patients <50 years old, and we found an interaction between migraine and age ($p_{interaction}$ = 0.075). (Table 2) The Kaplan-Meier curve (Figure 1) showed no difference in time to DCI between patients with and without a history of migraine (Log Rank test p = 0.474).

Clinical outcome was comparable between patients with and without a history of migraine. At 3-month follow-up after SAH 83% patients with migraine versus 74% of patients without migraine had an mRS ≤ 2 (aRR: 1.02; 95% CI: 0.90–1.17; data from UMCU, HMC), and at 6-month follow-up 68% patients with migraine versus 79% patients without migraine had an mRS ≤ 2 (aRR: 0.82; 95% CI: 0.65–1.05; data from Amsterdam UMC).

Figure 1. DCI rate over time in patients with and without migraine



Number at risk										
Migraine (n)	107	81	23	7	1	0	0	0	0	0
No migraine (n)	470	318	76	28	14	6	5	4	3	0

Table 2. Risk for delayed cerebral ischemia in patients with and without migraine, stratified by age and sex

Presence of DCI (n/N (%))	Migraine	MA	No migraine	Migraine vs. no migraine aHR (95% CI)	MA vs. no migraine aHR (95% CI)
All patients (n=582)	24/108 (22%)	11/55 (20%)	115/474 (24%)	0.89 (0.56–1.43)[1]	0.74 (0.39–1.43)[1]
Women (n=415)*	21/90 (23%)	10/47 (21%)	86/325 (27%)	0.88 (0.53–1.45)[2]	0.73 (0.37–1.46)[2]
Men (n=167)	3/18 (17%)	1/8 (13%)	29/149 (20%)	1.00 (0.30–3.36)[2]	0.81 (0.11–6.03)[2]
Age <50 years (n=151)	10/31 (32%)	4/13 (31%)	24/120 (20%)	1.59 (0.72–3.49)[3]	1.55 (0.53–4.57)[3]
Age ≥50 years (n=431)	14/77 (18%)	7/42 (17%)	91/353 (26%)	0.70 (0.39–1.26)[3]	0.56 (0.24–1.29)[3]

MA: Migraine with aura

Hazard ratio adjusted for age, sex and GCS at admission[1], for age and GCS at admission[2], and for sex and GCS at admission[3]

**Interaction between migraine and sex: 0.89 (0.24–3.26), p-value = 0.859; interaction between migraine and age (continuous): 0.93 (0.94 - 1.00), p-value = 0.075.*

Discussion

This study shows that patients with a history of migraine are in general not at increased risk of developing DCI. However, a possible association could not be excluded in the subgroup of patients <50 years since a statistically significant interaction was found between migraine and age. The subgroup of patients <50 years had a limited sample size leading to larger confidence intervals.

In one other study the association between DCI and migraine in aSAH patients was investigated. In that study migraine patients more often developed DCI (OR: 2.68; 95% CI: 0.99–7.29).[5] The study differed from our study on several important points. First, the study had a case-control design and included 36 young, female aSAH-patients who had developed DCI as cases and 36 age-matched female aSAH patients without DCI as controls. The women were younger (mean age 42 years) and more patients had a history of migraine (36%) than the participants of our study. Additionally, assessment of migraine was different (open questionnaire based on ICHD-criteria versus our migraine screener). Both studies used the same definition of DCI. Although we found no association between migraine and risk of DCI in our entire population, the interaction between migraine and age suggests that young migraine patients may have an increased risk of DCI, supporting the conclusion of the previous case-control study.[5] The association between young age and risk of DCI in migraine patients may be explained by a higher attack frequency and therefore more active migraine status in young patients.[21] Migraine activity may be related to an increased susceptibility to SDs, which could lead to increased risk of DCI development.

A study in mice with the mutation for familial hemiplegic migraine showed that development of ischemia may be facilitated by an increased susceptibility to SDs. These mice were studied between an age of 2–6 months, which is biologically equivalent to human young adult age.[23] The risk increase of ischemic stroke risk in migraine patients is also highest in patients under 45 years, and has clearly been associated with a high attack frequency. These findings may also be related to an increased susceptibility to SDs in these patient subgroups.[16, 24] However, also other pathophysiological processes may be underlying the potential relation between migraine and risk of DCI. Migraine has been linked with endothelial dysfunction, an association that appears to be particularly strong in young women.[25] In aSAH patients endothelial dysfunction also plays an important role in the development of DCI, thus aSAH patients with migraine – especially those of younger age – may be more susceptible for the pathophysiological cascade of events leading up to DCI.[26]

Several shortcomings of our study must be considered. First, our study population had a better clinical outcome than the average SAH patient population. This reflects the problem that the migraine screener could only be assessed in patients in a well enough condition to answer the questions during admission. Therefore, we cannot generalize our results to a more severe SAH population. Second, our migraine screener had several limitations. In a validation study the negative predictive value was found to be high and the positive predictive value moderate. For migraine with aura, negative predictive value was high but positive predictive value was low, hence we used the term 'possible aura'.[18] The potential misclassification bias in migraine diagnosis and aura symptoms might have diluted the effect sizes we found in our study. Further, because the questionnaire relates to history of migraine, patients who did not experience attacks for a long time may have forgotten information leading to recall bias. However, the migraine prevalence of 19% in our cohort was in line with the prevalence of 17% found by a previous study in patients with aneurysmal SAH.[20] Additionally, the majority of our study population consists of women, and migraine prevalence in women in the general population is found to be around 17%.[21] Unfortunately we did not have information about current attack frequency of migraine patients.

Strong points of this study include the relatively large sample size and the detailed and uniform assessment of DCI. The multi-center design including two academic and one large teaching hospital and the inclusion of men and women of all ages increases the generalizability of our study.

Conclusion

In the overall SAH population we found no association between DCI development and history of migraine. However, we found an interaction between migraine and age suggesting that young migraine patients may have an increased risk of DCI. Future studies with a larger number of young SAH patients are needed to further study the association between migraine and DCI in this particular subgroup.

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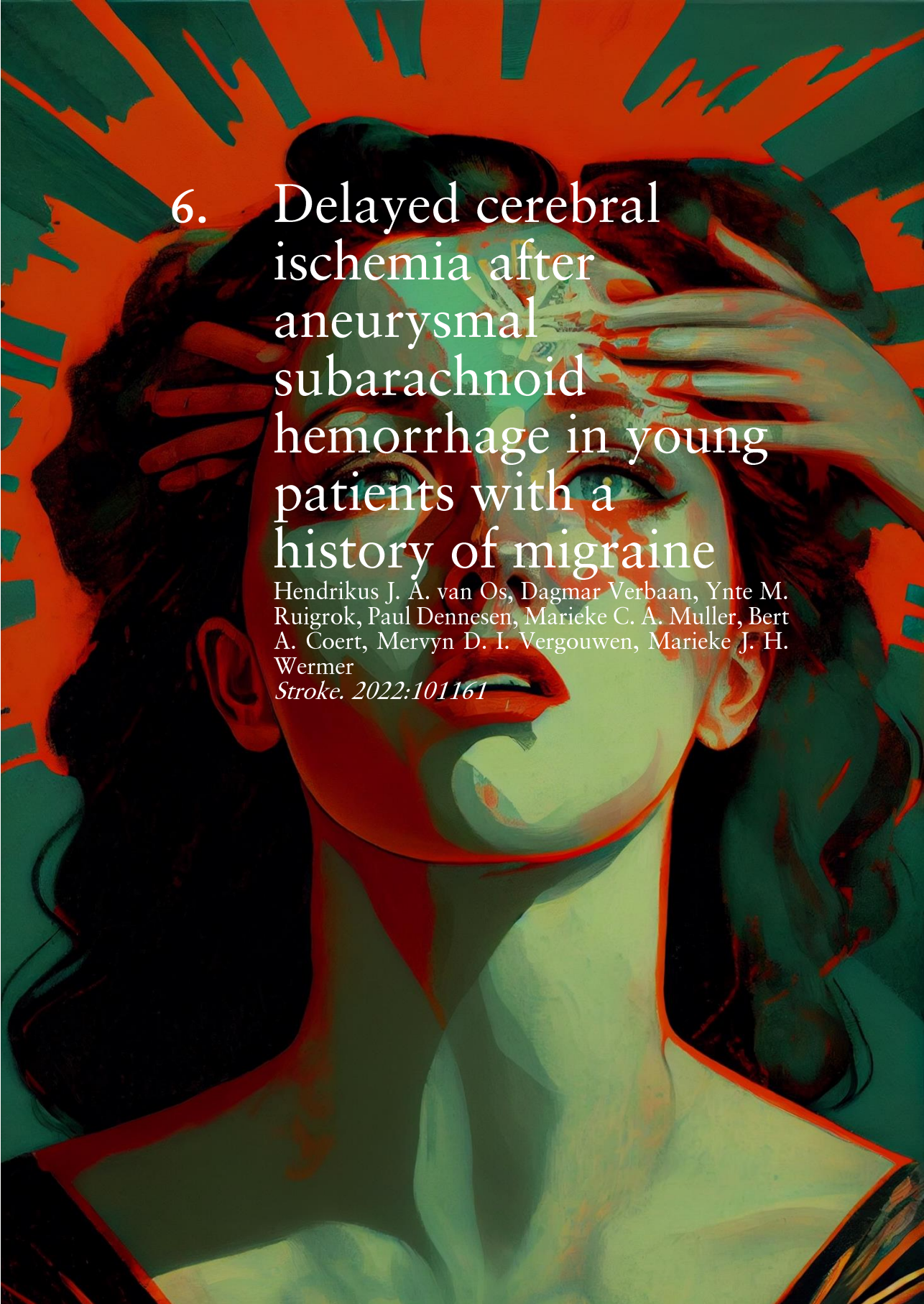

6. Delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage in young patients with a history of migraine

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Abstract

Background and purpose: Young patients with aneurysmal subarachnoid hemorrhage (aSAH) and a history of migraine may have an increased risk of delayed cerebral ischemia (DCI). We investigated this potential association in a prospective cohort of aSAH patients under 50 years of age.

Methods: We included patients with aSAH under 50 years from three hospitals in the Netherlands. We assessed life-time migraine history with a short screener. DCI was defined as neurological deterioration lasting >1 hour not attributable to other causes by diagnostic work-up. Adjustments were made for possible confounders in multivariable Cox regression analyses and adjusted hazard ratios (aHR) were calculated.

Results: We included 236 young aSAH patients (mean age 41 years, 64% women) of whom 44 (19%) had a history of migraine (16 with aura). Patients with aSAH and a history of migraine were not at increased risk of developing DCI compared with patients without migraine (25% versus 20%, aHR: 1.16; 95% CI: 0.57–2.35). Additionally, no increased risk was found in migraine patients with aura (aHR: 0.85; 95% CI: 0.30–2.44) or in women (aHR: 1.24; 95% CI: 0.58–2.68).

Conclusion: Patients with aSAH under the age of 50 years with a history of migraine are not at increased risk of DCI.

Introduction

Delayed cerebral ischemia (DCI) is a major contributor to the high morbidity and mortality in patients who survive subarachnoid hemorrhage from a ruptured aneurysm (aSAH). DCI occurs in around 30% of aSAH patients, mostly between days four and fourteen after hemorrhage onset.[1] The mechanisms underlying DCI are still largely unknown, although cortical spreading depolarizations (CSDs) may play a role.[2] CSDs are the presumed underlying mechanism of a migraine aura and are characterized by slowly spreading waves of intense neuroglial depolarizations followed by silencing of brain activity. Migraine with aura (MA) is associated with an approximately two-fold increased risk of ischemic and hemorrhagic stroke, especially in women.[3] One case-control study suggested that women with migraine might have an increased risk of developing DCI after aSAH compared with women without migraine. However, sample size was limited to 72 patients and only women were included.[4] Recently we found in a large prospective cohort (n=582) that adult aSAH patients with migraine were not at increased risk of DCI (adjusted hazards ratio: 1.55;95%CI:0.53–4.57). However, we found a statistically significant interaction between migraine history and age, indicating a potential association between risk of DCI and history of migraine in young patients.[5] Since then, additional patients under 50 years were included in this cohort. In the current study we assess the potential association between migraine history and development of DCI specifically in the cohort of aSAH patients under 50 years of age.

Methods

We included patients under the age of 50 admitted with aSAH between 2008-2021 to two University hospitals (the University Medical Center Utrecht [UMCU] and the Amsterdam University Medical Center, location Meibergdreef [Amsterdam UMC]) and one large teaching hospital (Haaglanden Medical Center [HMC]). In all centers baseline characteristics were collected, and outcome was assessed using the mRS score. Data on migraine were collected via a validated questionnaire.[6] Since for migraine with aura the positive predictive value is relatively low, we decided to use the term migraine with possible aura.[5, 6] For data collection on patients with aSAH, in the three centers medical ethical approval was waived.

DCI was defined based on a previously published consensus statement as the occurrence of focal neurological impairment or a decrease of at least two points on the Glasgow Coma Scale. The symptoms had to last for at least one hour, were not present immediately after aneurysm occlusion, and could not be attributed to other causes. DCI was prospectively assessed during hospitalization by neurologists, neurosurgeons, or neurology or neurosurgery residents.

We determined that the required sample size was 228 based on an alpha of 5%, a power of 80%, and the odds ratio from a previous observational study (OR: 2.68).[4] We performed survival analysis to investigate whether migraine (with and without possible aura combined or with possible aura only) is associated with occurrence of DCI. Adjustments were made for possible confounders (age, sex, GCS at admission) in multivariable Cox regression analyses, and hazard ratios (HR) and adjusted HR (aHR) with 95% confidence intervals (CI) were calculated. We constructed a Kaplan-Meier curve showing the cumulative incidence of DCI for patients with and without a history of migraine.

Results

In total, 236 patients under 50 years (mean age 41 years, 64% women) with complete data on both migraine and DCI were included (Table 1). Forty-four (19%) patients had a history of migraine of whom 22 (9%) had migraine with possible aura. Patients with a history of migraine were not at increased risk for developing DCI compared to patients without migraine (25% versus 20%, aHR: 1.16; 95% CI: 0.57–2.35). In addition, no increased DCI risk was found in patients with migraine with possible aura compared to SAH patients without migraine (18% versus 20%, aHR: 0.85; 95% CI: 0.30–2.44). After stratification for sex, we did not find an association between migraine and DCI development in women (aHR: 1.24; 95% CI: 0.58–2.68). The Kaplan-Meier curve (Figure) showed no difference in cumulative incidence of DCI between patients with and without a history of migraine (Log-rank test p = 0.52).

Table 1. Baseline characteristics of the participants

Characteristics	Migraine (n=44)	Migraine with aura (n=22)	No migraine (n=192)
Demographics			
Age, *mean years ± SD*	42±6	41±7	41±7
Women, *n (%)*	36 (82%)	18 (82%)	114 (59%)
History, *n (%)*			
Hypertension	13 (30%)	7 (33%)	47 (26%)
Diabetes mellitus	1 (2%)	1 (5%)	1 (1%)
Hyperlipidemia	4 (9%)	3 (14%)	11 (6%)
Cardiovascular disease*	2 (5%)	1 (5%)	8 (4%)
SAH	2 (5%)	0 (0%)	4 (2%)
SAH in family history	1 (5%)	0 (0%)	2 (3%)
Intracranial hemorrhage	1 (2%)	0 (0%)	0 (0%)
Smoking: current**	25 (57%)	14 (64%)	93 (50%)
Alcohol use: any**	16 (40%)	7 (37%)	120 (66%)
Medication use on admission, *n (%)***			
Oral anticoagulation	0 (0%)	0 (0%)	1 (1%)
Oral contraceptive	6 (33%)	2 (18%)	13 (33%)
Platelet aggregation inhibitor	2 (8%)	2 (13%)	1 (1%)
GCS on admission *(IQ range)*	15 (13–15)	15 (13–15)	15 (13–15)
GCS on admission < 13, *n (%)*	6 (20%)	3 (20%)	26 (21%)

**History of ischemic stroke, myocardial infarction or peripheral artery disease*

***Within 6 months before admission*

****Assessed in the UMCU and the HMC only*

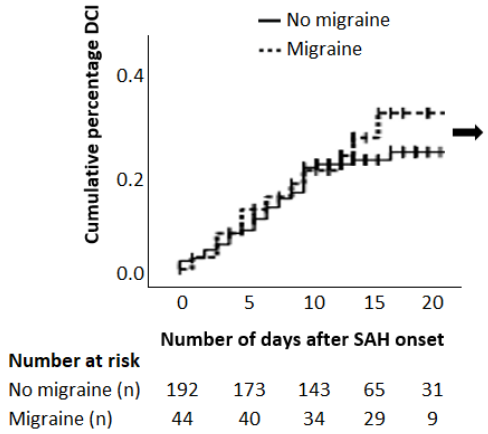
Table 2. Risk for delayed cerebral ischemia in patients with and without migraine, stratified by sex

Presence of DCI (n/N (%))	Migraine	MA	No migraine	Migraine vs. no migraine HR (95% CI)	Migraine vs. no migraine aHR (95% CI)	MA vs. no migraine aHR (95% CI)
All patients (n=236)	11/44 (25%)	4/22 (18%)	38/192 (20%)	1.25 (0.63–2.44)	1.16 (0.57–2.35)[1]	0.85 (0.30–2.44)[1]
Women (n=150)	10/36 (28%)	5/18 (22%)	27/114 (24%)	1.16 (0.56–2.39)	1.24 (0.58–2.68)[2]	1.01 (0.35–2.90)[2]
Men (n=86)	1/8 (13%)	0/4 (0%)	11/78 (14%)	0.81 (0.10–6.26)	0.65 (0.08–5.15)[2]	NA[2]

MA: Migraine with MA: Migraine with aura

Adjusted for age, sex and GCS at admission[1], for age and GCS at admission[2], and for sex and GCS at admission[3]

Figure. DCI rate over time in patients with and without a history of migraine



**The Kaplan-Meier curve has been cut off at 20 days, because after this time no more DCI occurred.*

Discussion

This study shows that patients under 50 years with a history of migraine are not at increased risk of developing DCI. Since migraine patients have a relatively more active form of migraine in young age, they may be more susceptible for CSDs compared with older patients in whom the last migraine attack is often many years before the aSAH.[7] In contrast with our hypothesis, we do not find an association between patients who were presumed to be more sensitive to CSDs and risk of DCI. This could indicate that the contribution of CSDs is relatively weak compared with other pathophysiological processes that may play a role in the development of DCI, such as microthrombosis or impaired cerebral autoregulation.[8]

For the current study, we expanded the number of young aSAH patients to increase our power. Our sample size calculations were based on a case-control study that included 72 age-matched women under 60 years and found an OR of 2.68 for the association between DCI and history of migraine.[4] However, as the authors of that study already acknowledged, this OR may have been an overestimation since it was based on a small dataset of matched pairs.[9] Although in our study no association between migraine and DCI was found, we still cannot completely exclude an effect size smaller than the odds ratio of 2.68 that could reach statistical significance when assessed in a larger cohort. However, based on our results it is unlikely that the association between migraine and DCI is substantial and clinically relevant.

Several shortcomings of our study must be considered. First, the migraine screener could only be assessed in patients in a well enough condition to answer the questions during admission. Therefore, we cannot generalize our results to a more severe aSAH population. Second, there are limitations on use of our migraine screener which have been described in the previous publication on this cohort.[5] Strong points of our study are the prospectively collected large sample of young patients with aSAH, and the detailed and uniform assessment of DCI. We conclude that a positive history of migraine is not a factor to take into account in treating patients with aSAH at risk of DCI.

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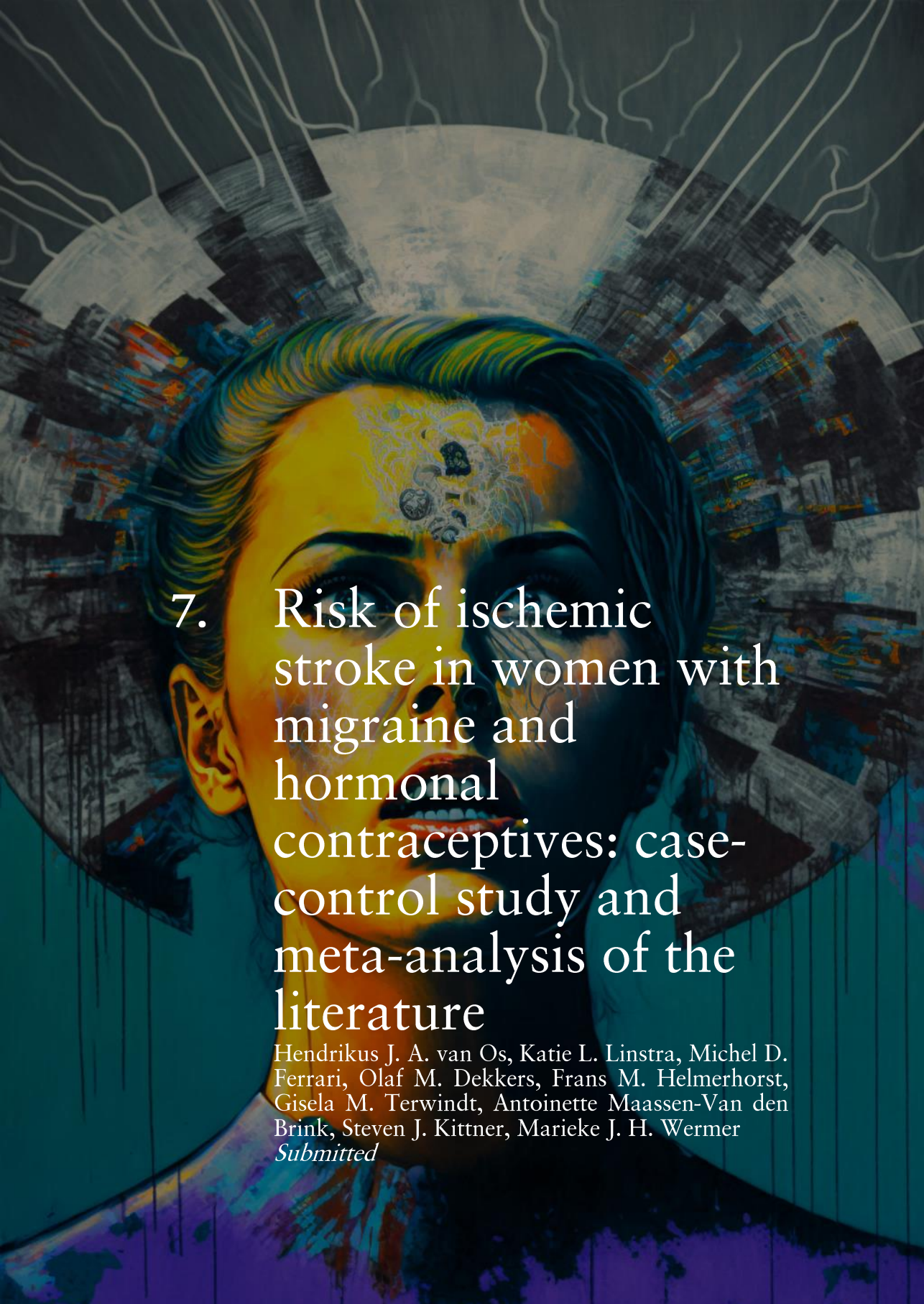

7. Risk of ischemic stroke in women with migraine and hormonal contraceptives: case-control study and meta-analysis of the literature

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Submitted

Abstract

Background and purpose: Migraine and the use of combined oral contraceptives (COCs) are both proven and independent risk factors for ischemic stroke. This study aims to investigate whether migraine and the use of COCs have a supra-additive risk-increasing effect on ischemic stroke.

Methods: We performed an interaction analysis of migraine, COC use and risk of ischemic stroke in a population-based, nested case-control study of women aged 18–49 years with no history of ischemic stroke. In addition we did a systematic review of the extant literature as well as an extended meta-analysis including the present study. We included cohort or case-control studies in premenopausal women with data on migraine and hormonal contraception status and first-ever ischemic stroke as clinical outcome. We extracted adjusted odds ratios (aORs) and performed a subanalysis based on a COC estrogen dose of <50 µg.

Results: Our nested case-control study included 617 women with first-ever ischemic stroke. Mean age was 37 years (SD ± 6.4). Of all cases, a history of migraine was registered for 18.6% in the primary care electronic patient record and 20.6% were COC users; we could not discern between migraine with or without aura. Comparing women with migraine who used COCs to women with neither of the two risk factors, we found a substantial increase in the risk of ischemic stroke (aOR: 6.83; 95% CI: 3.95–11.7). Women with migraine who used COC and also smoked compared with women without migraine and who did not smoke or use COCs, had an even higher risk of stroke (aOR: 30.2; 95% CI: 4.22–610). The systematic review identified 782 potentially eligible articles, of which six studies met the inclusion criteria. In these studies, including our nested case-control study, the risk of ischemic stroke in women who had migraine and used COCs compared with women who did not have either risk factor were all positively associated and ranged from an aOR of 2.04 to 16.9 (pooled aOR: 4.95; 95%CI: 2.13–11.5, I^2 = 84.7%). In a subanalysis based on estrogen dose, the risk of ischemic stroke in women who had migraine and used COCs containing <50 µg estrogen ranged from an aOR of 1.80 to 13.9 (pooled aOR: 3.14; 95%CI: 1.75–5.62; I^2 = 86.6%).

Conclusion: In women aged 18–49 years, the co-occurrence of migraine and use of COCs, even of low estrogen dose, results in a substantially increased risk of ischemic stroke. The additive effect of smoking appears to be large.

Introduction

Migraine, especially with aura, increases the risk of ischemic stroke approximately two times.[1] This risk increase appears to be strongest in women of reproductive age.[2] In women in this age group the use of hormonal contraceptives, especially combined oral contraceptives (COCs), is another common risk factor for ischemic stroke.[3] COCs are the most commonly prescribed form of hormonal contraceptives, and are used by approximately 20% of women of childbearing age in developed countries.[4] The absolute risk of ischemic stroke remains low because COC-users are usually young and healthy.[3, 5] Moreover, the risk of ischemic stroke associated with COC use depends on the estrogen dose, and has decreased significantly in recent decades as estrogen doses have fallen to <50 µg.[6,7] However, the use of COCs by women with migraine may lead to an increase in the risk of ischemic stroke, which seems supra-additive compared with the effect of the two risk factors alone.[8, 9] Smoking may have a further additive effect on the risk of ischemic stroke.[10] Consequently, the World Health Organization (WHO) and the American Congress of Obstetricians and Gynecologists (ACOG) have advised against the use of COCs in women with migraine, particularly with aura.[11, 12] However, this advice has been questioned due to the limited availability and quality of the evidence.[13, 14] Women with migraine represent up to 33% of the female population, of whom one third has migraine with aura.[15] Defining migraine as a contraindication to the use of COCs may therefore impose a significant burden on society, given the contraceptive and non-contraceptive importance of COCs.[16]

The evidence on the risk of ischemic stroke in women with migraine using COCs, including those with a low (<50 µg) estrogen dose, has been extensively reviewed. The prevailing conclusion is that too little data are available to draw strong conclusions about the safety of prescribing COCs in women with migraine.[17, 18, 19] Therefore, we firstly present data from a nested case-control study based on a prospective population-based cohort, in which we assessed the risk of ischemic stroke in women with migraine using COCs and the potential additive effect of smoking. We then integrated our results with previously published evidence using a systematic review and meta-analysis.

Methods

Nested case-control study

We used data from the STIZON database, which directly retrieves data from electronic patient records of a large number of healthcare providers throughout the Netherlands. From the STIZON general practitioner (GP) database we selected women from general practice centers which, based on their location, were in the catchment area of hospitals participating in the STIZON network. This enabled us to link information on hospital diagnoses with primary care data. The STIZON GP database contains International Classification of Primary Care (ICPC) diagnosis codes for clinical entities and Anatomical Therapeutic Chemical (ATC) medication prescriptions from primary care pharmacies.[20,21] ICD-9 and ICD-10 codes are present for all in-hospital diagnoses during follow-up, and ICPC diagnosis codes are in principle available from birth. The inclusion criteria for both cases and controls were women who were registered in a STIZON general practice between 1st of January 2007 and 31st of December 2020 for at least one year, and were aged between 18–49 years within this time window. We used a nested case-control design in which cases were defined as patients with a first-ever ischemic stroke based on either one ICD-9 or ICD-10 hospital or ICPC diagnosis code registered during follow-up. The date of the first-ever ischemic stroke was used as the index date. For each case we then randomly sampled ten controls who had the exact same age as the case on the index date, without replacement. The index date was used to define the baseline characteristics for cases and age-matched controls. The ascertainment of a history of migraine was clinic-based, and was defined using registrations in the electronic patient record of an ICD-9, ICD-10 or ICPC diagnosis code for migraine, or migraine-specific drugs (ATC-code: N02C* with * indicating all registration subcodes) before the index date. Migraine-specific drugs included ergot alkaloids, flumedroxone, triptans, and monoclonal antibodies against calcitonin gene-related peptide (CGRP) or its receptor. We defined current COC use based on the registration of one or more ATC medication prescription codes: current COC use (ATC: G03AA*, G03AB*), within 180 days before the index date. Further, we examined other risk factors for ischemic stroke including age, smoking, diabetes mellitus, hypertension, a history of hemorrhagic stroke, TIA, subarachnoid hemorrhage, myocardial infarction, angina pectoris, and peripheral artery disease. We could not sufficiently distinguish between past and present smoking status based on our data. The local medical research and ethics committee declared that this study was not within the scope of the Dutch Medical Research Involving Human Subjects Act.

To assess the interaction effect between COC use and migraine, we performed an analysis of additive interaction in a standard case-control comparison.[22] We used logistic regression analysis to estimate odds ratios (ORs) and associated 95% confidence intervals (CIs) as a measure of the relative risk of ischemic stroke for COC use alone, migraine only, and the presence of both compared with the reference category with neither risk factor. All ORs from the logistic regression models were adjusted for age, hypertension, hypercholesterolemia, diabetes and smoking (aORs). In addition, we performed an analysis of additive interaction for COC use, migraine, and smoking, for which we compared women who had all three risk factors with women without any of the three risk factors.

Systematic review and meta-analysis

The following inclusion criteria were used for the systematic review. First, we only included studies with a cohort or (nested) case-control design. Second, participants were women of reproductive age. Studies focusing on (peri)menopause were excluded. Third, studies had to contain information on both migraine and use of any form of hormonal contraception (i.e. COC as well as progestogen-only preparations in all available types of administration [oral, transdermal, vaginal ring, injection, intra-uterine device]). Hormonal contraceptive use was compared with non-use, defined as either never having been exposed to a hormonal contraceptive or being a former hormonal contraceptive user. To perform a meta-analysis of the combined effect of hormonal contraception and migraine on the risk of ischemic stroke compared with women without migraine who did not use hormonal contraception, we included only studies that reported data on the combined effect. COCs were classified according to the estrogen dose, as this is the likely thrombogenic component. Studies on emergency contraception were excluded. Fourth, we chose first-ever ischemic stroke as the clinical outcome, which was defined in the original publications. The outcome was measured at the end of the follow-up period of the study. Finally, Two authors (HO, KL) independently reviewed titles and abstracts of the records obtained from the electronic searches and excluded irrelevant studies. Of the remaining records, full copies were obtained to identify studies suitable for inclusion. We settled disagreements by discussion with an independent third review author (MW). We searched in the following databases: PubMed, Embase, Web of Science, Cochrane Database of Systematic Reviews, CENTRAL, CINAHL, PsycINFO, Academic Search Premier, ScienceDirect, LWW, and Wiley. The search strategy was amended for each database. We have not set a language restriction on the study search, and searched for meeting abstracts in Embase and Web of Science to find additional studies. Databases were searched on February 5th 2022, from the date of their inception. The complete search strategy can be found in Appendix I.

Statistical analysis

We extracted adjusted odds ratios (aORs) or adjusted risk ratios (aRRs) depending on what was reported in the original publications. To assess the influence of both migraine and hormonal contraceptive use on risk of ischemic stroke, we pooled effect estimates for migraine versus no migraine, contraceptive use versus no contraceptive use, and for both factors combined versus neither of both factors present. For the pooling of effect estimates of the included studies, we used random-effects models and pooled by weighing the log of the odds ratios or hazard ratios by the inverse of their variance. Cochran's Q and Higgin's I^2 statistic were reported to assess heterogeneity across studies. Since differences in estrogen dose of COCs across studies may be an important source of heterogeneity, a subanalysis based on use of COCs with <50 µg estrogen was performed. R version 4.1.0 was used for all analyses.

Risk of bias assessment

We used a version of the Newcastle-Ottawa tool that was customized for risk of bias assessment in case-control studies.[5] The following risk of bias assessment criteria were customized: 1. Selection of participants (low risk of bias: study with controls/ unexposed sampled from source population or same community as cases/ exposed; high risk of bias: controls not representing the study population). 2. Adjustments for confounding (low risk of bias: adjustment for age or adjustments by design such as matching; high risk of bias: no adjustments in analyses). 3. Hormonal contraceptive exposure evaluation (low risk of bias: database record selection or written self-report, type and dosage reported, differentiation made between current and past; high risk of bias: no description). 4. Migraine exposure evaluation (low risk of bias: migraine diagnosis according to International Headache Society-criteria (version I, II or III); high risk of bias: self-report without diagnostic criteria). 5. Outcome (low risk of bias: (pre)defined outcome assessment, objectively confirmed stroke in all cases by MRI or CT, and distinction between ischemic and hemorrhagic stroke; high risk of bias: no (pre)defined outcome assessment, or not objectively confirmed in in all cases or unclear).

Results

Nested case-control study

From the 1st of January 2007 to the 31st of December 2020, 617 of all 258,828 women aged between 18–49 years had a first ischemic stroke. This corresponded to an average annual cumulative incidence of 26 strokes per 100,000 women. We included these 617 cases and 6170 age-matched controls. The mean age was 37 years. Of all cases, 115 (18.6%) women fulfilled our defined criteria for clinic-based migraine, versus 556 (9.0%) women in the control group, resulting in an increased risk of ischemic stroke of aOR: 1.67 (95% CI: 1.31–2.61). Women who currently used COCs also had an increased risk of ischemic stroke compared with those who did not currently use COC (20.6% versus 9.4%; aOR: 2.40; 95% CI: 1.91–2.65).

Table 1. Baseline characteristics of ischemic stroke cases and controls of ages 18–49 years

Baseline characteristics	Cases (n = 617)	Controls (n = 6170)
Age (mean ± SD)	37.3 (6.4)	37.3 (6.4)
Cardiovascular risk factors, *n (%)*		
Smoking (ever)	91 (14.7)	382 (6.2)
Hyperlipidemia	80 (13.0)	158 (2.6)
Hypertension	199 (32.3)	723 (11.7)
Diabetes mellitus	27 (4.4)	120 (1.9)
Hemorrhagic stroke	7 (1.1)	0 (0.0)
TIA	13 (2.1)	5 (0.1)
Subarachnoid hemorrhage	4 (0.6)	0 (0.0)
Myocardial infarction	6 (1.0)	11 (0.2)
Angina pectoris	4 (0.6)	8 (0.1)
Peripheral artery disease	9 (1.5)	48 (0.8)
Migraine	115 (18.6)	556 (9.0)
Preeclampsia	23 (3.7)	119 (1.9)
Hormonal contraceptive use, *n (%)*	127.0 (20.6)	583.0 (9.4)

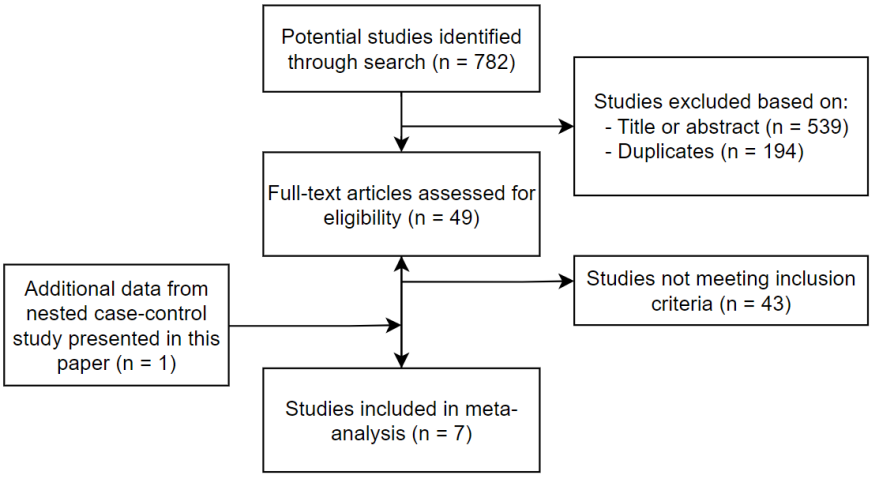
For combined migraine and COC use versus neither factor we found a significant increase in the risk of ischemic stroke (3.1% versus 0.4%; aOR: 6.83; 95% CI: 3.95–11.7), which was supra-additive to what would be expected from the presence of migraine (aOR: 1.52; 95% CI: 1.16–1.97) or COC use alone (aOR: 2.19; 95%

CI: 1.71–2.79, Table 2a). Women with migraine who both smoked and used COCs versus women without migraine who neither smoked nor used COCs, had a clearly increased risk of stroke (aOR: 30.2 95% CI: 4.22–610, Table 2b).

Systematic review

Our systematic review identified 782 potentially eligible articles through an electronic search, of which 194 were duplicates. We excluded 534 articles based on title and abstract assessment. In addition, 49 articles were excluded after a full review. Seven studies, including the case-control study presented in this paper, met the inclusion criteria[9, 10, 23-25] (Figure 1).

Figure 1. PRISMA study flow diagram



Authors of one included study shared additional data on the joint effect of migraine and COC use, the joint effect of migraine, COC use and smoking on risk of ischemic stroke, and on the subanalysis based on low estrogen dose.[24] All seven included studies had a case-control design, with ischemic stroke as the outcome measure.[9, 10, 23-25] Two included studies also performed a subanalysis for hemorrhagic stroke as outcome measure.[10, 25] Hormonal contraception consisted mainly of COC use, and no studies reported isolated effect estimates for other hormonal contraceptives. Two studies distinguished between migraine with and without aura[23, 24], and two studies assessed the joint effect of migraine, hormonal contraceptives and smoking on the risk of ischemic stroke.[9, 24] Characteristics of the seven included studies are listed in Table 3. One study reported only the aOR for migraine with and without aura separately, while all other studies reported the aOR for migraine with and without

aura combined. To include this study in the quantitative analysis, we combined the OR from migraine with and without aura.[23]

Risk of ischemic stroke in women with migraine, use of COCs, or both

In the seven included studies, the aORs for ischemic stroke in women without migraine who used COCs compared with women without migraine who did not use COC ranged from 1.11–4.90 (pooled aOR: 1.85; 95% CI: 1.24–2.74; Q: 30.2, $p < 0.001$; I^2: 87.7%). The risk of ischemic stroke in women with migraine compared with women without migraine, the aORs ranged from 1.03–3.70 (pooled aOR: 1.57; 95% CI: 1.22–2.01; Q: 10.9, $p = 0.03$; I^2: 72.1%). The risk of ischemic stroke in women with migraine and use of COCs compared with women who did not have migraine and did not use COCs, the aORs ranged from 2.04–16.9 (pooled aOR: 4.44; 95% CI: 2.40–8.21; Q: 22.6, $p < 0.001$; I^2: 84.7%, Figure 2).

Risk of ischemic stroke in women with migraine with aura versus those without aura

Two studies distinguished between migraine with and without aura. One study found an aOR of 6.08 (95% CI: 3.07–12.1) for the risk of ischemic stroke in women with migraine with aura and using COCs compared with women without migraine and using COCs. In women with migraine without aura and using COCs compared with women without migraine and using COCs, the aOR was 1.77 (95% CI: 1.09 – 1.88).[23] The second study found an aOR of 2.34 (95% CI: 1.09–5.00) for risk of ischemic stroke in women with migraine with probable visual aura who used COC compared with women without migraine and using COCs. In the same study, the risk of ischemic stroke in women with migraine with and without aura combined who used COC versus women with no migraine who did not use COCs resulted in an aOR of 2.21 (95% CI: 1.16–4.21).[24]

Table 2a. Risk of ischemic stroke: interaction analysis of migraine and combined oral contraceptive use

	COC* use	Cases	Controls	OR (95% CI)	aOR** (95% CI)
Migraine	Yes	19 (3.1)	23 (0.4)	9.78 (5.86–16.2)	6.83 (3.95–11.7)
	No	52 (8.4)	311 (5.0)	2.1 (1.63–2.69)	1.52 (1.16–1.97)
No migraine	Yes	108 (17.5)	560 (9.1)	2.28 (1.79–2.87)	2.19 (1.71–2.79)
	No	438 (71.0)	5276 (85.5)	Ref.	Ref.

**COC = combined oral contraceptive; aOR = adjusted odds ratio*

***Odds ratio adjusted for age, smoking, diabetes, hypertension, hyperlipidemia*

Table 2b. Risk of ischemic stroke: interaction analysis of migraine, combined oral contraceptive use, and smoking

	COC* use + smoking	Cases	Controls	OR (95% CI)	aOR** (95% CI)
Migraine	Yes	5 (0.8)	1 (0.0)	68.2 (11.0–1308)	30.2 (4.22–610)
No migraine	Neither	68 (11.0)	473 (7.7)	Ref.	Ref.

**COC = combined oral contraceptive; aOR = adjusted odds ratio*

***Odds ratio adjusted for age, smoking, diabetes, hypertension, hyperlipidemia*

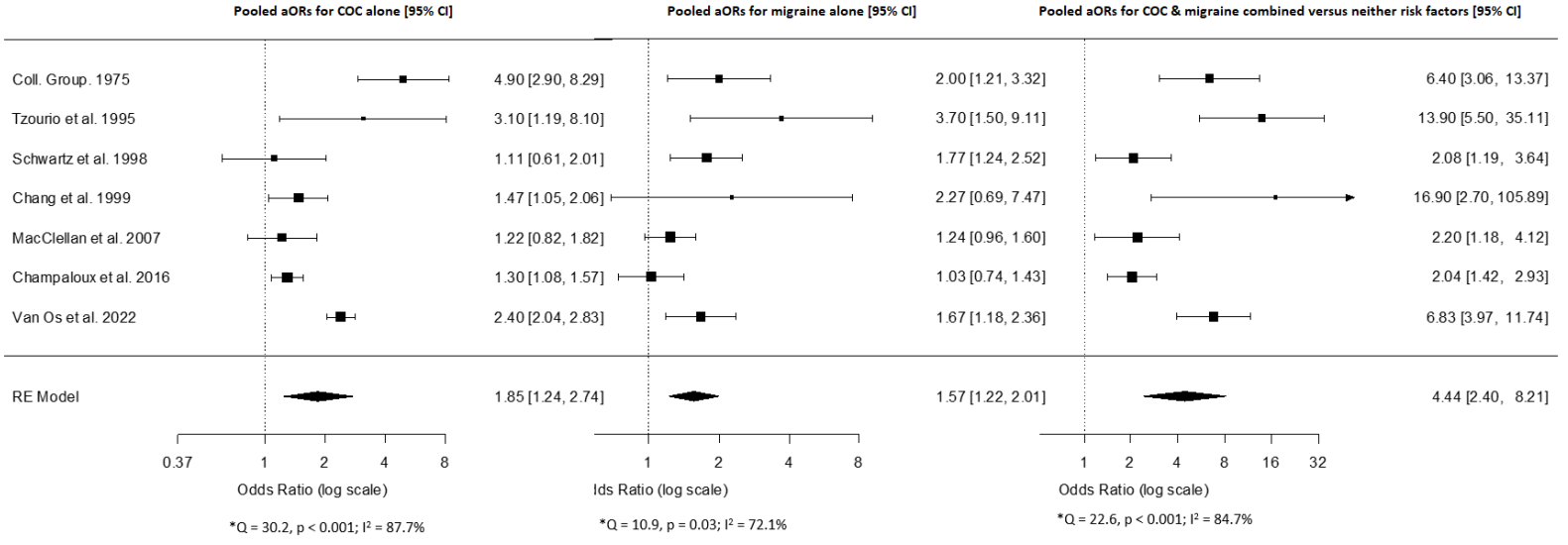
Table 3. Characteristics of studies included in the systematic review

Author, Year, Setting	Design	Population	Age	Migraine	Contraceptive use	Outcome	Adjustments
Collaborative Group 1975, hospitals in 12 cities, US	Case-control, inclusion 1969-1971	598 cases, 429 hospital controls matched for age, race and geographical area, 451 neighbourhood controls matched for race and age	15-44	Self-reported during structured interview not based on IHS-criteria. No subspecification with/without aura	Data from participant questionnaire. Dose: 100 µg and 50 µg, distribution of dose not further specified*	Ischemic and hemorrhagic stroke based on discharge diagnosis, confirmed by neurologist	None
Tzourio et al. 1995, five hospitals in France	Case-control, inclusion 1990-1993	72 cases, 173 hospital controls with rheumatologic of orthopedic diagnoses	18-44	Neurologist interview based on IHS criteria. No subspecification with/without aura	Data from participant questionnaire. Distribution estrogen dose: 30-40 µg (73%), 50 µg (15%), 20 µg (7%), progestin only (5%)	Ischemic stroke, defined clinically using WHO criteria, confirmed by imaging	None
Schwartz et al. 1998, from Kaiser Permanente (KP) Medical Care Plans and University of Washington Study	Case-control, inclusion 1991-1995	175 cases, 1191 population controls, for Kaiser Permanente study matched on exact year of birth and facility of usual care	18-44	Self-reported: migraine diagnosis from clinician or having visited clinical for migraine	Self-reported. Distribution estrogen dose: <50 µg for all patients	Ischemic stroke, 2 physicians reviewed medical records or single board-certified neurologist reviewed the records	Treated hypertension, treated diabetes, smoking ethnicity, BMI, and menopausal status
Chang et al. 1999, hospitals in eight cities in Europe	Case-control, inclusion 1990-1993	291 cases, 736 hospital controls from same hospital as matched cases, matched for age and time of admission	20-44	Neurologist interview based on IHS criteria, stratified for migraine with and without aura	Data from patient questionnaire, distribution estrogen dose: ≥50 µg (31%), <50 µg (69%)	Ischemic and hemorrhagic stroke based on clinical diagnosis, confirmed by review medical records	High blood pressure, education, smoking categories, family history of migraine, alcohol, and social class;
MacClellan et al. 2007, 59 hospitals in Baltimore, US	Case-control, inclusion 1992-2003	386 cases, 614 population controls matched for geographic area, race and age	15-49	Standardized questionnaire using IHS-criteria, differentiated between migraine with probable visual aura and migraine without	Data from patient questionnaire, estrogen dose specified in 75% of participants, in whom: ≥50 µg (3%), <50 µg (97%)	Ischemic stroke discharge diagnosis, confirmed by review medical records and imaging (CT/MRI)	Age, race, geographic region, study period
Champaloux et al. 2016, National Healthcare claims database, US	Case-control, inclusion 2006-2012	1884 cases, 7536 age-matched controls from database	15-49	ICD-9 codes in database, recorded prior to stroke	Data from pharmaceutical claims database, estrogen dose not specified	Ischemic stroke, ICD-9 codes in database	Hypertension, diabetes, obesity, smoking, ischemic heart disease, and valvular heart disease;
Van Os et al. 2022, population-based open cohort in The Netherlands	Nested case-control, inclusion 2007-2020	617 cases, 6170 age-matched controls	18-49	ICPC-, ICD-9 and ICD-10 codes including migraine specific drugs (ATC N09C)	Data from pharmaceutical database (ATC codes), estrogen dose not specified	Ischemic stroke, ICD-9 and ICD-10 codes in database	Ischemic stroke, ICD-9 and ICD-10 codes in database

Table 4. Risk of bias assessment of included studies

Author, year	Selection of participants	Adjustments for confounding	OC exposure evaluation	Migraine exposure evaluation	Outcome
Collaborative Group 1975	Low	Low	High	High	High
Tzourio et al. 1995	High	Possible	Low	Low	Low
Schwartz et al. 1998	High	Low	Low	High	Low
Chang et al. 1999	High	Low	Low	Low	Low
MacClellan et al. 2007	Low	Low	Low	Low	Low
Champaloux et al. 2016	Low	Low	High	High	High
Van Os et al. 2023	Low	Low	High	High	High

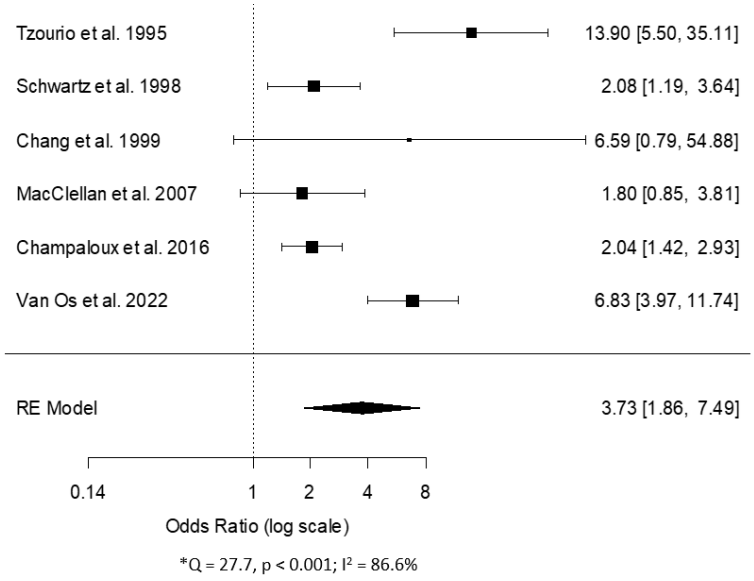
Figure 2. Association of hormonal contraceptives and migraine alone, and both combined with risk for stroke



Three-way interaction between migraine, use of COCs, and smoking

One study found an aOR of 34.4 (95% CI: 3.27–361) for the risk of ischemic stroke in women with migraine who used COCs and were current smokers (nine in the cases and two in the controls) versus women without any of these three risk factors.[10] In another study, a similar comparison resulted in an aOR of 5.33 (95% CI: 1.81–15.7) (unpublished data, see supplement).[24] In our nested case-control study, we found an aOR of 30.2 (95% CI: 4.22–610), which was also based on a very small number of exposed cases and controls (five cases and one control with migraine who used COC and smoked).

Figure 3. Association of hormonal contraceptives with estrogen dose of <50µg and migraine combined with risk for stroke



Risk of ischemic stroke in women with migraine and use of low dose estrogen COCs

One study reported the subanalysis based on use of COC with <50 µg estrogen in the original publication,[10] and authors of another study shared data on this subanalysis with us.[24] For one case control study from 2017 and our nested case-control study no information on COC estrogen dose was available. However, it can be assumed that during this follow-up period more than 75% of all women used low estrogen dose.[23] In the six studies included in the subanalysis of low dose

estrogen, aORs for ischemic stroke in women with migraine with aura and use of COCs ranged from 1.80–13.9 (aOR: 3.14; 95%CI: 1.75–5.62; Q = 27.7, $p < 0.001$; $I^2 = 86.6\%$, Figure 3).

Risk of bias in included studies

Four studies sampled controls from the general population, two studies used hospital-based controls and in one study controls came from the US National Health Claims database, and the exact origin of controls was unknown. All studies adjusted for confounding either with matching or through multivariate analysis, or both. Three studies reported distribution of estrogen dose of COCs across the study population. Three studies collected migraine data with International Headache Society-criteria, and two studies explicitly reported ascertainment of stroke diagnosis with imaging (Table 4).

Discussion

We first conducted a nested case-control study in women aged 18–49 years and found that migraine, use of COCs, and smoking were independent and supra-additive risk factors for first-ever ischemic stroke. The additive relative effect of smoking was substantial, but remained small in absolute terms. We then conducted a systematic review of the literature and identified six studies that reported on the joint effect of migraine and use of COCs on the risk of ischemic stroke. A pooled analysis of these six previous studies together with our novel nested case-control study showed that migraine and the use of COCs have an supra-additive increasing effect on the risk of first-ever ischemic stroke in women. Pooled estimates for migraine and COCs use together resulted in high heterogeneity ($I^2 = 84.7\%$), indicating that there was a large discrepancy between reported odds ratios. Importantly, all studies showed that the risk of ischemic stroke for migraine and COC use was positively associated, meaning that the studies are in agreement that the combination of migraine and COC increases the risk of ischemic stroke. In a subanalysis in women with migraine who used COCs containing <50 µg of estrogen, the pooled effect estimate for the risk of ischemic stroke remained supra-additive, although the aOR was lower (pooled aOR: 3.14; 95%CI: 1.75–5.62) compared with total COCs use and migraine (pooled aOR: 4.44; 95% CI: 2.40–8.21). This analysis also suffered from a high heterogeneity ($I^2 = 86.6\%$).

Compared with the extant literature[17, 18], the present study adds unpublished data from a previously published case-control study[24], our nested case-control study, as well as a meta-analysis of all six “old” studies plus our “seventh new” study,

meeting the critical inclusion criteria. The findings of our nested case-control study provide an additional argument that migraine and the use of COCs – even those with low-dose estrogen – have a supra-additive increasing effect on the risk of ischemic stroke, consistent with the findings of other studies.[9, 10] Our nested case-control study and meta-analysis, however, could not distinguish between migraine with and without aura. This distinction is important, because based on the literature it seems to be specifically migraine with aura that is associated with an increased risk of ischemic stroke.[26] Further, one previous study found a clearly supra-additive effect of migraine with aura and concomitant COC use on the risk of ischemic stroke[23], while this could not be confirmed in another study.[24]

Strengths of our nested case-control study include the linkage of multiple data sources (primary care data, hospital diagnosis codes, and pharmacy registrations) and the prospective collection of data. A strong point of our systematic review and meta-analysis is that we were able to retrieve previously unpublished data from one study.[24] Our study has several potential limitations. First, the migraine definition in our nested case-control study was derived from electronic patient record registrations, and may have suffered from underreporting.[27] The cumulative lifetime incidence of migraine in our nested case-control study was 18.6% in cases and 9% in controls, which is substantially higher compared with a previous report on Dutch primary care electronic patient record registrations of migraine (2.5%).[28] This was potentially because we used multiple sources of electronic patient record registrations for our migraine definition (primary care, hospital, and medication registrations) and we included women of reproductive age in whom active migraine prevalence is highest.[29] However, the lifetime incidence of migraine in our nested case-control study was still lower than the estimated cumulative lifetime incidence of migraine according to population based studies, in which the migraine diagnosis was verified using the International Headache Society criteria (up to 33%).[15, 29] The underreporting of migraine may be due to the fact that a substantial proportion of migraine patients do not visit the general practitioner for their migraine[29] and when they do, migraine may not be accurately reported by the GP in the electronic patient record.[27] However, differential misclassification of migraine by case-control status was unlikely, as all data were routinely and prospectively recorded and problems such as recall bias were absent. Therefore, the underreporting of migraine may have led to an underestimation of the association between migraine and the risk of ischemic stroke which we found in this study.[30] Because we used a clinic-based definition of migraine in our nested case-control study, our migraine group likely consists of women who have searched for help in primary or hospital care or are treated for migraine. In this subgroup of migraine patients, the risk of ischemic stroke may be relatively more increased compared with the overall migraine population.[31] Second, in Dutch electronic patient records, often overall stroke

classification codes are used instead of codes specific to ischemic or hemorrhagic stroke. Therefore, we included the codes for overall stroke in our definition of ischemic stroke. Of all events in our nested case-control study, only 23% were based on codes for overall stroke. Since about 80% of strokes are ischemic, it is likely that less 5% of all stroke registrations in our nested case-control study represents hemorrhagic stroke. Misclassification of hemorrhagic as ischemic strokes may have caused a small dilution of the observed effects. Third, we found significant heterogeneities in the random-effect analyses, which complicates interpretation of the pooled aORs. Multiple potential sources of bias for the included studies could be identified in our risk of bias assessment, which made it difficult to identify a primary cause for the heterogeneities and to perform meta-regression or sensitivity analyses.

Implications for clinical practice

Recently, the European Headache Federation (EHF) and the European Society of Contraception and Reproductive Health (ESC) published a consensus statement in which authors suggested against prescription of COCs in women with migraine with aura. The supra-additive increase in the risk of stroke in the migraine patients who use COCs, which was found in our nested case-control study, likely constitutes a lower limit of the risk increase in migraine patients with aura because of the following. Although we could not distinguish between migraine with or without aura based on our data, we do know that migraine with aura constitutes only 30% of all migraine cases. Moreover, since more than a decade the Dutch national primary care guideline for hormonal contraceptive use mentions migraine with aura as a risk factor for ischemic stroke, and states migraine with aura in combination with smoking as a contraindication for the prescription of COC.[32] It is, therefore, likely that a substantial number of GPs have refrained from prescribing COC to women with migraine with aura, which would result in a relatively smaller fraction of women with migraine with aura in our overall migraine group. Because the effect of migraine with aura on the risk of ischemic stroke appears to be much stronger than that of migraine without aura, the effect we found in our nested case-control study could have been diluted compared with the true effect of migraine with aura. However, if the supra-additive increase in the risk of ischemic stroke would have only been caused by the smaller migraine with aura subgroup, this implies that the effect of migraine with aura would be many times higher than the effect that we found in our study. Compared with findings from previous studies this is unlikely[23, 24], and, therefore, we cannot exclude the possibility of a supra-additive effect on the risk of ischemic stroke in migraine patients who use COCs. Regarding women without aura who have additional cardiovascular risk factors, authors of the EHF and ESC consensus statement suggest non-hormonal contraception or progestogen-

only contraceptives as the preferential option.[33] Given the supra-additive effect of smoking in addition to migraine and the use of COCs in our case-control study (aOR: 30.2), our study supports this suggestion. Although the absolute risk of ischemic stroke in young women is low (11–25 per 100.000[23]), migraine, COCs use and smoking can still significantly increase the risks and stroke at young age will often result in many years of disability.[34] Based on our results, we advise healthcare professionals – and in particular general practitioners – to (i) be careful in prescribing COCs to women with migraine without aura who also smoke, (ii) to actively ask about migraine including aura status in this context, and (iii) to invest in the quality of routine care registrations of migraine diagnoses.

Future research should focus on more personalized advice on the use of COCs in women with migraine. This includes explaining relative and absolute risks of ischemic stroke for different doses of estrogen and taking into account migraine attack frequency and aura status[2, 31] and the presence of traditional cardiovascular female-specific and psychosocial risk factors.[35, 36] For many women with migraine, the contraceptive and non-contraceptive benefits of COCs (e.g. reduction in the risk of ovarian and endometrial cancer[37]may outweigh the relatively small increase in absolute risk of ischemic stroke.

Conclusion

In young women, migraine with aura and possibly also without aura, COC use and smoking have supra-additive effects on the risk of ischemic stroke. This effect may be slightly lower but still significant for COCs containing low doses of estrogen.

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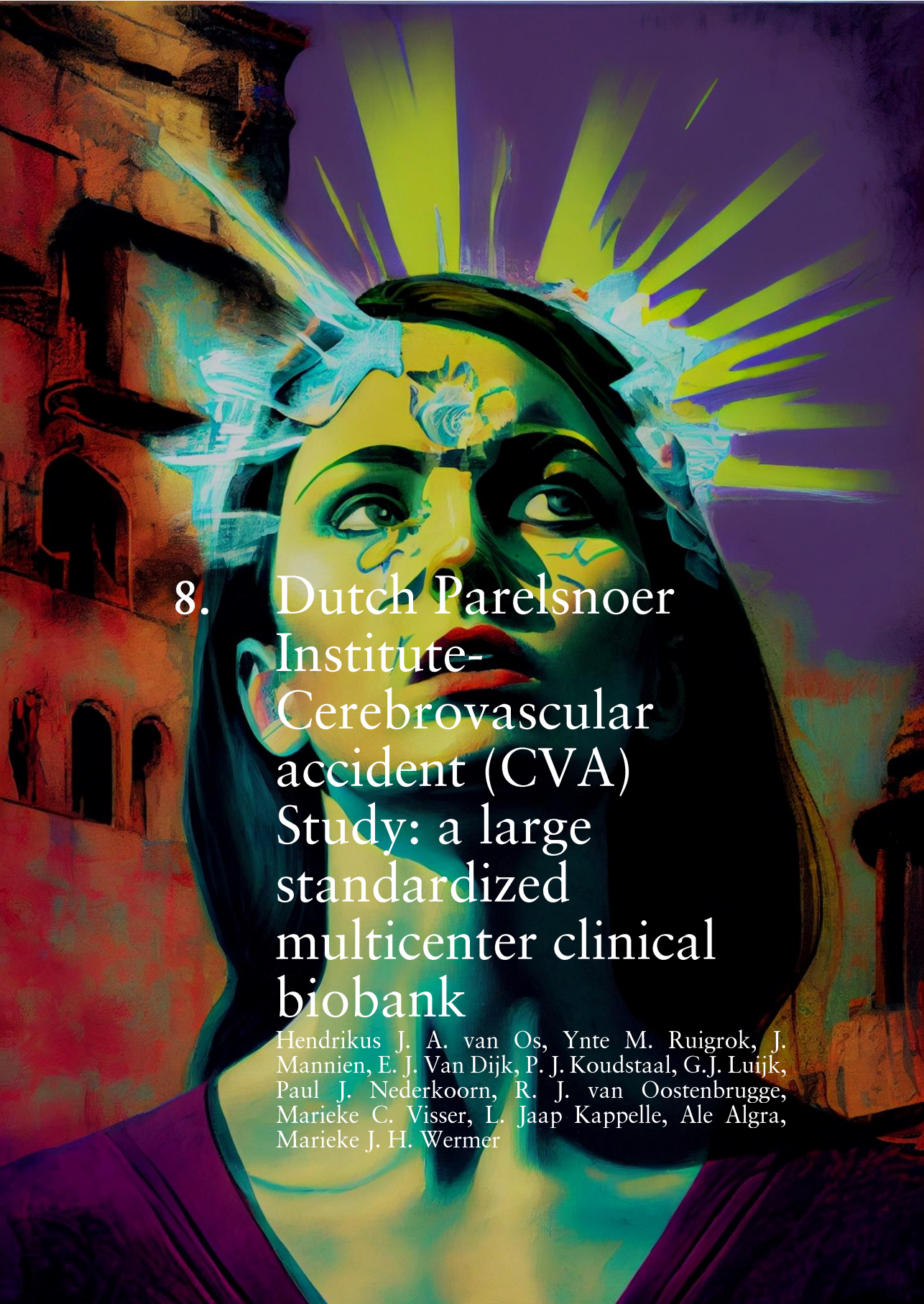

8. Dutch Parelsnoer Institute-Cerebrovascular accident (CVA) Study: a large standardized multicenter clinical biobank

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Abstract

Background and purpose: The Dutch Parelsnoer Institute-Cerebrovascular accident (CVA) Study is part of the Parelsnoer Institute (PSI), initiated in 2007 by the Netherlands Federation of University Medical Centers (NFU). PSI is a cooperation of all eight Dutch University Medical Centers (UMCs) and aims at building large prospectively collected datasets with uniformly and standardized storage of biomaterials for complex diseases. Currently, PSI covers 18 disease-specific cohorts called 'Pearls', and this number is still growing. One of these cohorts is the Stroke or CVA Pearl. For each of the cohorts, PSI offers the UMCs an infrastructure and standard procedures for storing the specific biomaterials in their certified biobanks.

Methods: Clinical data are stored in a central database after being pseudonymized to ensure patient privacy. For the Parelsnoer Institute-CVA Study, blood for genetic analysis, serum and plasma are collected according to nationally agreed standards. Currently (November 2017) the Stroke Pearl has stored blood samples with prospectively obtained clinical data of around 6000 patients in all UMCs combined. Blood samples and data are available for all researchers with a methodologically valid research proposal.

Introduction

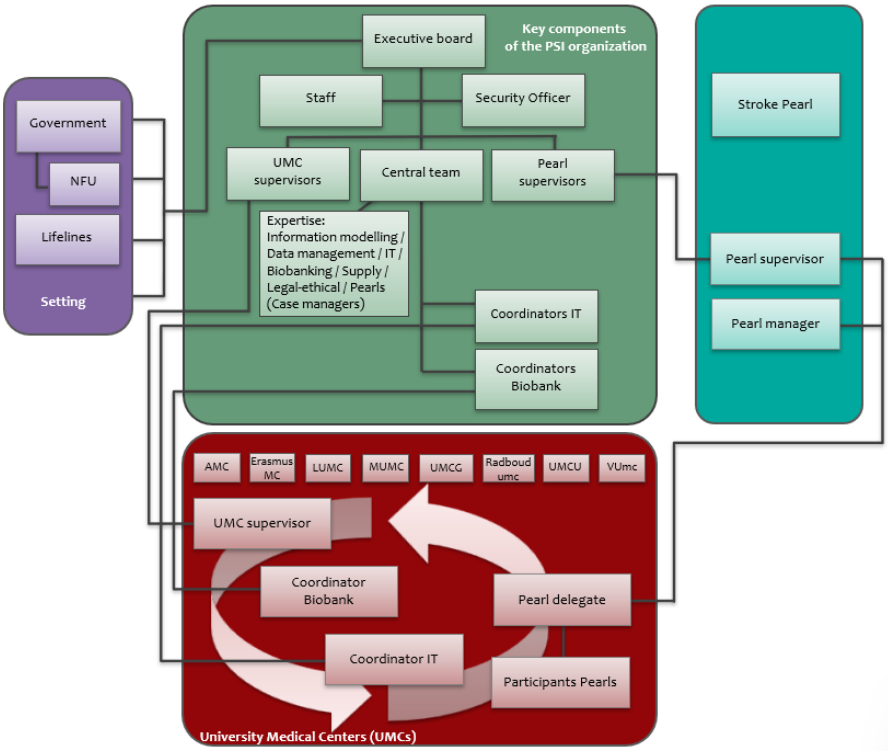
Project description

The Dutch Parelsnoer Institute-Cerebrovascular accident (CVA) Study is part of the Parelsnoer Institute (PSI), initiated in 2007 by the Netherlands Federation of University Medical Centers (NFU).[1] PSI is a cooperation of all eight Dutch University Medical Centers (UMCs) and aims at building large prospectively collected datasets with uniform and standardized storage of biomaterials for complex diseases. Currently, PSI covers 18 disease-specific cohorts called 'Pearls', and this number is still growing.[2-18] PSI is centrally organized and has an executive board for operational management to ensure collective standardization strategies. Additionally, a team of PSI experts supports researchers and the executive boards of the participating UMCs with implementing these strategies. Standardization between and within UMCs is established via multiple standard operating procedures (SOPs) regarding i) storing of biobank materials in the certified biobanks of the UMCs. These SOPs are developed by biobank coordinators from all UMCs together and cover all phases of biobanking. ii) managing the clinical database for every specific disease, hosted via a web based application (ProMISe).[1, 19] (Figure 1)

For the Dutch Parelsnoer Institute-CVA Study, each UMC stores blood for genetic analysis, serum, and plasma in their own certified biobank. The creation of large stroke cohorts is currently of great importance in genetic stroke research, illustrated by genome-wide association studies (GWASs) performed in the last years.[20-23] Stroke is a heterogeneous disease consisting of several etiological subtypes with different underlying pathophysiological mechanisms. These subtypes include ischemic stroke and transient ischemic attack (TIA), cerebral venous sinus thrombosis, intracerebral hemorrhage and subarachnoid hemorrhage. Ischemic stroke mainly consists of the subtypes large vessel atherosclerosis, cardio-embolism and small vessel disease. Large etiological subtypes of intracerebral hemorrhage are small vessel disease and vascular malformations. Aneurysmal subarachnoid hemorrhage can be classified as aneurysmal or perimesencephalic.

Most subtypes are thought to have a specific genetic architecture, as GWASs have found multiple genetic loci to be subtype-specific. Future genetic stroke research may lead to management approaches more tailored to the different subtypes and novel therapeutical targets.[20, 21, 24]

Figure 1. Organogram of the Parelsnoer Institute



The aim of the Dutch Parelsnoer Institute-CVA Study is first to create a large prospective cohort of stroke patients with blood samples and DNA collected through standardized procedures and stored in an uniform way. These samples are coupled with stroke subtypes according to the TOAST classification and the ASCO system. The Trial of Org 10172 Acute *Stroke* Treatment (TOAST) classification distinguishes i) large-artery atherosclerosis, ii) cardio-embolism, iii) small vessel occlusion, iv) stroke of other determined etiology and v) stroke of undetermined etiology as etiological stroke subtypes.[25] The ASCO system (where A stands for atherosclerosis, S for small vessel disease, C for Cardiac source, O for other cause) classifies similar subtypes, though both classification schemes have been found to have different characteristics in practice.[26, 27] These classifications enable us to investigate associations between genetic risk loci and stroke subtypes and to enable pooling with data of other ongoing genetic stroke studies.[20, 21, 25, 27] Second, besides genetic research the Parelsnoer Institute-CVA Study population is also very well suited for epidemiological studies because of its prospective, multicenter design and large sample size.[28]

Classification

Human: biological samples and associated clinical data

Context

Spatial coverage

All eight Dutch University Medical Centers: Academic Medical Center (Amsterdam), Erasmus Medical Center (Rotterdam), Leiden University Medical Center, Maastricht University Medical Center, Radboud University Medical Center (Nijmegen), University Medical Center Groningen, University Medical Center Utrecht, VU University Medical Center (Amsterdam).

Temporal coverage

For the Parelsnoer Institute-CVA Study, the UMCU started collecting data in 2009, the seven other UMCs started in 2010. Data collection is ongoing in five UMCs, no end date has been determined.

Temporal coverage for accessibility:

The blood samples are available for researchers with a methodological valid research proposal (see *access criteria* for more information); no end date has been determined.

Methods

Patients

Inclusion criteria for the Dutch Parelsnoer Institute-CVA Study are a diagnosis of TIA or stroke, presenting in one of the eight Dutch UMCs within one month after stroke onset. Stroke encompasses ischemic stroke, cerebral venous sinus thrombosis, intracerebral hemorrhage, and subarachnoid hemorrhage (both aneurysmal and perimesencephalic hemorrhage). Further inclusion criteria are age > 18 years and the provision of informed consent. Informed consent is defined as written consent by the donors to collect data and biological samples in a Biobank for future scientific purposes in order to study etiopathogenesis and the clinical course of CVA. Informed consent includes the option for the donors to revoke their consent any time, after which the data and biomaterials will be removed from the CVA Biobank, except for the data and samples already included in research protocols. These very broad inclusion criteria result in the incorporation of nearly all stroke patients seen in Dutch UMCs in the Dutch Parelsnoer Institute-CVA

Study database. For every patient, data on medical history, family history, vascular risk factors, medication use and exact time of stroke symptom onset are recorded. Deficits in neurological examination at baseline are recorded according to the National Institutes of Health Stroke Scale (NIHSS), a graded assessment of consciousness, eye movements, visual fields, motor and sensory impairments, ataxia, speech, cognition and inattention.[29] Ischemic stroke subtype is defined according to both the TOAST classification and the ASCO system.[26, 27] Data are collected on treatment such as intravenous thrombolysis, neurosurgical (clipping or decompressive surgery) or endovascular (coiling of aneurysms, intraarterial thrombectomy or thrombolysis) intervention, start of oral anticoagulation treatment in case of atrial fibrillation, and start of secondary prophylactic treatment. Additionally, we collect data on laboratory investigations and on imaging, i.e. brain CT and CT angiography, brain MRI and MR angiography and ultrasound investigations. After three months functional outcome is prospectively recorded via a structured telephone interview, using the modified Rankin Scale.[30]

Steps

For the Parelsnoer Institute-CVA Study, a specific Parelsnoer Repository for Information Specification, Modelling and Architecture (PRISMA) has been defined. PRISMA is an information model enabling us to reuse electronic health record (EHR) information for scientific purposes. This reuse of information minimizes registration burden while at the same time routine care procedures are taken into account. The architecture is in agreement with national and international classifications such as International Classification of Diseases and Related Health Problems (ICD-10), SNOMED CT and the Logical Observation Identifiers Names and Codes (LOINC®).[1] For all stroke patients included in the Parelsnoer Institute-CVA Study, all predefined demographic and clinical variables including data on functional outcome are recorded as coded data via PRISMA and are sent to the central PSI database, a validated web based application (ProMISe).[19] Additionally, blood for genetic analyses, serum and plasma are collected, preferably during routine clinical procedures. Blood samples are then stored in certified UMC biobanking facilities adhering to the PSI biobanking protocol. This protocol covers all phases of biobanking, from collection to storage of the samples. Metadata on blood samples and the unique sample code are registered in the central database together with the clinical data.

Stabilization/preservation

Table 1 gives a summary of procedures on collection, processing and storage of samples defined in the biobanking protocol of PSI.

Quality assurance measures

PSI uses two main strategies to guarantee uniform collection and storage of clinical data between UMCs which are i) limiting the number of collected variables to only the essentials and ii) using existing EHR infrastructure within UMCs infrastructure for recording of data.
As there is no possibility to improve quality of biomaterials afterwards, strict adherence to biobank related SOPs optimizing integrity of biomaterials is needed. Biobank coordinators from all UMCs have together developed the PSI biobanking protocol, encompassing all phases of biobanking, i.e. sample collection, pre-analysis, registration, processing and storage.
The biobanking protocol according to Biospecimen Reporting for Improved Study Quality (BRISQ) is as follows.[31] Blood collection for the CVA Biobank is performed according to the biobank SOP. EDTA blood (10 ml) and Serum blood (10 ml) are collected by venipuncture in the arm. Collection of smaller tubes and pooling of samples is not allowed. Clotting time for serum is defined at 60 minutes at room temperature. Blood is to be stored at room temperature until centrifugation. Centrifugation is to be performed at 2000 g either at room temperature or at 4 ºC. Aliquoting is in volumes of 0.5 ml in at least 5 quantities. Processing time from venipuncture to storage in freezer at -80ºC is predefined at preferably 2 hours with a maximum of 4 hours. All samples are stored under unique identifiers without identifiable patient information. DNA samples from EDTA blood are to be processed within 4 weeks when stored at 4 ºC or within 3 months when stored at ≤ -20 ºC. Processed DNA should be stored as at least 2 stock solution aliquots at ≤ 4 ºC with unique samples codes, including concentration and quality data based on the OD 260/280 ratio. All processing and quality data, including specific time points to assess processing time and track and trace of the samples are registered in a local Biobank Management Information System. Core samples data are provided to the central infrastructure of the Parelsnoer Institute CVA Biobank. In addition to the processing data deviations from the Biobank SOP per individual sample, if applicable, are also registered in the database. These SOP deviations include: hemolytic, lipemic, icteric, wrong blood tube, incomplete filling of the blood tube, temperature deviation, processing time deviation, mixing problems, centrifugation deviation, storage problems and free text remarks. (Table 1)

Table 1. Summary of procedures on collection, processing and storage of samples defined in the biobanking protocol of PSI

Sample	Volume/number	Processing	Time	Aliquoting	Storage	Additional information
Serum	10 ml clotted blood	2000 x g at room temperature or 4°C for 10 minutes	Within 2–4 hours	≥ 5 x 0.5 ml	–80°C	SOP deviations*
EDTA plasma	10 ml	2000 x g at room temperature or 4°C for 10 minutes	Within 2–4 hours	≥ 5 x 0.5 ml	–80°C	SOP deviations*
DNA (blood)	10 ml EDTA blood	Whole blood or cell pellet, to UMC specifications	Within 4 weeks (4°C) or 3 months (< –20°C)	≥ 2 stock aliquots	4°C or lower	OD ratio 260/280, concentration in µg/ml*

**See the 'Quality assurance measures' section for detailed additional information*

Source of associated data

Data are recorded from electronic health records and laboratory reports. Each UMC has its own research IT infrastructure that delivers the data to their local database in ProMISe, a web based application. The information supplied by each UMC is first validated and then periodically uploaded to the central Parelsnoer Institute-CVA Study database in ProMISe for storage on a national level. During uploading, identifying patient data are encrypted using special software of a trusted third party (Trusted Reversible Encryption Service®, Houten, Utrecht, The Netherlands). As additional measure for protection of privacy, the identifying data are encrypted again when exported from the central database for research purposes. In specific situations, e.g. in case of incidental findings that need feedback to the patient or in case of data-linkage, de-pseudonymization can be performed by authorized personnel. The PSI IT infrastructure is in agreement with privacy and international security standards.[1]

Ethics Statement

The Parelsnoer Institute-CVA Study Group uses a patient information brochure, regulations and a consent form, approved by the local Medical Ethical Committees (MECs) of all UMCs. Subsequently, both MECs and Board of Directors of the remaining participating UMCs approved local implementation of the biobanking activities.[1] The study is performed according to the principles of the Declaration of Helsinki and in accordance with the Medical Research Involving Human Subjects Act and codes on 'good use' of clinical data and biological samples as developed by the Dutch Federation of Medical Scientific Societies.[32, 33] All patients should give written informed consent prior to inclusion.

Constraints

Only patients who have provided written informed consent are included. The PSI does not include healthy controls. After inclusion, patients may withdraw their consent at any time. The patient can express the wish to withdraw to his/her doctor, in which case the doctor will ensure that data and materials are destroyed unless needed for validation of earlier issuance.

Biosource description

Object name

The Parelsnoer Institute-CVA Study

Bioresource name

The Parelsnoer Institute-CVA Study

Bioresource location

All eight University Medical Centers across the Netherlands participate in PSI:

1. Academic Medical Center, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands
2. Erasmus Medical Center, 's-Gravendijkwal 230, 3015 CE Rotterdam, The Netherlands
3. Leiden University Medical Center, Albinusdreef 2, 2333 ZA Leiden, The Netherlands
4. Maastricht University Medical Center, P. Debyelaan 25, 6229 HX Maastricht, The Netherlands
5. Radboud University Medical Center, Geert Grooteplein-Zuid 10, 6525 GA Nijmegen, The Netherlands
6. University Medical Center Groningen, Hanzeplein 1, 9713 GZ Groningen, The Netherlands
7. University Medical Center Utrecht, Heidelberglaan 100, 3584 CX Utrecht, The Netherlands
8. VU University Medical Center, De Boelelaan 1117, 1081 HV Amsterdam, The Netherlands

Bioresource contact

Parelsnoer Institute, Jaarbeursplein 6, 3521 Al Utrecht, The Netherlands, Email: info@parelsnoer.org

http://parelsnoer.org/page/en/Parels?mod[Parelsnoer_Module_Pearl][n]=23

Bioresource type

For the Dutch Parelsnoer Institute-CVA Study blood for genetic analysis, serum and plasma are collected and stored. (Table 1)

Type of sampling

The Dutch Parelsnoer Institute-CVA Study is a disease based cohort with longitudinal collections, sampled in clinical care.

Anatomical site

The brain and cerebral vasculature, including cervical vessels.

Clinical characteristics of patients/source:

For the Dutch Parelsnoer Institute-CVA Study, a full clinical characterization, including extensive diagnostics, demographics, therapeutics and clinical follow-up is specified.

Vital state of patients/source

All patients are alive at inclusion.

Clinical diagnosis of patients/source

Ischemic stroke and transient ischemic attack (TIA), cerebral venous sinus thrombosis, intracerebral hemorrhage, and subarachnoid hemorrhage (both aneurysmal and perimesencephalic hemorrhage).

Control samples

The Parelsnoer Institute does not collect control samples from healthy individuals.

Biospecimen type

For the Dutch Parelsnoer Institute-CVA Study blood samples for genetic analysis, serum and plasma are collected and stored. Table 1 gives a summary of procedures on collection, processing and storage of samples defined in the biobanking protocol of PSI.

Size of the bioresource

As of November 3rd 2017, clinical data of 6074 and blood samples of 5769 patients were available in the Dutch Parelsnoer Institute-CVA Study. Of all patients with clinical data, 4390 had a final diagnosis of ischemic stroke (72%), 786 of subarachnoid hemorrhage (13%), 599 of intracerebral hemorrhage (10%), 114 of cerebral venous sinus thrombosis (2%). Further, 48 patients (1%) had another final stroke diagnosis and of 137 patients (2%) final diagnosis was missing. PSI has no end date.

Release date

Data and samples of the Dutch Parelsnoer Institute-CVA Study are currently available. Regarding all disease cohorts, the research projects based on PSI data and samples have led to several scientific publications.[2-16, 18]

Access criteria

PSI has an online open access catalogue with up-to-date information about the content of the Dutch Parelsnoer Institute-CVA Study, providing insight for researchers worldwide and offering them the opportunity to submit a research proposal to the Dutch Parelsnoer Institute-CVA Study and request its data and blood samples.[17] These proposals are reviewed by the scientific committee of the Dutch Parelsnoer Institute-CVA Study, consisting of representatives of the Pearl and independent scientific experts. This committee judges whether the proposed study is relevant, methodologically valid, compliant with the scientific aims of the Dutch Parelsnoer Institute-CVA Study Group and with the privacy protection rules. In addition to this scientific committee, the Research Ethical Committee of the coordinating UMC and several other participating centers have to grant permission according to local policy. When the proposal is accepted by all committees, data from the central PSI facilities will be delivered by the PSI data manager to the researcher. Requested biomaterials will be delivered by the biobank coordinators of the UMCs. If the subsequent research project results in new individual data on the biosamples, PSI demands these newly acquired data to be made publicly available for future research purposes. For researchers using PSI data, costs are involved. These costs include direct costs for retrieval of the samples from the UMC biobanks and shipment of the samples. In addition, depending on the defined collaboration with external researchers, consortia or industrial partners additional costs will be negotiated for the Biobank related acquisition costs, sample and data collection, research project costs and contribution to the sustainability of the Parelsnoer Institute CVA-Biobank.

Reuse potential

Samples from the same donor may be used for multiple projects. The researcher may only receive samples and data on two conditions: i) they share their scientific findings with PSI and provide PSI with a copy of the published paper, and ii) they acknowledge the Dutch Parelsnoer Institute-CVA Study Group in all publications of studies using PSI data and samples.

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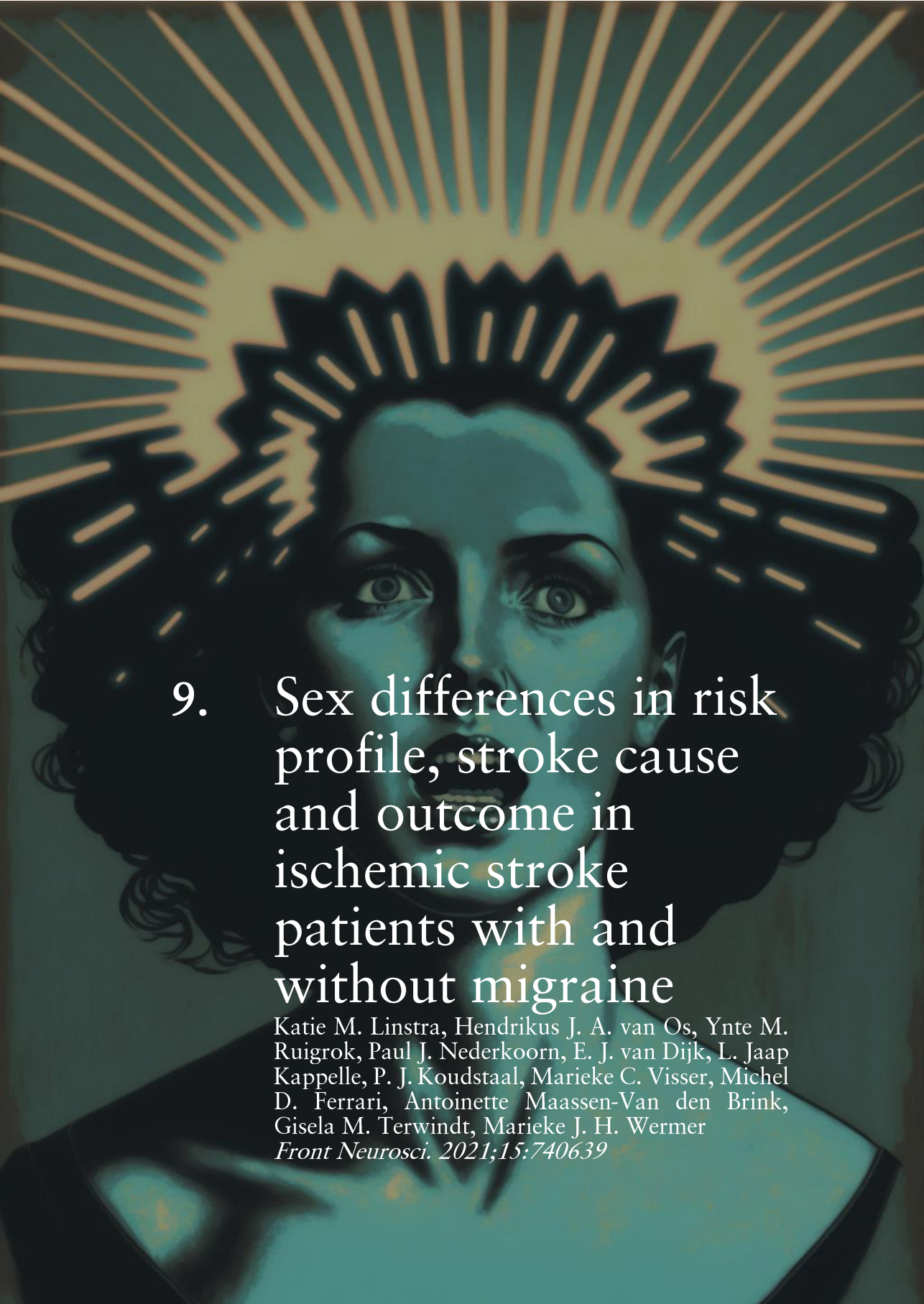

9. Sex differences in risk profile, stroke cause and outcome in ischemic stroke patients with and without migraine

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Abstract

Background and purpose: An increased risk of stroke in patients with migraine has been primarily found for women. The sex-dependent mechanisms underlying the migraine-stroke association, however, remain unknown. This study aims to explore these sex differences to improve our understanding of pathophysiological mechanisms behind the migraine-stroke association.

Methods: We included 2492 patients with ischemic stroke from the prospective multicenter Dutch Parelsnoer Institute Initiative study, 425 (17%) of whom had a history of migraine. Cardiovascular risk profile, stroke cause (TOAST classification) and outcome (modified Rankin scale [mRS] at 3 months) were compared for both sexes between patients with and without migraine.

Results: A history of migraine was not associated with sex differences in the prevalence of conventional cardiovascular risk factors. Women with migraine had an increased risk of stroke at young age (onset <50 years) compared with women without migraine (RR: 1.7; 95%CI: 1.3–2.3). Men with migraine tended to have more often stroke in the TOAST category other determined etiology (RR: 1.7; 95%CI: 1.0–2.7) in comparison with men without migraine, whereas this increase was not found in women with migraine. Stroke outcome was similar for women with or without migraine (mRS ≥3 RR 1.1; 95%CI 0.7–1.5) whereas men seemed to have a higher risk of poor outcome compared to their counterparts without migraine (mRS ≥3 RR: 1.5; 95%CI: 1.0–2.1).

Conclusion: Our results indicate possible sex differences in the pathophysiology underlying the migraine-stroke association, which are unrelated to conventional cardiovascular risk factors. Further research in larger cohorts is needed to validate these findings.

Introduction

Migraine is a prevalent brain disorder and important risk factor for cardiovascular disease (CVD), including stroke.[1] The increased risk is especially evident in women and less clear in men.[1] In addition, sex differences in ischemic stroke are increasingly acknowledged. Women more often suffer from ischemic stroke compared with men, especially after menopause, and have an increased risk of poor outcome. Although it has been recognized that cardiovascular pathophysiology is partly different between women and men, the role of sex in the migraine-stroke association remains poorly understood.[1–3] Missing gaps in the association are the role of conventional and non-conventional vascular risk factors, the relation with underlying stroke cause and the effect of migraine susceptibility on brain tissue recovery after ischemia. Until now it is unknown how sex affects these factors.

This explorative study aims to investigate differences in cardiovascular risk profiles, stroke cause and stroke outcome between men and women to improve our understanding of pathophysiological mechanisms underlying the migraine-stroke association.

Methods

We selected patients with ischemic stroke for whom information on a history of migraine was available from the prospective registry and biobank "Dutch Parelsnoer Institute Cerebrovascular Accident (PSI-CVA) Initiative" in eight university hospitals in the Netherlands.[4]The PSI-CVA registry is a large cohort of stroke patients in which comprehensive clinical data, detailed phenotyping of stroke, imaging data and biomaterials were prospectively and uniformly collected. The registry started in 2009 and ended in 2019. The Ethics Committees of all participating centers approved the PSI-CVA Initiative. Data on cardiovascular risk profile (conventional risk factors including smoking, diabetes mellitus, hyperlipidemia, previous stroke, myocardial infarction, atrial fibrillation, BMI ≥ 25 and hypertension) and stroke classification were obtained prospectively upon hospital admission. Ischemic stroke was defined according to the WHO criteria and confirmed on CT or MRI and further specified according to the trial of ORG 10172 in acute stroke treatment (TOAST) classification in the subcategories large-artery atherosclerosis, cardioembolism, small-vessel occlusion, stroke of other determined etiology and stroke of undetermined etiology.[5] The modified Rankin Scale (mRS) was used to grade stroke outcome. A poor outcome was defined as mRS at 3 months after discharge ≥ 3. Migraine history was prospectively obtained at hospital admission using a short, validated questionnaire that was specially developed to establish migraine diagnosis in patients with stroke (MISS questionnaire, see supplementary material).[6] We performed a complete case analysis with respect to

migraine status. Poisson regression analysis was performed to calculate risk ratios (RR) including 95% confidence intervals (CI) for the associations between age of stroke onset, cardiovascular risk factors, stroke subtype and outcome and migraine diagnosis, for all patients and for each sex separately. The analyses were adjusted for potential confounders.

Results

In total 6259 participants were included in the PSI-CVA database, of whom 4273 had ischemic stroke and 2492 (40% women) also information on migraine status. A lifetime history of migraine was present in 425/2492 (17% overall, 10% in men and 27% in women) of the participants. Age, sex and cardiovascular risk profile were similar between patients with or without available information about migraine status. There were no differences in cardiovascular risk factor profile in stroke patients with versus without migraine overall or between sexes (Table 1).

Women with migraine had their stroke on average seven years ($p<0.0001$) and men five years earlier than stroke patients without migraine ($p<0.0001$). Stroke onset <50 years occurred more often in women with than in women without migraine (RR: 1.7; 95%CI: 1.3–2.3, Table 1 and Figure 1). This increased risk could not be confirmed in men (RR: 1.4; 95%CI: 0.9–2.1). Men with migraine tended to have a higher risk for stroke of other determined etiology compared with men without migraine (RR: 1.7; 95%CI: 1.0–2.7), whereas no differences in this TOAST category were found in women (RR: 0.9; 95%CI: 0.6–1.4, Table 2, Figure 1). Other stroke subtypes were comparable in men and women with and without migraine although the effect estimate had an opposite direction for the category small vessel occlusion.

Outcome after stroke seemed to be comparable in women regardless of migraine diagnosis (RR: 1.1; 95%CI 0.7–1.5) whereas men tended to have a worse outcome compared to their counterparts without migraine (RR: 1.5; 95%CI: 1.0–2.1, Table 3 and Figure 1).

Table 1. Demographics, cardiovascular risk factors, medication

	All				Women				Men			
	Migraine	No migraine	RR	aRR[a]	Migraine	No migraine	RR	aRR[b]	Migraine	No migraine	RR	aRR[b]
Demographics												
Number	425 (1)	2067 (83)	-	-	264 (62)	730 (35)	-	-	161 (38)	1337 (65)	-	-
Age, years	61 ± 15	67 ± 14*	-	-	61 ± 17	68 ± 15*	-	-	61 ± 13	66 ± 14*	-	-
Age of onset < 50	93 (22)	266 (13)	1.7 (1.3–2.1)	-	65 (25)	105 (14)	1.7 (1.3–2.3)	-	28 (17)	161 (12)	1.4 (0.9–2.1)	-
Age of onset ≥ 50	332 (78)	1801 (87)	0.8 (0.8–0.9)	-	199 (75)	625 (86)	0.9 (0.7–1.0)	-	133 (83)	1176 (88)	0.9 (0.8–1.1)	-
Pre-stroke mRS	29 (7)	164 (9)	0.8 (0.5–1.2)	0.9 (0.6–1.3)	21 (8)	82 (12)	0.7 (0.4–1.1)	0.8 (0.5–1.3)	8 (5)	82 (7)	0.8 (0.4–1.5)	0.9 (0.4–1.8)
CV risk factors												
Hypertension[c]	226 (54)	1115 (54)	1.0 (0.9–1.1)	1.1 (1.0–1.3)	138 (53)	412 (57)	0.9 (0.8–1.1)	1.1 (0.9–1.3)	88 (55)	703 (53)	1.0 (0.8–1.3)	1.1 (0.9–1.4)
DM[d]	58 (14)	304 (15)	0.9 (0.7–1.2)	1.1 (0.8–1.4)	35 (13)	113 (16)	0.9 (0.6–1.2)	1.0 (0.7–1.5)	23 (14)	191 (14)	1.0 (0.6–1.5)	1.1 (0.7–1.7)
Hyperlipidemia[e]	145 (35)	752 (37)	0.9 (0.8–1.1)	1.1 (0.9–1.3)	89 (34)	240 (34)	1.0 (0.8–1.3)	1.2 (0.9–1.5)	56 (35)	512 (39)	0.9 (0.7–1.2)	1.0 (0.7–1.3)
Previous Stroke	115 (28)	515 (26)	1.1 (0.9–1.3)	1.2 (1.0–1.5)	69 (27)	169 (24)	1.1 (0.9–1.5)	1.3 (1.0–1.7)	46 (29)	346 (27)	1.1 (0.8–1.5)	1.2 (0.9–1.6)
History of MI	34 (8)	262 (13)	0.6 (0.4–0.9)	0.9 (0.6–1.3)	15 (6)	57 (8)	0.7 (0.4–1.3)	0.9 (0.5–1.6)	19 (12)	205 (16)	0.8 (0.5–1.2)	1.0 (0.6–1.5)
Atrial fibrillation	42 (10)	259 (13)	0.8 (0.6–1.1)	1.1 (0.8–1.6)	22 (9)	81 (11)	0.8 (0.5–1.2)	1.0 (0.6–1.7)	20 (13)	178 (14)	0.9 (0.6–1.5)	1.2 (0.8–2.0)
Smoking ever[f]	25 (6)	186 (9)	0.7 (0.4–1.0)	0.8 (0.5–1.2)	15 (6)	50 (7)	0.8 (0.5–1.4)	0.9 (0.5–1.7)	10 (6)	136 (10)	0.6 (0.3–1.1)	0.7 (0.3–1.3)
BMI ≥25	258 (62)	1267 (64)	1.0 (0.8–1.1)	1.1 (0.9–1.2)	147 (57)	349 (51)	1.1 (0.9–1.4)	1.1 (0.9–1.3)	111 (69)	918 (71)	1.0 (0.8–1.2)	1.0 (0.8–1.2)

*Abbreviations: mRS: modified Rankin Scale, CV: cardiovascular; DM: diabetes mellitus, MI: Myocardial infarction, BMI: body mass index (kg/m²). Data are represented as mean ± SD or number of subjects (%). *migraine vs no migraine: p<0.001. [a] Adjusted for age and sex. [b] Adjusted for age. [c] Ever or current diagnosis or treatment with antihypertensive drugs. [d] Ever or current diagnosis or treatment with antidiabetic drugs. [e] Total cholesterol >3.5 mmol/L, low-density lipoprotein cholesterol >2.5 mmol/L or treatment with lipid-lowering agents. [f] Current smokers and smokers who stopped smoking >6*

Table 2. Stroke subtype according to TOAST classification

	All				Women				Men			
	Migraine	No migraine	RR	RR[a]	Migraine	No migraine	RR	RR[b]	Migraine	No migraine	RR	RR[b]
LAA	84 (20)	530 (26)	0.8 (0.6–1.0)	0.9 (0.7–1.2)	45 (17)	147 (21)	0.8 (0.6–1.2)	0.9 (0.7–1.3)	39 (24)	383 (29)	0.8 (0.6–1.1)	0.9 (0.7–1.3)
Cardioembolism	50 (12)	296 (15)	0.8 (0.6–1.1)	0.9 (0.7–1.2)	32 (12)	102 (14)	0.7 (0.6–1.3)	1.0 (0.7–1.5)	18 (11)	194 (15)	0.8 (0.5–1.2)	0.8 (0.5–1.3)
SVO	72 (17)	373 (18)	0.9 (0.7–1.2)	0.9 (0.7–1.2)	43 (17)	158 (22)	0.8 (0.5–1.0)	0.8 (0.6–1.1)	29 (18)	215 (16)	1.1 (0.7–1.6)	1.1 (0.7–1.6)
Other determined	47 (11)	137 (7)	1.7 (1.2–2.3)	1.1 (0.8–1.6)	27 (10)	59 (8)	1.3 (0.8–2.0)	0.9 (0.6–1.4)	20 (12)	78 (6)	2.1 (1.3–3.4)	1.7 (1.0–2.7)
Undetermined	167 (40)	692 (34)	1.2 (1.0–1.4)	1.1 (0.9–1.3)	113 (43)	250 (35)	1.2 (1.0–1.6)	1.2 (0.9–1.5)	54 (34)	442 (34)	1.0 (0.8–1.3)	1.0 (0.7–1.3)

Abbreviations: TOAST: Trial of ORG 10172 in acute stroke treatment, LAA: Large-artery atherosclerosis, SVO: Small-vessel occlusion

Data are represented as mean ± SD or number of subjects (%). [a] Adjusted for age and sex. [b] Adjusted for age

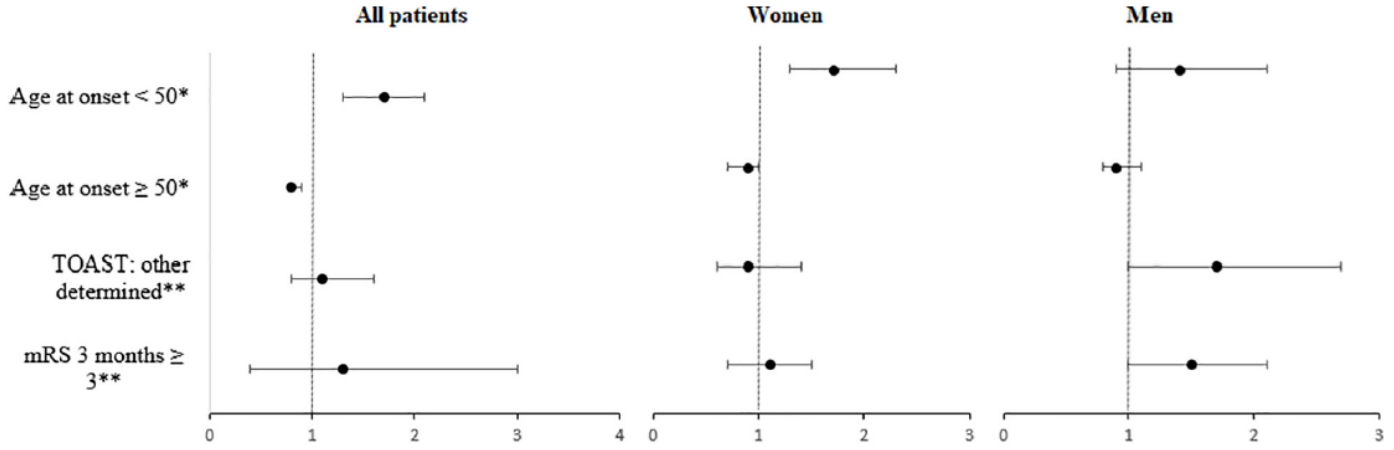
Table 3: Stroke severity and outcome

	All				Women				Men			
	Migraine	No migraine	RR	RR[a]	Migraine	No migraine	RR	RR[b]	Migraine	No Migraine	RR	RR[b]
NIHSS ≥ 7[C]	67 (17)	340 (18)	0.9 (0.7–1.2)	0.9 (0.7–1.2)	36 (15)	131 (20)	0.7 (0.5–1.1)	0.8 (0.5–1.1)	31 (21)	209 (17)	1.2 (0.8–1.1)	1.2 (0.8–1.8)
mRS discharge ≥ 3	102 (30)	238 (32)	1.0 (0.8–1.2)	1.1 (0.9–1.4)	59 (28)	184 (32)	0.9 (0.7–1.2)	1.2 (0.8–1.6)	43 (33)	307 (32)	1.1 (0.8–1.4)	1.2 (0.8–1.6)
mRS 3 months ≥ 3	73 (20)	368 (20)	1.0 (0.7–1.2)	1.3 (0.9–1.7)	41 (18)	142 (22)	0.8 (0.6–1.1)	1.1 (0.7–1.5)	32 (23)	226 (19)	1.2 (0.8–1.7)	1.5 (1.0–2.1)

Abbreviations: NIHSS: National Institute of Health Stroke Scale, mRS: modified Rankin Scale. Data are represented as mean ± SD or number of subjects (%)

[a] Adjusted for pre-stroke mRS, NIHSS at admission (for mRS at discharge and at 3 months), age and sex. [b] Adjusted for pre-stroke mRS, NIHSS at admission (for mRS at discharge and at 3 months) and age. [c] NIHSS on admission

Figure 1. Forest plot of the most important findings on associations between migraine and risk factors, etiology or outcome of stroke, stratified for Sex



*On the X-axis the odds ratio for association with migraine is displayed. *No adjustments; **Adjustments for age and sex in all patients, and adjustment for age in analyses stratified for women and men.*

Discussion

Our explorative study suggests that sex differences in stroke pathophysiology in patients with migraine cannot be explained by differences in conventional vascular risk factors. Women with migraine had a higher risk for stroke under the age of 50. Men tended to more often have stroke of other determined etiology and a worse outcome compared with men without migraine. Evidence in the literature about the relationship between conventional vascular risk factors and migraine is conflicting and rarely data of men and women are analyzed separately.[7] In general, the association between migraine and stroke is thought to be more prominent in patients without a traditional vascular risk profile and with a lower Framingham Risk Score.[7,8] Only little is known about the association between migraine and sex-specific cardiovascular risk factors. Unfortunately, our PSI-CVA database did not contain all factors needed to construct Framingham Risk score. Also, our database did not include non-conventional sex-dependent vascular risk factors such as (pre)-eclampsia, sex hormone disorders or use of hormones. Future studies are therefore needed to investigate the effect of these non-conventional risk factors. A younger age at stroke onset in patients with migraine in general has been reported previously.[1,8]

Previous studies on stroke etiology reported lower frequencies of large vessel and cardio-embolic stroke etiology in female migraine patients and more infarcts of unknown origin in migraine patients in general.[8,9]In a recent study, migraine with aura was strongly associated with cryptogenic stroke whereas such association was not found in migraine without aura.[14] The association of migraine with aura with stroke was independent of vascular risk factors or patent foramen ovale. The association was present in both women and men, although the odds ratios were higher in women. We observed an increase in stroke of other determined etiology only in men with migraine (with and without aura combined). Sex differences in migraine pathophysiology are likely multifactorial and may reflect genetic and hormonal sex differences. In addition, migraine is associated with cerebral hyperexcitability and spreading depolarization (SD), the neurophysiological correlate of migraine aura. SD is associated with neurovascular uncoupling and can also be found in the penumbra of cerebral ischemia.[10] These mechanisms may be associated with a sex-specific systemic vascular pathology in migraine patients.[7] Since the increased stroke risk in migraine patients is not associated with enhanced atherosclerosis, alternative pathology, including micro-embolisms, vasospasms in the microvasculature and endothelial dysfunction, may be involved.[7,10–13] These "non-conventional" mechanisms may explain the higher proportion of other determined causes in men with migraine. We have no good explanation why the higher risk was only found in men and not in women with migraine.

Existing literature on functional stroke outcome in patients with migraine is limited to the Women's Health Study, which only included female health care employees and reported a relatively favorable mRS at hospital discharge after ischemic stroke for women with migraine with aura.[9] In general, female sex has been associated with a less favorable stroke outcome in terms of disability and mortality[2,3]. Our study found no differences in outcome between women with and without migraine but did not investigate women with migraine aura separately. In men with migraine, our data cautiously suggested a worse outcome compared to their counterparts without migraine. As these are the first data on stroke outcome in men specifically, further research is needed to confirm these findings and investigate underlying causes.

Strengths of our study are the relatively large sample size, prospective design and the use of standardized definitions of cardiovascular risk factor and stroke characteristics. Also, we compared men and women with stroke directly with their counterparts without migraine. Migraine diagnosis was established with a validated questionnaire and migraine prevalence was as expected for this population. Our study also has limitations. Firstly, the MISS questionnaire has only moderate positive predictive value for aura symptoms. Therefore, we did not distinguish between migraine with and without aura, although the migraine-stroke connection is particularly apparent in migraine with aura. Secondly, from 4273 participants with ischemic stroke in our cohort, only 2492 had complete data on migraine. Not all PSI-CVA study centers participated in our migraine study. We consider this selection to be random and assume that it did not result in selection bias. Thirdly, we did not correct for multiple comparisons. Finally, although our study included almost 2500 stroke patients the sample size in several sub-analyses was low and, therefore, our study should be considered explorative and hypothesis-generating. To confirm our findings and to study sex differences in migraine with aura patients separately, studies with far with over ten thousands of stroke patients will be necessary (because of the relative low prevalence of migraine with aura). Future studies are also needed to study sex-specific non-conventional cardiovascular risk factors and investigate stroke causes in more detail to enable sex specific prevention of strokes in patients with migraine.

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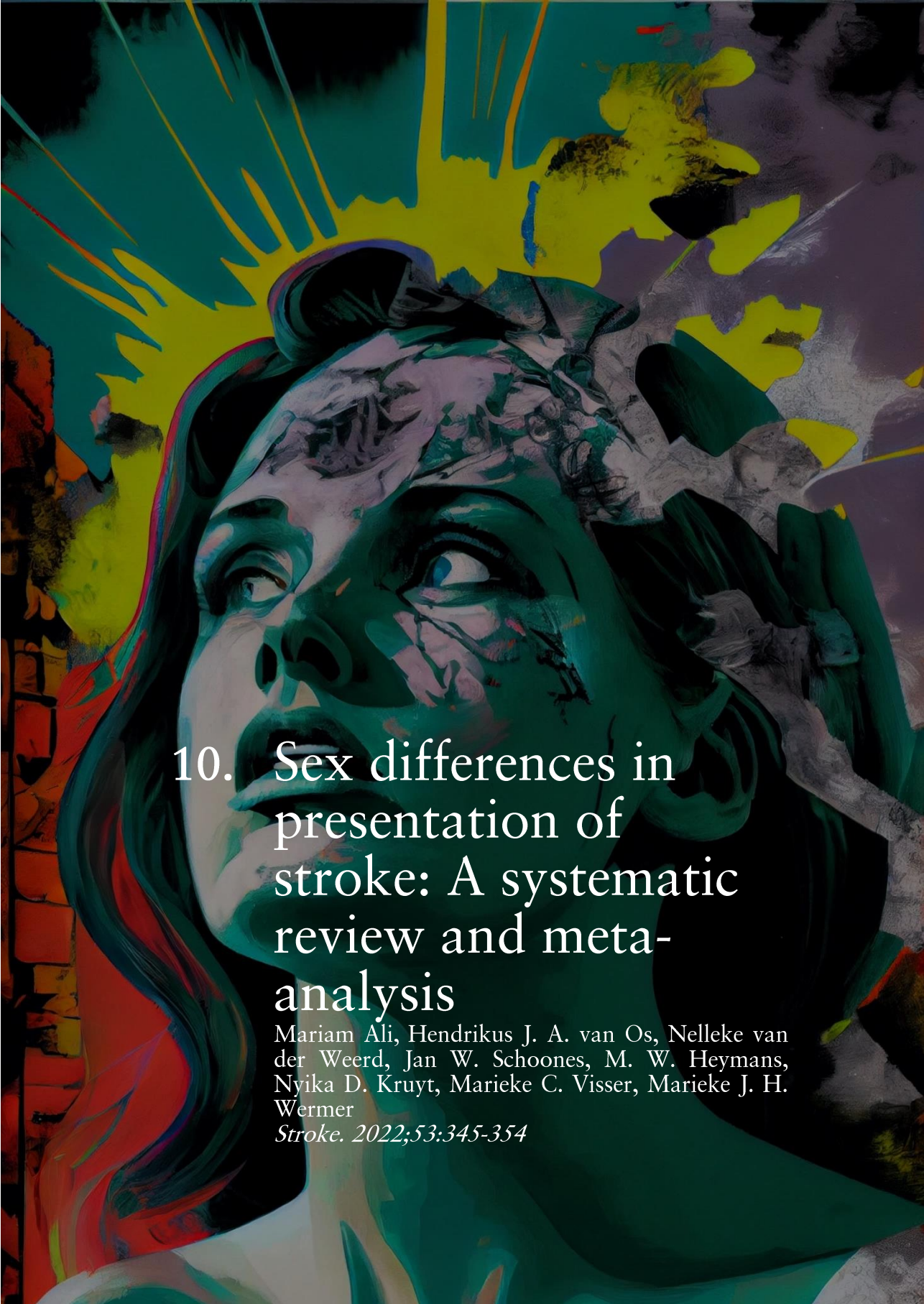

10. Sex differences in presentation of stroke: A systematic review and meta-analysis

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Abstract

Background and purpose: Women have worse outcomes than men after stroke. Differences in presentation may lead to misdiagnosis and, in part, explain these disparities. We investigated whether there are sex differences in clinical presentation of acute stroke or transient ischemic attack.

Methods: We conducted a systematic review and meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement. Inclusion criteria were (1) cohort, cross-sectional, case-control, or randomized controlled trial design; (2) admission for (suspicion of) ischemic or hemorrhagic stroke or transient ischemic attack; and (3) comparisons possible between sexes in ≥1 nonfocal or focal acute stroke symptom(s). A random-effects model was used for our analyses. We performed sensitivity and subanalyses to help explain heterogeneity and used the Newcastle-Ottawa Scale to assess bias.

Results: We included 60 studies (n=582 844; 50% women). In women, headache (pooled odds ratio [OR], 1.24 [95% CI, 1.11–1.39]; I^2=75.2%; 30 studies) occurred more frequently than in men with any type of stroke, as well as changes in consciousness/mental status (OR, 1.38 [95% CI, 1.19–1.61]; I^2=95.0%; 17 studies) and coma/stupor (OR, 1.39 [95% CI, 1.25–1.55]; I^2=27.0%; 13 studies). Aspecific or other neurological symptoms (nonrotatory dizziness and non-neurological symptoms) occurred less frequently in women (OR, 0.96 [95% CI, 0.94–0.97]; I^2=0.1%; 5 studies). Overall, the presence of focal symptoms was not associated with sex (pooled OR, 1.03) although dysarthria (OR, 1.14 [95% CI, 1.04–1.24]; I^2=48.6%; 11 studies) and vertigo (OR, 1.23 [95% CI, 1.13–1.34]; I^2=44.0%; 8 studies) occurred more frequently, whereas symptoms of paresis/hemiparesis (OR, 0.73 [95% CI, 0.54–0.97]; I^2=72.6%; 7 studies) and focal visual disturbances (OR, 0.83 [95% CI, 0.70–0.99]; 2=62.8%; 16 studies) occurred less frequently in women compared with men with any type of stroke. Most studies contained possible sources of bias.

Conclusions: There may be substantive differences in nonfocal and focal stroke symptoms between men and women presenting with acute stroke or transient ischemic attack, but sufficiently high-quality studies are lacking. More studies are needed to address this because sex differences in presentation may lead to misdiagnosis and undertreatment.

Introduction

Women with stroke have a higher mortality rate and a worse functional outcome compared with men.[1] It has been hypothesized that this is, at least in part, due to misdiagnosis with consequent delays to or even deferral of acute or secondary preventive treatment.[2,3] The higher frequency of misdiagnosis in women may in turn be explained by a higher prevalence of nonfocal or atypical stroke symptoms compared with men.[4–7] These nonfocal symptoms include confusion, impaired consciousness, headache, generalized weakness, and non-neurological symptoms such as chest pain and palpitations. Nonfocal symptoms could mistakenly be interpreted as symptoms with another pathophysiology than stroke (a so-called stroke mimic) such as a conversion disorder or a migraine attack.[8] Interestingly, a previous cohort study indicated that women who presented with a transient ischemic attack (TIA) or minor stroke more frequently received a diagnosis of stroke mimic compared with men with similar symptomatology.[3] However, stroke recurrence rates within 90 days were similar for both sexes, raising the possibility of biases or sex-specific differences in TIA/stroke diagnosis.[9,10] Several pathophysiological mechanisms could explain sex differences in acute stroke symptoms, including differences in cause of stroke or stroke subtype, presence of comorbidities, or sex aspects resulting in different subjective experiences of symptoms.[11] We systematically reviewed and meta-analyzed the literature on possible disparities between stroke symptoms in women and men to investigate whether there are sex differences in clinical acute stroke symptoms.

Methods

This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[12] Data not published within the article are available from the corresponding author on reasonable request. We systematically searched PubMed, Embase, Emcare, Web of Science, and the Cochrane Library for published articles from their inception until May 2020, to identify studies that reported comparisons between men and women in acute stroke symptomatology. The complete search strategy is provided in Supplemental Material.

Classification of Stroke or TIA Symptoms

The definition of nonfocal symptoms and focal symptoms was based on a previous classification.[13] We added lightheadedness to the classification nonfocal symptoms and unilateral numbness, discoordination/ataxia, and paresis/hemiparesis to the classification focal symptoms. Nonfocal symptoms thus included lightheadedness, mental status change/change in level of consciousness (confusion, altered mentality,

mental status change, disorientation, and drowsiness defined as Glasgow Coma Scale [GCS] score ≤14; coma/stupor/loss of consciousness/unconsciousness defined as GCS score ≤8), headache including migraine, aspecific neurological or other neurological symptoms (nonrotatory dizziness and non-neurological symptoms), and atypical symptoms including chest pain, palpitations, shortness of breath, nausea, hiccups, and generalized weakness (Table 1).

Table 1. Inclusion of Nonfocal Symptoms

Mental status change/change in level of consciousness
Confusion, altered mentality, mental status change, disorientation, and drowsy defined as GCS score ≤14
Coma, stupor, loss of consciousness, and unconscious defined as GCS score ≤8
Lightheadedness
Headache including migraine
Atypical symptoms (chest pain, palpitations, and shortness of breath, nausea, hiccups, and generalized weakness)
Aspecific neurological or other neurological symptoms (nonrotatory dizziness and non-neurological symptoms)

GCS indicates Glasgow Coma Scale

Focal symptoms included unilateral numbness, discoordination/ ataxia, paresis/hemiparesis, aphasia, dysarthria, gait disturbance, imbalance, facial weakness, vertigo with or without nausea/vomiting, diplopia, other focal visual disturbances, and pain of neurological origin (face or hemibody pain; Table 2). Rare stroke symptoms such as binocular blindness, speaking with a foreign accent, hemiballismus, and alien hand syndrome were excluded.

Table 2. Inclusion of Focal Symptoms

Dysarthria
Unilateral numbness
Diplopia
Other focal visual disturbances
Aphasia
Pain of neurological origin (face or hemibody pain)
Discoordination/ataxia
Gait disturbance
Imbalance
Paresis/hemiparesis
Facial weakness
Vertigo with or without nausea/vomiting

Selection criteria

We applied the following selection criteria for inclusion of studies: (1) patients admitted consecutively because of a diagnosis or suspicion of acute stroke including TIA; (2) use of a cohort, cross-sectional, case-control, or randomized controlled trial design; (3) diagnosis of stroke based on neurological examination and neuroimaging (either computed tomography or magnetic resonance imaging). The diagnosis of TIA had to be based on the anamnesis, neurological examination performed by an emergency medicine doctor or a neurologist (in training) in combination with normal neuroimaging. Patients with TIA had to be examined at specialized TIA centers (TIA clinic or emergency department of a stroke center). A TIA was defined as acute focal neurological symptoms lasting <24 hours. Preferably, analyses for intracerebral hemorrhage (ICH) and subarachnoid hemorrhage (SAH) were performed separately; (4) included patients were ≥18 years of age; (5) presence of ≥1 nonfocal or focal stroke symptoms is quantified in the article; (6) possible differences in stroke symptoms between women and men could be retracted; and (7) articles written in English, Dutch, German, French, Spanish, or Italian. If multiple publications originated from the same cohort, we included the study reporting on the largest number of symptoms by sex. In case similar data were presented, we included the study with the largest population. Data extraction Two reviewers (M.A. and N.v.d.W.) independently performed 2 rounds of screening: (1) title and abstract and (2) full-text versions of the remaining studies after the first selection. Data extraction forms included details on the study characteristics (publication year, country of study population, setting, study period, stroke subtype, study design,

study size, proportion women, and mean or median age). In cases of doubt, a consensus meeting was held with a third reviewer to determine whether articles met the inclusion criteria.

Assessment of Risk of Bias

The quality assessment of included studies was conducted with the Newcastle-Ottawa Scale.[14,15] For this study, we developed a customized version of the Newcastle-Ottawa Scale with adjustments for the assessment of stroke and TIA symptoms. Studies were scored low risk, high risk, or possible/unclear on the domains (1) validation of diagnosis, (2) assessment of symptoms, (3) adjustment for confounding, and (4) generalizability (Supplemental Methods).

Statistical Analysis

Statistical analyses were performed using R. We weighted the log of the odds ratios (ORs) by the inverse of their variance to obtain pooled estimates. We used a random-effects model because we expected heterogeneity to be present due to known differences in stroke patient characteristics and symptom definitions. We used the sex-specific number of symptom occurrences provided in the study, along with the total number of women or men studied to calculate ORs. We also used this information to calculate the corresponding 95% CIs and the degree of overlap in symptom presentation between men and women in percentages. In case a patient presented with multiple symptoms, we included this patient in multiple analyses relating to these symptoms. We intended to use the adjusted effect estimates. If not available, the crude effect estimates were pooled. Meta-analyses per symptom were conducted if at least 2 independent studies quantified the same symptom. The overall effect estimate and 95% CI of the forest plots per symptom were used to create summary forest plots for both nonfocal and focal symptoms. Statistical heterogeneity was assessed by the Higgin I^2 statistics.[16] We considered study-level estimates to be heterogeneous if the I^2 value was >50%. I^2 from 50% to 75% was considered as substantial heterogeneity, and I^2 >75% was indicated as considerable heterogeneity. We used funnel plots to examine potential publication bias of symptoms that were reported by at least 10 studies. Furthermore, we intended to perform subgroup analyses for stroke subtypes.

Results

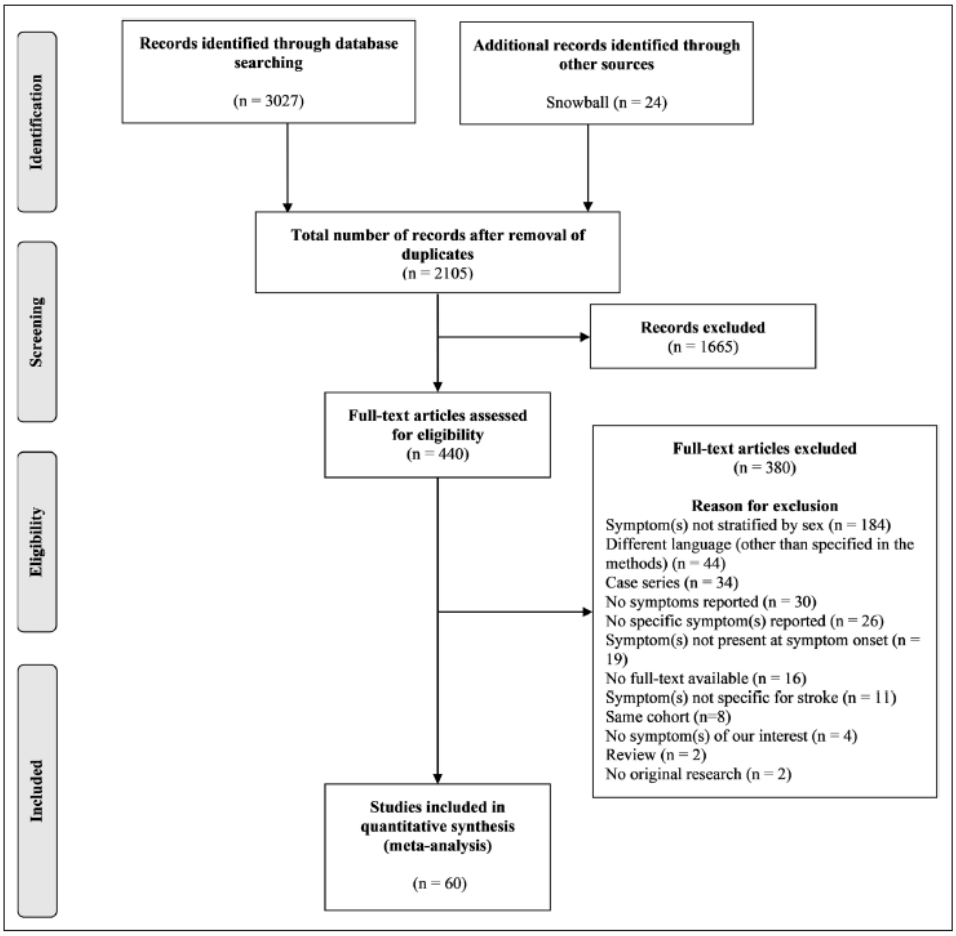
A total of 3051 publications were retrieved of which 60 studies were included (Figure 1).[3–7,13,17–70] Study characteristics are summarized in Table S1. An overview of reported symptoms in included studies is given in Table S2. The 60 studies[3–7,13,17–70] included a total of 582 844 patients (50% women). The median age was 74 years for women (interquartile range, 69–75) and 69 years for men (interquartile range, 64–70). Eighteen studies included ischemic strokes with a total of 51 824 patients (49% women),[5,7,19,22,23,27,29,30,32,40,41,49,52,54,56,62,65,68] 4 studies included TIAs with 8004 patients (50% women),[3,31,38,50] 3 studies included both ischemic strokes and TIAs with 5130 patients (45% women),[6,51,63] and 3 studies included 842 patients (46% women) with ICH without data available on possible inclusion of SAH.[20,48,53] Twenty-four[7,17,19,20,24,27,31,36,38,43,45,48,49,51,53,54,58,59,63,65,66,68,69,71] of these 60 studies (68 958 patients) reported on nonfocal symptoms. Fourteen studies[25,26,29,30,32,35,37,39–41,46,47,61,64] (18 299 patients) assessed focal symptoms. Twenty-two studies reported on both nonfocal and focal symptoms (496 187 patients).[3–6,13,18,21–23,28,33,34,42,44,50,52,55,56,60,62,67,70] Thirty-three studies (56%) were multicenter cohorts.[3–5,7,13,17,19,20,22–25,27,28,33,34,36,39,42,46,48–51,55,56,58–60,63,65,66,69] The total number of patients per study ranged from 59 to 398 798.

Risk-of-Bias Assessment of Included Studies

Most studies contained 1 or 2 sources of bias, and no study fulfilled our criteria of high methodological quality. Therefore, the outcomes of our risk-of-bias assessment were not suitable to perform a subgroup analysis with studies containing low or relatively low risk of bias.

Fifty-one studies confirmed stroke through clinical evaluation and neuroimaging and were classified as having low risk of bias.[3,5–7,13,17–23,25,27–36,39–49,52–54,56–61,63–70] Other articles assessed stroke through the International Classification of Diseases, Tenth Revision, codes (n=2)[4,50] and medical records (n=5).[24,26,38,55,62] Only 2 of the 60 studies provided both crude and age-adjusted comparisons between men and women.[36,62] In total, 31 studies included all subtypes of stroke and imposed no selection criteria for their patient population and, therefore, had a low risk of bias.[4,13,17,18,20,24,25,28,33–37,39,41–43,45–47,55,57–61,64,66,67,69,70] Moreover, 2 studies that included hemorrhagic stroke did not make a clear distinction between ICH and SAH.[48,53] The remaining studies were classified as having high risk of bias. The results of the risk-of-bias assessment and the funnel plots are presented in Table S3 and Figure S8.

Figure 1. PRISMA flowchart of inclusion of studies.

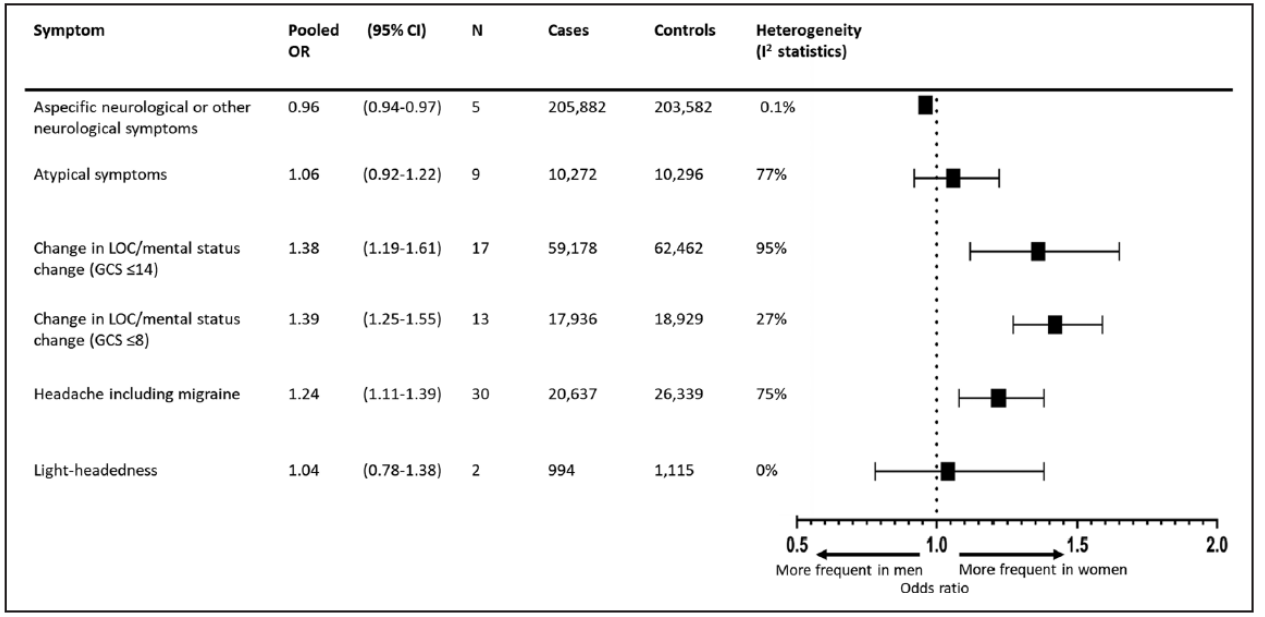


Meta-analysis for Any Type of Stroke

The overall pooled OR of occurrence of nonfocal symptoms in women versus men was 1.24 (95% CI, 1.16–1.33) with a summary incidence of 27% for men versus 31% (95% CI, 30%–33%) for women and considerable heterogeneity (I^2=91.9%). Headache including migraine (OR, 1.24 [95% CI, 1.11–1.39]; summary incidence: 16% for men versus 19% [95% CI, 17%–21%] for women; I^2=75.2%; 30 studies; 47 254 patients), minor change in level of consciousness or mental status change (GCS score, ≤14; OR, 1.38 [95% CI, 1.19–1.61]; summary incidence: 17% for men versus 22% [95% CI, 20%–25%] for women; I^2=95.0%; 17 studies; 122 465 patients), and coma or stupor (GCS score, ≤8; OR, 1.39 [95% CI, 1.25–1.55];

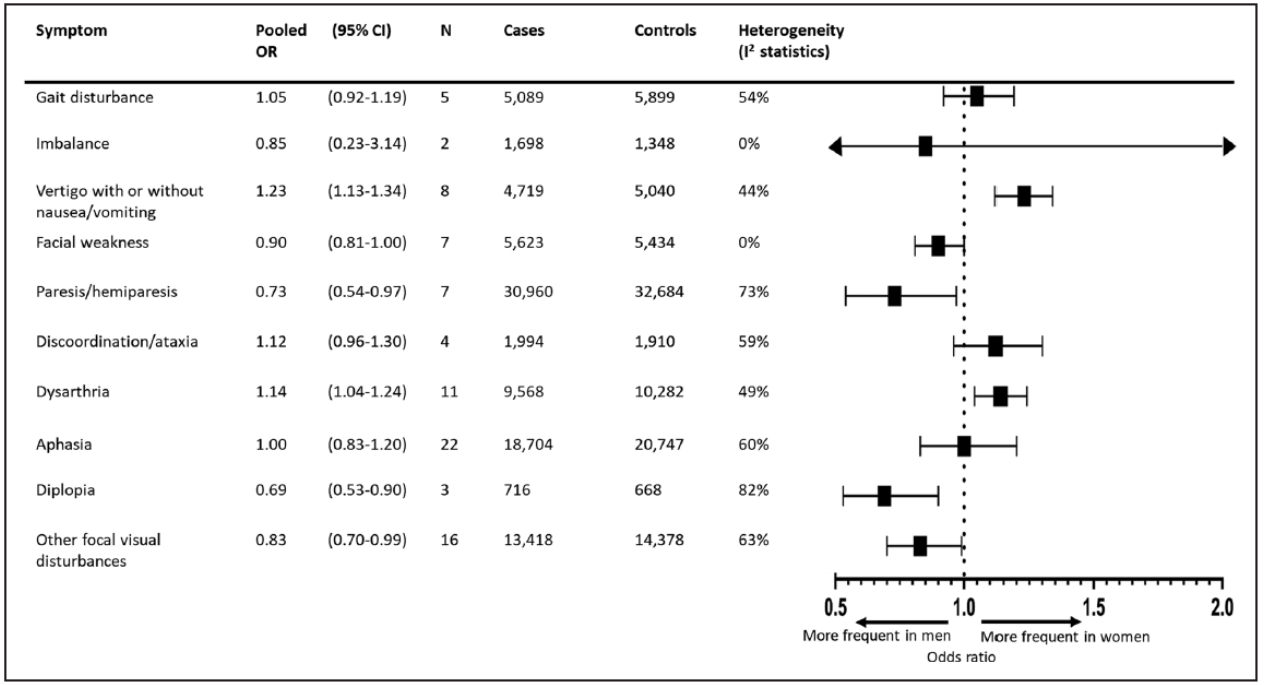
summary incidence: 6% for men versus 8% [95% CI, 7%–9%] for women; I^2=27.0%; 13 studies; 37 196 patients) occurred more frequently in women compared with men. However, aspecific neurological or other neurological symptoms occurred less frequently in women (OR, 0.96 [95% CI, 0.94–0.97]; summary incidence: 32% for men versus 31% [95% CI, 31%–31%] for women; I^2=0.1%; 5 studies; 409 464 patients; Figure 2; Figure S1). Because 1 study with risk of bias on the domain validation of diagnosis had a very large sample size (398 798 patients; 68% of the total number of patients), we chose to assess impact of this study on the association between aspecific neurological or other neurological symptoms and female sex.[55] A post hoc sensitivity analysis was, therefore, performed by excluding this study, which showed no significant differences between women and men in occurrence of aspecific neurological or other neurological symptoms (OR, 0.95 [95% CI, 0.84–1.07]; I^2=8.9%; 4 studies; 10 666 patients; Figure S2). The overall pooled estimate of all focal symptoms was not associated with sex (OR, 1.03 [95% CI, 0.97–1.09]; summary incidence: 40% for men versus 41% [95% CI, 39%–42%] for women), but there was considerable heterogeneity (I^2=78.8%). However, dysarthria (OR, 1.14 [95% CI, 1.04–1.24]; summary incidence: 37% for men versus 40% [95% CI, 38%–42%] for women; I^2=48.6%; 11 studies; 20 385 patients) and vertigo with or without nausea/vomiting (OR, 1.23 [95% CI, 1.13–1.34]; summary incidence: 19% for men versus 22% [95% CI, 21%–24%] for women; I^2=44.0%; 8 studies; 9759 patients) occurred significantly more frequently in women. In contrast, the focal symptoms paresis/hemiparesis (OR, 0.73 [95% CI, 0.54–0.97]; summary incidence: 73% for men versus 66% [95% CI, 59%–72%] for women; I^2=72.6%; 7 studies; 63 605 patients), diplopia (OR, 0.69 [95% CI, 0.53–0.90]; summary incidence: 5% for men versus 4% [95% CI, 3%–5%] for women; I^2=81.8%; 3 studies; 1384 patients), and other focal visual disturbances (OR, 0.83 [95% CI, 0.70–0.99]; summary incidence: 16% for men versus 14% [95% CI, 12%–16%] for women; I^2=62.8%; 16 studies; 27 796 patients) occurred significantly less frequently in women compared with men (Figure 3; Figure S3).

Figure 2. Summary forest plot for nonfocal symptoms in patients with any type of stroke.



Cases: total number of women; controls: total number of men. GCS indicates Glasgow Coma Scale; LOC, level of consciousness; and OR, odds ratio.

Figure 3. Summary forest plot for focal symptoms in patients with any type of stroke.



Cases: total number of women; controls: total number of men. OR indicates odds ratio.

Ischemic Stroke (Non-TIA)

For a subgroup analysis for sex differences in ischemic stroke, we included 18 studies with ischemic stroke only[5,7,19,22,23,27,29,30,32,40,41,49,52,54,56,62,65,68] and 3 studies that provided separate analyses for ischemic and hemorrhagic stroke.[17,39,44] In total, 53 226 ischemic stroke patients were included. Most of the effect estimates (including headache with or without migraine) failed to reach significance. However, the association between female sex and change in level of consciousness/mental status change (GCS score ≤8: OR, 1.50 [95% CI, 1.20–1.88]; I^2=34.1%; n=4 studies and GCS score ≤14: OR, 1.38 [95% CI, 1.27–1.50]; I^2=29.3%; n=4 studies) remained statistically significant. The results of the subgroup analysis are provided in Figure S4 (nonfocal symptoms) and Figure S5 (focal symptoms). Heterogeneity of the overall pooled analysis in the ischemic stroke subgroup decreased from 93.6% to 85.0% for nonfocal and from 87.9% to 79.0% for focal symptoms.

Transient Ischemic Attack

In patients with TIA, we were only able to conduct a subgroup meta-analysis for headache. Headache was reported by all the studies that reported exclusively on a TIA population.[3,31,38,50] The OR of headache occurrence in women compared with men was 1.42 ([95% CI, 1.27–1.58] I^2=0.0%; 4 studies; 8004 patients; Figure S6).

Subgroup Analysis for ICH or SAH

Due to the limited number of studies available on ICH, subgroup analysis for ICH was only possible for the symptom headache. Headache occurrence by ICH was reported by 5 studies[17,20,44,48,53] with 1096 patients in total. SAH was reported to be excluded in 2 studies[17,20] and included in another study.44 It was not clear whether the remaining 2 studies[48,53] analyzed SAH as a separate entity and not in combination with ICH. The subgroup analysis showed no statistical differences in headache occurrence by women and men (OR, 1.27 [95% CI, 0.80–2.02]; I^2=67.6%; n=5 studies; Figure S7). No studies were available that reported exclusively on SAH.

Discussion

In our systematic review and meta-analysis, the occurrence of nonfocal symptoms in women with stroke was higher than in men. More frequently occurring nonfocal symptoms were changes in level of consciousness/mental status and headache including migraine. In addition, significant sex differences were found for certain focal symptoms. Dysarthria and vertigo with or without nausea/vomiting were more common in women, whereas paresis/hemiparesis, diplopia, and other focal visual

disturbances were more common in men. Significant heterogeneity, however, limits the reliability of these results. The subgroup analysis of patients with ischemic stroke resulted in low-to-moderate heterogeneity in several subgroups of symptoms and showed that most of the effect estimates were no longer statistically significant compared with the main analysis possibly because of loss of power. Although the association between headache and female sex disappeared, the association with change in level of consciousness was still apparent. Four previously published reviews on stroke in women and sex differences in the evaluation and treatment of acute ischemic stroke also concluded that a higher proportion of women presented with nonfocal symptoms. In these studies, however, no formal meta-analyses were performed.[2,11,72,73]

Several individual studies have reported comparable incidences of nonfocal symptoms in men and women.[3,42,50,61] Discrepancies between these individual studies and the reviews and our meta-analysis may be explained by the limited number of patients and various sources of potential bias in the individual studies. In contrast to the subgroup analysis of our meta-analysis, a recently published review based on 11 studies on stroke-related headache reported a higher incidence of headache during or after ischemic stroke in women (OR, 1.25 [95% CI, 1.07–1.46]).[74] Differences in inclusion criteria most likely explain the difference with our results. In our subgroup analysis, we excluded studies that combined TIA and ischemic stroke and studies that did not enroll participants consecutively. In addition, because of our extensive literature search covering 5 databases and cross-reference check of included articles and relevant reviews, we were able to include 4 studies that were not identified by the previous systematic review.[5,22,44,62]

To interpret our results, several methodological challenges must be considered. First, significant heterogeneity hampered interpretation of the pooled effect estimates. The heterogeneity may be explained by characteristics that vary between studies, such as inclusion of heterogeneous study populations in terms of patient and stroke characteristics, study designs and data collection methods, definition of stroke end points, presence of several sources of bias, and differences in adjustment for confounders. In our subgroup analysis for ischemic stroke, the heterogeneity of pooled effect estimates was indeed substantially reduced for several symptoms, indicating that stroke subtype was an important contributor to heterogeneity. Second, adjustment for confounding factors was performed in a minority of the included studies. Only 2 studies adjusted for age, and after adjustment, several symptoms did not significantly differ from men.[36,62] We, therefore, were only able to pool the unadjusted effect estimates. However, median age difference between women and men was on average limited (±5 years). In addition, our version of the Newcastle-Ottawa Scale was not validated. Third, the majority of the studies

contained at least 2 sources of bias, and no study fulfilled our criteria of high methodological quality. Fourth, although we included 60 studies for this meta-analysis, for several symptoms not enough studies were available to draw robust conclusions. Fifth, examination of patients with stroke varied considerably among studies. From the studies that reported the timing of symptom assessment, 5 studies examined stroke patients admitted within 72 hours after the onset of stroke symptoms,[3,7,21,52,63] 3 other studies within 7 days after onset,[39,56,71] and 1 study retrieved information on clinical presentation within 14 days from onset.[22] The timing was unknown in the remaining studies. Sixth, some of the studies reported symptoms combined or defined symptom categories that could not be grouped in our symptom classification system. Thus, misclassification of several symptoms might have occurred since several symptom categories that were derived from the studies contained considerable overlap in definition. Seventh, asymmetry was observed in the funnel plot for studies reporting on aphasia, minor change in level of consciousness/mental status change, and coma or stupor possibly indicating publication bias. Furthermore, recall bias regarding presenting symptoms may have resulted in underestimation of the symptom occurrences. Moreover, selection bias attributable to the use of stroke-specific inclusion criteria may have influenced the external validity of the results. In addition, our meta-analysis is subject to within-study reporting bias: studies meeting selection criteria are more likely to contain significant results, as opposed to excluded or (non)published studies that could have reported appropriate, nonsignificant data. This may also explain a substantial proportion of the observed heterogeneity. Eight, we were unable to make a distinction between ICH and SAH in our analyses. From our included studies, 24 studies included a study population with ischemic stroke or TIA only and 7 studies included all stroke subtypes except SAH. None of our studies reported exclusively on SAH. However, SAH is a relatively small contributor to overall stroke (around 5%).[75] We, therefore, expect the influence of SAH in overall stroke or hemorrhagic stroke specifically to be small and consider it unlikely that the inclusion of SAH has importantly influenced our conclusion. It is remarkable that no studies on sex differences in clinical presentation of SAH exist. Given the importance of knowledge about sex differences in hemorrhagic stroke subtypes for daily clinical care, we recommend this should be further investigated in future studies.

The strengths of our systematic review and meta-analysis include the large number of included studies using all known contemporary data from almost 600 000 patients, the subgroup analysis by stroke type to assess impact on effect estimates and heterogeneity, and the evaluation of a wide variety of nonfocal and focal symptoms. We have performed a sensitivity analysis, performed subgroup analyses by stroke type, and produced a table describing the risk of bias of the included studies to help explain heterogeneity and give the reader information to interpret

the results given the limitations. Because of the substantial amount of limitations, our findings should be interpretated cautiously. Several hypotheses exist for mechanisms underlying possible sex differences in stroke symptomatology. First, cardioembolic stroke and SAH occur more frequently in women.[61,76] Second, sex differences in neurobiology should be considered. Women may, for example, be more sensitive to peri-infarction depolarizations that may lead to headache.[77] Third, women tend to be older at stroke onset and have more comorbidities.[78] The increased prevalence of dementia, psychosocial stressors, and depression among women could impact stroke presentation.[11] Fourth, one study reported that women are more likely to be diagnosed with a stroke mimic such as migraine, seizure, or other psychiatric disorders, which could point toward caregivers' biases toward patients' sex.[3] In addition, there are sex aspects on perceiving and acting on stroke symptoms; while women generally have a better knowledge of stroke symptoms, men are more likely to call an ambulance for themselves.[79]

Until more high-quality prospective cohort studies become available, we feel it is important that physicians are at least aware of the possible sex differences in presentation of stroke, especially for nonfocal symptoms such as headache and mental status changes. This awareness might be particularly important in women with acute onset of nonfocal symptoms without obvious focal symptoms of stroke.

Conclusion

We found that women have a significant higher odds of presenting with nonfocal symptoms during acute stroke compared with men. Furthermore, significant sex differences were observed regarding focal stroke symptomatology. However, given the heterogeneity and poor methodological quality of our included studies, our findings should be considered as hypothesis generating. Additional research is required for more conclusive results. Future prospective cohort studies should be specifically designed to assess sex differences; should take confounding factors into account and adjust for at least age, stroke subtype, and comorbidity; and should report presenting nonfocal and focal symptoms by stroke subtype, timing, and location. Finally, studies need to assess the association between presenting symptoms and clinical diagnosis and should compare the symptoms of women and men with and without confirmed stroke to improve the diagnosis of stroke in clinical practice.

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11. Role of atherosclerosis, clot extent, and penumbra volume in headache during ischemic stroke

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Abstract

Background and purpose: To investigate the role of large vessel atherosclerosis, blood clot extent, and penumbra volume in relation to headache in ischemic stroke patients

Methods: In this cross-sectional study, we performed non-contrast CT, CT-angiography (CTA), and CT-perfusion (CTP) in 284 participants from the Dutch acute stroke study and Leiden Stroke Cohort within 9 hours after ischemic stroke onset. We collected headache characteristics prospectively using a semi-structured questionnaire. Atherosclerosis was assessed by evaluating presence of plaques in extra- and intracranial vessels and by quantifying intracranial carotid artery calcifications. Clot extent was estimated by the clot burden score on CTA and penumbra volume by CTP. We calculated risk ratios with adjustments (aRR) for possible confounders using multivariable Poisson regression.

Results: Headache during stroke was reported in 109/284 (38%) participants. Participants with atherosclerosis in the extracranial anterior circulation less often had headache than those without (35% versus 47%; RR:0.72;95%CI:0.54–0.97). Atherosclerosis in the extracranial posterior circulation and in the intracranial arteries was also associated with less headache, but these associations were not statistically significant. Penumbra volume (aRR:1.08; 95%CI:0.63-1.85) and clot extent (aRR:1.02; 95%CI:0.86-1.20) were not related with headache.

Conclusions: Headache in the early phase of ischemic stroke tends to occur less often in patients with atherosclerosis than in patients without atherosclerosis in the large cerebral arteries. This finding lends support to the hypothesis that vessel wall elasticity is a necessary contributing factor in the occurrence of headache during acute ischemic stroke.

Introduction

Acute ischemic stroke is frequently associated with concomitant headache but the underlying mechanisms are largely unknown.[1-5] Several hypotheses have been put forward, including a crucial role for blood vessel wall elasticity because ischemic stroke-associated headache is less common in older patients and in patients with hypertension.[1, 3, 5-7] Direct pressure on the vessel wall, e.g. by a large blood clot, is another possible mechanism as headache is a common feature during balloon inflation and wire manipulation in neurointerventional procedures.[8, 9] Several studies have shown that headache during acute ischemic stroke is more common in patients with ischemia in the posterior circulation or with a history of migraine, which possibly might be attributed to increased susceptibility to spreading depolarizations (SDs).[5, 7] SDs are slowly spreading waves of intense neuroglial depolarizations associated with profound changes in cerebral blood flow.[10] They are the likely underlying mechanism for migraine aura and a putative trigger for migraine headache by stimulating sensory afferents of the trigeminovascular system.[11, 12] SDs may also occur in the penumbra of large middle cerebral artery infarctions[13] and may thus potentially activate headache-generating mechanisms.[4, 13, 14]

In the present study we performed non-contrast CT (NCCT), CT-angiography (CTA) and CT-perfusion (CTP) to assess the association of atherosclerosis of large cerebral arteries, clot extent and penumbra volume with headache concomitant to acute ischemic stroke in a large cohort of well characterized stroke patients.[15] We tested the following three hypotheses: (i) if stiffness of cerebral arteries would protect against headache, then ischemic stroke-associated headache would be expected to be less common in patients with atherosclerosis than in patients without; (ii) if vasodilatation of large vessels is important, then patients with high clot extent are expected to more frequently have headache associated with ischemic stroke than patients with low clot extent; and (iii) if SDs are involved, patients with large cortical penumbras are expected to experience more often headache than patients with small penumbra volumes.

Methods

Patients

We included patients from the Dutch acute stroke study (DUST), a large prospective multicenter cohort study performed between May 2009 and August 2013.[15-18] The aim of DUST was to investigate the value of CT-angiography (CTA) and CT-perfusion (CTP) for predicting outcome after ischemic stroke. Inclusion criteria for the study were: age ≥18 years, onset of stroke symptoms <9 hours and NIHSS ≥2 or

≥1 if intravenous thrombolysis with rtPA was indicated. Exclusion criteria were known renal failure and contrast agent allergy.[15] For the current study, patients from 5 of the 14 participating DUST centers (Leiden University Medical Center (LUMC), University Medical Center Utrecht, Medical Center Haaglanden, VU University Medical Center and the St. Antonius Hospital Nieuwegein) were asked to answer questions from a headache questionnaire upon admission. The inclusion period was from May 2012 until August 2013. In the LUMC, patients from the Leiden Stroke Cohort who underwent non-contrast CT (NCCT), CTP and CTA according to the DUST protocol but who could not be included in DUST because they already participated in another study were also approached for participation in the headache study. In LUMC, inclusion for the headache study also continued after conclusion of DUST from August 2013 until March 2014. All patients were prospectively included with the same imaging protocol and questionnaires. All patients underwent NCCT, CTA and CTP on admission with standardized scan protocols between centers. Scan parameters of the NCCT were: 120 kVp, 300 mAs and 1 mm reconstructed slice thickness. For CTA 60–80 ml of contrast agent (300 mg I/ml) was injected into the antecubital vein (18-gauge needle) at a rate of 6 mL/s followed by a 40-mL saline flush at a rate of 6 mL/s. The scan parameters for the CTA were: 120 kVp, 150 mAs and 1 mm reconstructed slice thickness. Radiologic parameters were assessed by trained neuroradiologists with good inter observer variability.[15]

Standard protocol approvals, registrations, and patient consents

DUST was approved by the Medical Ethical Committee of the participating hospitals. In addition, the Medical Ethical Committee of LUMC approved the headache research protocol. Informed consent was obtained from all patents for use of the data.

Patient characteristics

We assessed the following clinical baseline characteristics during admission: demographic features, cardiovascular risk factors, a history of cardiovascular disease or migraine, baseline National Institutes of Health Stroke Scale (NIHSS) and blood pressure on admission. NIHSS ≥7 was used to distinct between mild and moderate/ severe stroke. Stroke-to-imaging time was recorded and measured in minutes. Clinical outcome was prospectively assessed by telephone with the modified Rankin Score (mRS) at 3-month follow up. Good outcome was defined as mRS ≤ 2.

Headache questionnaire

Headache characteristics were collected during admission by research nurses with a semi-structured questionnaire. The questionnaire contained the following questions:1. Did you have headache during or shortly after the ischemic stroke? 2. At what time exactly did the headache appear? 3. Did you have this type of headache before? 4. What kind of headache did you experience during the ischemic stroke? 5. What was the location of the headache? 6. How long did the headache last? 7. Were there any concomitant symptoms? Patients who answered 'I don't remember' at question 1 were excluded from the study. The time between hospital admission and filling in of the questionnaire was registered.

Radiological parameters

We identified patients with any sign of atherosclerosis in extracranial and intracranial vessel segments of the anterior and posterior circulation on CTA. Extracranial vessel segments were divided into anterior (common and internal carotid arteries) and posterior circulation (vertebral arteries). Signs of atherosclerosis were defined as non-calcified, calcified or mixed plaque. We measured intracranial atherosclerotic burden by assessing intracranial internal carotid artery (ICA) calcification volume, using calcium as a measure for atherosclerosis since these two parameters are highly correlated.[19] Intracranial ICA calcification was quantified by measuring calcium volumes from the petrous part to the top of the intracranial carotid arteries on NCCT using dedicated software (customized research version of CalcScore V11.1 by Medis Specials bv, The Netherlands). After setting a threshold, regions of interest were drawn to discern intracranial ICA calcifications from the skull base. A small pilot study was performed to find an optimal threshold for visually discerning ICA calcifications from the skull base on NCCT. Since DUST was a multicenter study with CT data from different vendors, we tested several thresholds on 10 randomly selected data sets per center. We found the optimal threshold to be 160 Hounsfield units, which resulted in a spread of ICA calcification volume data that did not notably vary between centers. Continuous intracranial ICA calcification volume data were subsequently divided into tertiles (small, medium and large ICA calcification volume). The presence of a clot was assessed in both the anterior and posterior circulation. In addition, for the anterior circulation the clot burden score (CBS) was assessed on CTA. The CBS is a scoring system to evaluate the extent of thrombus in the anterior circulation by location and scored on a scale 0-10. A score of 10 is normal, implying clot absence; a score of 0 implies complete multi-segment vessel occlusion. Two points should be subtracted if thrombus is found in the supraclinoid ICA, proximal and distal M1 segment. One point should be subtracted if thrombus is found in the infraclinoid ICA, ACA or for each of the M2 branches.[20] For the

patients with an anterior circulation stroke confirmed on CTA the CBS was subdivided into tertiles of clot extent. Patients with visible clots on CTA in a M3 branch of the middle cerebral artery were not included in the analysis because the CBS does not include M3 branches. Also, patients with a thrombus in the posterior circulation were not included because the CBS can only be applied in the anterior circulation. We assessed penumbra volume in the anterior circulation by first defining the total ischemic area as a relative measure of mean transit time (MTT) ≥145% compared with the contralateral (unaffected) hemisphere. Within the ischemic area, the infarct core is separated from the penumbra by an absolute threshold value of cerebral blood volume (CBV) < 2.0 ml/100 g. Penumbra volume, measured in mm^3, was divided into tertiles for analysis.[21]

In addition to our three main radiologic parameters of interest we evaluated the following other CT parameters that might be related to headache at stroke onset. On NCCT: presence of a hyperdense vessel sign, early CT signs of ischemia and the size of initial lesions in the anterior circulation measured by ASPECTS (Alberta Stroke Program Early CT Score). ASPECTS is a 10-point quantitative topographic score representing early ischemic change in the middle cerebral artery territory, with a normal scan receiving an ASPECTS of 10 points.[22, 23] For ASPECTS, both cortical and subcortical components were taken into account. ASPECTS scores were dichotomised at the median. On CTA source images (CTA-SI) we also assessed extent of ischemia using the ASPECTS, as well as presence and location of vascular occlusion. On CTP (CBV, MTT) we assessed the location and the volume of the infarct core and the penumbra.

Statistical analysis

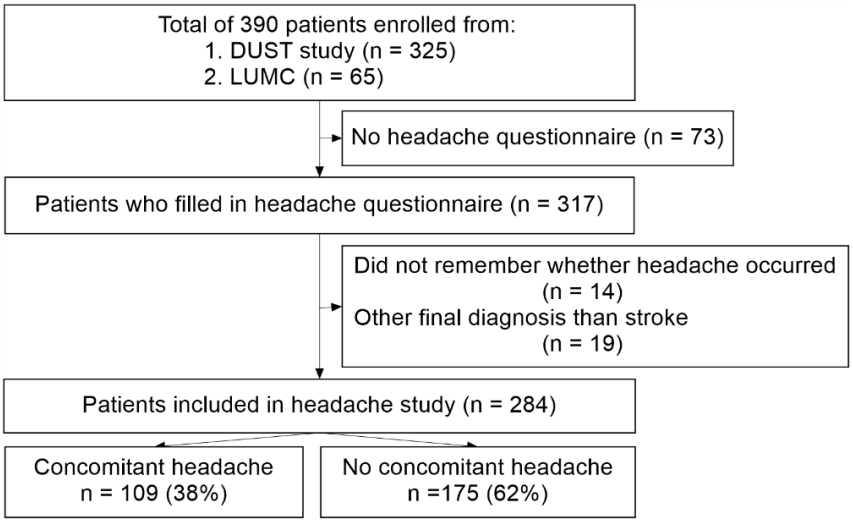
We performed univariable Poisson regression analyses to identify clinical and radiological parameters associated with headache at stroke presentation. Adjustments were made for possible confounders in multivariable Poisson regression analysis. For cerebral vessel atherosclerosis no adjustments were made for age and sex or other cardiovascular risk factors since these factors were considered to be intermediates in the causal pathway of the disease. For the clot burden score adjustments were made for age, sex and stroke-to-imaging time. For all other radiological characteristics except clot localisation on CTA, adjustments were made for stroke-to-imaging time. Risk ratios (RR) and adjusted RR (aRR) with 95% confidence intervals (CI) were calculated.

Results

Patients

In total 284 patients were included in this study (Figure 1). Of these patients, 109 (38%) experienced concomitant headache during the early phase of ischemic stroke. Mean age of all patients was 68 ± 13 (SD), median NIHSS was 4 and median stroke-to-imaging time was 131 minutes. Mean age, median NIHSS and median stroke-to-imaging time did not differ between patients with and patients without headache. The baseline characteristics are shown in Table 1. Headache was more common in patients without a history of hypertension and in patients with a history of migraine. Clinical follow up data were available of 273 patients. There were no differences in baseline characteristics in the patients with and without follow-up. Overall 71% of the patients had a good outcome (mRS ≤ 2).

Figure 1. Flowchart of patients



Radiological parameters

Table 3 shows headache prevalence in patients in presence or in absence of a specific radiological characteristic. Headache was less prevalent in patients with than in patients without atherosclerosis in the extracranial anterior circulation (35% versus 47%; RR: 0.72; 95% CI: 0.54–0.97). We found no relation between the presence of headache during the early phase of stroke and clinical outcome at three months follow up. Headache characteristics are shown in Table 2. In almost one third of the patients, headache preceded stroke onset.

The effect estimates of presence of extracranial atherosclerosis in the posterior circulation, presence of intracranial atherosclerosis and highest versus lowest tertile intracranial ICA calcification volume were all in the same direction with less headache prevalence, though these findings were not statistically significant. There was no difference in headache prevalence in patients with and patients without an observed clot (40% versus 39%; aRR: 1.00; 95% CI: 0.73–1.37). Clot burden score was assessed in the 82 patients (29%) with anterior circulation stroke confirmed on CTA. Headache prevalence in patients with large clot extent was not different from those with small clot extent (aRR: 1.02 for highest versus lowest tertile; 95% CI: 0.86–1.20).

Penumbra volume data were available for 110 patients. There was no difference in headache prevalence in patients with or without a perfusion defect (aRR: 0.98; 95% CI: 0.72–1.35). In addition, headache presence did not vary according to penumbra volume (RR: 1.08 for tertile with largest volume versus tertile with lowest volume; 95% CI 0.63–1.85). On NCCT, other radiological characteristics did not show any significant relation with headache at stroke onset, nor did infarct core volume on CTP. As assessed with CTA headache was more prevalent in patients with infarctions in the posterior circulation than in the anterior circulation (RR 1.78; 95% CI: 1.15–2.76).

Table 1. Baseline characteristics of the 284 participants according to presence or absence of concomitant headache

Clinical characteristics	% headache with characteristic: Present	Absent
Demographics		
Age under 50, n (%)*	15 (44%)	94 (38%)
Women, n (%)	49 (37%)	60 (39%)
History, n (%)		
Previous stroke or TIA	24 (40%)	83 (38%)
Hypertension	41 (29%)	67 (49%)
Diabetes mellitus	13 (34%)	95 (39%)
Hyperlipidemia	35 (37%)	71 (39%)
Myocardial infarction	11 (38%)	96 (39%)
Atrial fibrillation	15 (42%)	93 (38%)
Peripheral artery disease	4 (50%)	104 (38%)
Migraine	34 (51%)	74 (34%)
Smoking	72 (41%)	36 (36%)
Alcohol use	66 (45%)	34 (34%)
Bloodpressure on admission, n (%)		
Systolic BP > 160 mm Hg (±SD)	41 (37%)	67 (41%)
Diastolic BP > 90 mm Hg (±SD)	33 (34%)	75 (42%)
NIHSS ≥ 7 on admission, n (%)**	32 (36%)	73 (40%)
mRS ≤ 2 at 3-month follow up	70 (36%)	35 (44%)

**Dichotomization of age under 50 is used as a measure for young stroke*

***National Institutes of Health Stroke Scale, dichotomized at <7 and≥ 7*

Table 2. Headache characteristics of the 109 patients with headache based on semi-structured questionnaire

Question	n (%)	Question	n (%)
Headache onset		Nature of headache	
Before symptoms	34 (31%)	Pressure/ sore	72 (66%)
Simultaneous with symptoms	12 (11%)	Throbbing/ lancinating	18 (17%)
Seconds after symptoms	1 (1%)	Other	10 (9%)
Minutes after symptoms	11 (10%)	Unknown	9 (8%)
Hours after symptoms	37 (34%)	Headache duration	
Unknown	14 (13%)	Seconds	2 (2%)
Familiar with headache		Minutes	6 (5%)
This type	35 (32%)	Hours	29 (26%)
Other type	20 (18%)	Days	22 (20%)
None	49 (45%)	Still present*	44 (40%)
Unknown	5 (4%)	Unknown	6 (6%)
Headache location		Concomitant symptoms**	
Left side of head	9 (8%)	Photophobia	14 (13%)
Right side of head	17 (16%)	Phonophobia	9 (8%)
Occipital	10 (9%)	Nausea	19 (17%)
Anterior	23 (21%)	Vomiting	17 (16%)
Diffuse (entire head)	14 (13%)	Dizziness	25 (23%)
Like a band around head	12 (11%)	None	40 (37%)
Unknown	24 (22%)		

**'Still present' is defined as time difference in headache onset and time of collection of questionnaire, which is 2.5 days on average.*

***Patients can experience multiple symptoms, explaining the total percentage of over 100%*

Table 3. Radiological characteristics of the 284 participants according to presence or absence of concomitant headache

Radiological characteristics	% headache with characteristic: Present	Absent	RR (95%CI)	aRR (95%CI)
Main characteristics of interest				
Presence of extracranial atherosclerosis	72/204 (35%)	35/74 (47%)	0.75 (0.55–1.01)	x°
Anterior circulation	69/198 (35%)	39/81 (48%)	0.72 (0.54–0.97)	x°
Posterior circulation	39/101 (39%)	67/172 (39%)	0.99 (0.73–1.35)	x°
Presence of intracranial atherosclerosis	77/216 (36%)	30/62 (48%)	0.74 (0.54–1.01)	x°
ICAC volume (tertiles)				x°
T2 (medium ICA calcification volume)	34/84 (41%)	39/88 (44%)*	0.91 (0.64–1.30)	x°
T3 (high ICA calcification volume)	31/88 (35%)	39/88 (44%)*	0.80 (0.55–1.15)	x°
Clot burden score: presence of clot	43/108 (40%)	65/169 (39%)	1.04 (0.77–1.40)	1.00 (0.73–1.37)†
Clot burden score: clot extent (tertiles)				
T2 (medium clot extent)	9/25 (36%)	9/25 (36%)**	1.00 (0.85–1.18)	1.02 (0.87–1.20)†
T3 (large clot extent)	8/23 (35%)	9/25 (36%)**	1.01 (0.86–1.19)	1.02 (0.86–1.20)†
Presence of perfusion defect	55/142 (39%)	48/125 (38%)	1.01 (0.75–1.37)	0.98 (0.72–1.35)‡
Penumbra volume (tertiles)				
T2 (medium penumbra volume)	14/38 (37%)	15/36 (42%)***	0.88 (0.50–1.56)	0.87 (0.50–1.53)‡
T3 (large penumbra volume)	16/36 (44%)	15/36 (42%)***	1.07 (0.63–1.82)	1.08 (0.63–1.85)‡
Other characteristics				
Non-contrast CT				
Hyperdense vessel sign	16/40 (40%)	92/241 (38%)	1.05 (0.69–1.58)	1.08 (0.71–1.64)‡
Early CT sign	23/60 (38%)	69/177 (39%)	0.98 (0.68–1.42)	1.01 (0.69–1.48)‡
ASPECTS score < 9	13/25 (52%)	18/51 (35%)	1.47 (0.87–2.50)	1.32 (0.75–2.31)‡
CT angiography				
Detection ischemia (CTA-SI)	34/80 (43%)	74/198 (37%)	1.14 (0.83–1.55)	1.11 (0.80–1.55)‡
ASPECTS < 8	13/34 (38%)	22/55 (40%)	0.96 (0.56–1.63)	0.95 (0.56–1.61)‡
Posterior circulation localization	15/25 (60%)	28/83 (34%)	1.78 (1.15–2.76)	x°
Infarct core volume (tertiles)				
T2 (medium volume)	15/37 (41%)	14/36 (39%)*4	1.04 (0.59–1.85)	1.02 (0.58–1.79)‡
T3 (high volume)	16/37 (43%)	14/36 (39%)*4	1.14 (0.64–2.02)	1.09 (0.63–1.88)‡

ICA: internal carotid artery. ASPECTS: Alberta Stroke Progam Early CT Score. CTA-SI: CT angiography, source images

†Adjusted for age, sex and stroke-to-imaging time. ‡Adjusted for stroke-to-imaging time. °Adjustments not desirable

**headache prevalence in T1 (small or no ICA calcification volume). **headache prevalence in T1 (small clot extent)*

****headache prevalence in T1 (small penumbra volume). *4 headache prevalence in T1 (small infarct core volume).*

Discussion

We found that headache during the early phase of ischemic stroke is less common in patients with extracranial carotid atherosclerosis. Also, less headache was present in patients with atherosclerosis in the extracranial posterior or intracranial circulation although this difference was not statistically significant. However, clot extent and penumbra volume were not associated with headache during ischemic stroke.

The mechanisms for headache during the early phase of ischemic stroke are not well understood. Our data suggest that vessel wall integrity and elasticity might be important factors, possibly facilitating the activation of perivascular nerve fibers leading to headache.[7, 24, 25] Since the posterior circulation has a denser perivascular innervation, this hypothesis might explain why headache is relatively more common in patients with infarctions in the posterior circulation.[26] Our findings do not provide support for the hypotheses that headache can be elicited by direct compression of the vessel wall by a large blood clot or by activation by peri-infarct core SDs of perivascular sensory trigeminal afferents.[27] No relation was found between increasing penumbra volume as proxy for presence of SDs and prevalence of concomitant headache. It should be noted, however, that we could not assess the penumbra of the posterior circulation in our study. This study confirms previously reported associations of ischemic-stroke associated headache and posterior circulation infarcts or a history of hypertension or migraine.[3, 7] In contrast to other studies[5, 7] we failed to find associations between ischemic-stroke associated headache and female sex, young age, or clinical outcome. In line with previous studies, the headache was pressing in 66% and throbbing in 17% and preceded stroke onset in nearly one third of patients. Pre-stroke headache had no specific characteristics and time between headache onset and stroke symptom onset varied from seconds to several days. Its mechanism is puzzling.

Our study also has limitations. Not all radiological parameters could be assessed in all patients. Intracranial internal carotid artery calcium (ICA) calcification volume, clot burden score, and ASPECTS scores can by definition only be assessed in the anterior circulation. Penumbra and infarct core volume could only be assessed in the anterior circulation because of lack of validated thresholds for the posterior circulation. Additionally, penumbra and infarct core are defined by relative mean transient time measurements for which comparison with a healthy hemisphere is needed, whereas posterior circulation infarctions are often bilateral. CTP in general is software dependent. Since thresholds for defining infarct core and penumbra are uncertain, quantification bears uncertainty as well. Additionally, we used the arbitrary threshold of 160 Hounsfield units to assess the intracranial ICA

calcification volumes. This does not correspond with the threshold of 130 Hounsfield units reported in the literature, though this threshold was derived from the Agatston score for coronary artery calcifications.[28, 29] We based our 160 Hounsfield units on optimal distinction between intracranial ICA calcifications and skull base in data from all different vendors, variation of calcification volume data did not differ notably between centers. Finally, as participants had to be able to answer the headache questionnaire, patients with a severe disease course were not included. This might affect the generalizability of the results to this group of patients. In 73 patients the headache questionnaire was not filled in. This was mainly because of logistic reasons and the baseline characteristics of these patients were not different from the participants. Fourteen patients (5%) did not remember whether they had headache at stroke onset. These patients had more often severe strokes and were more often aphasic than patients who were included in the study. However, because of the small number of patients the influence of this possible source of selection bias is likely to be small.

Strong points of our study include the large number of participants, prospective assessment of the headache, and use of state-of-the-art imaging methods enabling detailed assessment of the radiological characteristics of interest. With emerging novel imaging techniques such as arterial spin labeling with MR[30, 31], we might be able in the near future to assess perfusion of the posterior circulation as well. This would certainly facilitate the deciphering of the pathophysiological mechanisms of acute ischemic stroke-associated headache.

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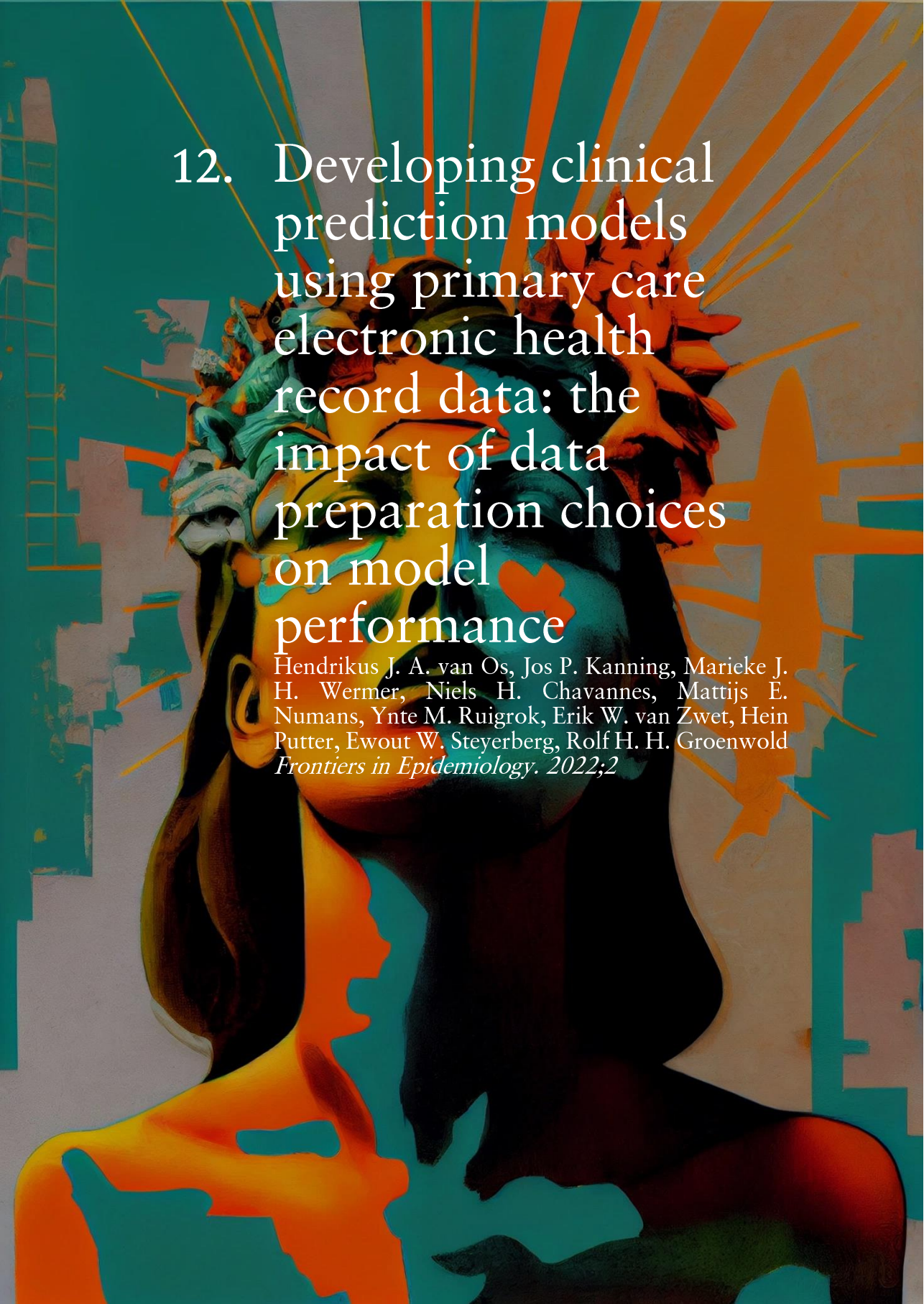
Part II.
Prediction of the risk of stroke in women



12. Developing clinical prediction models using primary care electronic health record data: the impact of data preparation choices on model performance

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Abstract

Background and purpose: To quantify prediction model performance in relation to data preparation choices when using electronic health records (EHR).

Methods: Cox proportional hazards models were developed predicting first-ever main adverse cardiovascular events using Dutch primary care EHR data. The reference model was based on a one-year run-in period, cardiovascular events were defined based on both EHR diagnosis and medication codes, and missing values were multiply imputed. We compared data preparation choices regarding i) length of the run-in period (two- or three-year run-in); ii) outcome definition (EHR diagnosis codes or medication codes only); and iii) methods addressing missing values (mean imputation or complete case analysis) by making variations on the derivation set and testing their impact in a validation set.

Results: We included 89,491 patients in whom 6,736 first-ever main adverse cardiovascular events occurred during a median follow-up of eight years. Outcome definition based only on diagnosis codes led to systematic underestimation of risk (calibration curve intercept: 0.84; 95% CI: 0.83 – 0.84), while complete case analysis led to overestimation (calibration curve intercept: -0.52; 95% CI: -0.53 – -0.51). Differences in length of run-in period showed no relevant impact on calibration and discrimination.

Conclusion: Data preparation choices regarding outcome definition or methods to address missing values can have a substantial impact on the calibration of predictions, hampering reliable clinical decision support. This study further illustrates the urgency of transparent reporting of modelling choices in an EHR data setting.

Introduction

Electronic health records (EHRs) enable the improvement of quality of care through providing structured information stored in a digital format, straight forwardly derived from routine health care.[1,2] Besides advantages related to the clinical workflow, increased standardization and pooling of EHR data lead to very large datasets that can be of great value for the development of clinical prediction models. EHR-based datasets can reach an unprecedented scale and variety of recorded data which is practically impossible to achieve in traditional cohort research.[3,4] However, EHRs are designed to record data that are routinely collected during the clinical workflow under a time constraint, in contrast to dedicated prospective cohort studies in which data are collected by trained personnel in a highly standardized manner.[5] Consequently, numerous data quality problems are relatively more pronounced in EHR data.[6] Previous studies have already enumerated the challenges that the EHR data quality limitations pose for the development of valid clinical prediction models. To overcome these challenges, in many cases the researcher is faced with difficult or seemingly arbitrary choices in data preparation, for example regarding the handling of missing predictor values.[6-8] Consequently, it may occur in research practice that different data preparation choices will be made for model derivation (or validation) compared with the context of model deployment, which may impact the predictive performance of the model when deployed in clinical practice. The quantification of such choices has not received much attention. In this paper we aimed to evaluate the impact of three previously identified data preparation challenges for EHR-derived prediction models: i) using a run-in period to define predictors at time zero, ii) outcome definition, and iii) methods used to address missing values.[6-8] As a case study, we focussed on the estimation of cardiovascular risk in Dutch primary care EHR data.

Methods

Data source

Patient information was derived from general practitioner (GP) practice centers affiliated with the Extramural LUMC Academic Network (ELAN), Leiden, the Netherlands. From the ELAN data warehouse we defined an open cohort of patients enlisted with ELAN GP practice center within the period of January 1st 2007 to and including December 31st 2018. Patient data included anonymized prescribed medication coded according to the Anatomical Therapeutic Chemical (ATC) classification, laboratory test results performed in primary care, symptoms and diagnoses coded according to the WHO-FIC recognized International Classification of Primary Care (ICPC).[9, 10] For many GP practice centers the EHR data on ATC and laboratory test result data became available shortly before or after 2007.

Inclusion criteria were age between 40 and 65 years, and absence of a history of cardiovascular disease at cohort entry at the end of the run-in period (see section 2.4.1 for details on the run-in period).

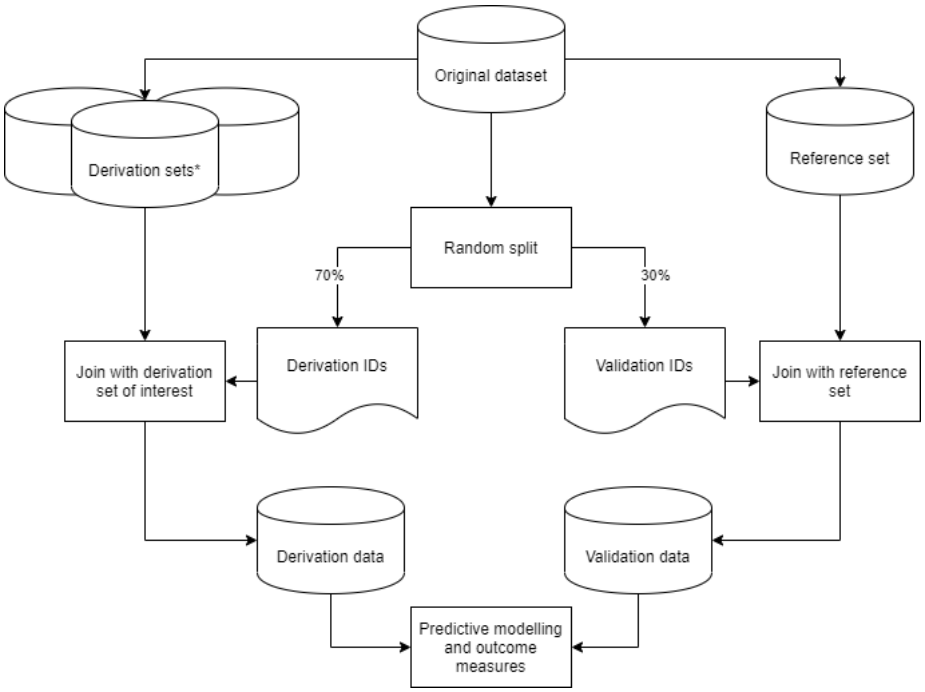
Study design

From our original dataset we derived nine datasets based on the predefined data preparation challenges. We considered the dataset with a one-year run-in period, an outcome defined as either ICPC or ATC code for first-ever main adverse cardiovascular events and multiple imputation as method for addressing missing values as the reference dataset. In addition to the reference set, we created two derivation sets with a variation in run-in time, four with varying outcome definitions, and two with different methods to address missing values. These eight variations on the reference dataset are described in more detail in the sections below. For each derived dataset, we took a random 70% to 30% sample from the original dataset IDs to generate a list of derivation- and validation IDs. Derivation IDs were joined with the derived dataset of interest in order to generate a derivation set. Validation IDs were joined with the reference set to generate a validation set. Through this approach, we ensured that no individual ID could be in both the derivation and validation sets. We subsequently performed data preparation steps on the derivation and validation sets, fitted the predictive model and recorded outcome measures. This process was repeated 50 times per derived dataset in a bootstrap procedure for a robust estimate of outcome measures. The study design is graphically displayed in Figure 1.

Model development

A multivariable Cox proportional hazards model was developed predicting first-ever main adverse cardiovascular events. The following predictors were selected based on prior knowledge: age, sex, mean systolic blood pressure, mean total cholesterol, and smoking as predictors, conform to the European SCORE model for prediction of cardiovascular mortality.[11]

Figure 1. Graphic display of the study design



*Graphic display of the study design. *Derivation sets (nine in total: one reference and eight variations) were derived from our original data set, with data preparation steps based on the predefined data preparation challenges.*

Data preparation challenges at model development

Defining predictors at time zero and a run-in period

Time zero (or t_0) is usually defined as the time of enrolment or baseline assessment of covariates. The start of the recording of data in EHRs is in principle the first contact with the healthcare system, which for an individual could be birth or in the prenatal or preconception period. However, as many countries do not have a single, national EHR, health data may be fragmented across EHRs of different healthcare providers resulting in left-truncation within an EHR database. Hence, there generally is not one clear baseline assessment of predictors. When the time of EHR entry is chosen as t_0 usually no values for laboratory or vital parameter predictors are available. This initial absence of recorded data is in computer sciences also known as the 'cold start' problem.[12] A possible solution is to define a run-in period, in which all data routinely acquired during a predefined time interval are aggregated

into summary variables at the end of this time interval.[13] Because of left truncation in our EHR dataset we chose the start date of our data window as January 1st, 2007. We then defined a run-in period of one year, meaning that the t_0 was defined as one year after the first moment a patient entered the database since January 1st, 2007. Additional requirements were age between 40 and 65 years old at t_0. Follow-up ran until the end of the data window at 31st of Dec 2018, or until unregistering with an ELAN GP practice center, death or first-ever main adverse cardiovascular event, whichever came first. Baseline predictors were assessed based on predictor values up until the end of the run-in period. If within this period multiple measurements of systolic blood pressure or total cholesterol were present, the mean value was taken as baseline measurement. As derivation set variations we defined run-in periods of two and three years (see Table 3). The reason we chose the one year run-in period as a reference was to maximize follow-up time. We chose the mean value as aggregation method for multiple measurements during run-in, as within this one year period measurement values were relatively recent with respect to t_0. Patients who suffered from main adverse cardiovascular events during the run-in period were excluded from analyses.

Outcome definition

EHRs are designed to record data that are routinely collected during the clinical workflow. This is different from traditional research, where data are collected by trained personnel in a highly standardized manner.[5] This difference could lead to several EHR data quality issues. For instance a clinical outcome may be present in reality, but has not been recorded in the EHR at all or under a different code, possibly leading to misclassification of outcomes.[14] What is more, in an EHR data context one has many more options for outcome definition than in traditional cohort data, such as constructing outcome using medication or diagnosis codes, or both. Differences in outcome definition in the derivation and target population may cause poor model performance in the target population. The clinical outcome of this study was the 10-year risk of a first-ever major adverse cardiovascular event, and was based on either event specific ICPC codes for primary care diagnoses of acute stroke [K90], TIA [K89], acute myocardial infarction [K75], or the start of prescription of event specific ATC codes for thrombocyte aggregation inhibitors (ticagrelor, picotamide, clopidogrel, dipyridamole, acetylsalicylic acid). In different derivation sets, the outcome was defined i) based on ATC codes (without acetylsalicylic acid) or ICPC codes; ii) based on ATC codes only (including acetylsalicylic acid); iii) based on ATC codes only, excluding acetylsalicylic acid; or iv) based on ICPC codes only. The reason for emitting acetylsalicylic acid from the outcome definition is that in the period of our t0 (2007) it was also prescribed as analgesic in primary care.[15] In addition, Dutch guidelines recommend prescription

of acetylsalicylic acid for stable angina pectoris.[16] Consequently, although it may increase sensitivity for predicting major adverse cardiovascular events, it could come at a cost for specificity. Ticagrelor, picotamide, clopidogrel, and dipyridamole can be regarded as more specific for main adverse cardiovascular events. Although non-cardiovascular mortality could be considered as a competing event, we did not perform a competing risk analysis to limit the complexity of analyses in this paper.

Missing values

Since EHR data result from routine care processes, virtually all health data are recorded during clinical contacts for a clinical reason. The missingness of a predictor value is therefore most likely related to clinical choices of the healthcare professional. In dealing with missing values it is essential to consider the mechanism of missingness.[17] For e.g. a missing measurement of systolic blood pressure in the EHR, missing completely at random (MCAR) is very unlikely because in clinical practice blood pressure assessment generally requires a medical indication. Missing at random (MAR) will occur if contextual information present in the EHR fully captures the clinician's motives – including those related to the outcome – to assess systolic blood pressure. Arguably, this is unlikely as clinical decision making takes a large number of biological, psychological and social factors into account. Missing not at random (MNAR) is therefore the most likely mechanism in this case. In case of MNAR commonly used imputation strategies such as multiple imputation may result in biased imputed values.[18] The combination of an MNAR mechanism with large extent of missingness in many predictors in EHR data may further increase risk of biased imputations.[19,20] One way of still leveraging information from the data without requiring sophisticated imputation is the missing indicator method. However, also in this case similarity of the missingness mechanism between the derivation and target populations is needed.[21] Complete case analysis in EHR data could introduce a bias towards the selection of e.g. sicker patients.[22] One should therefore assess how risk of bias resulting from handling missing values may affect the validity of predictions in the target population, and thus the clinical safety of future implementation of the model. Based on this assessment it may be advisable to discard predictors with a very high extent of missingness and possibly MNAR mechanism altogether. We imputed the missing continuous predictors systolic blood pressure and cholesterol using Multivariate Imputation by Chained Equations (MICE). As input for the MICE algorithm we used the 30 most important predictors according to a Cox PH model with an elastic net penalty predicting first-ever cardiovascular events. Although missing values in systolic blood pressure or total cholesterol predictors are unlikely MAR, we multiply imputed because these are important baseline predictors which are used in virtually all cardiovascular risk prediction models. In addition, the aim of this study is not to produce prediction

models that can be transported to true clinical settings, but the comparison of different data preparation choices in an EHR data context. Imputations were performed for all derivation and validation sets separately to prevent cross-contamination. We performed multiple visualizations of the complete and completed datasets. Further, we compared the results of the different imputation strategies with the Dutch population means for our age distribution.[23] For binary variables we assumed that absence of a registration of a clinical entity meant the clinical entity itself was absent. We defined two derivation set variations in which we addressed missing values in the continuous predictors using complete case analysis and mean imputation instead of MICE.

Assessment of model performance at validation

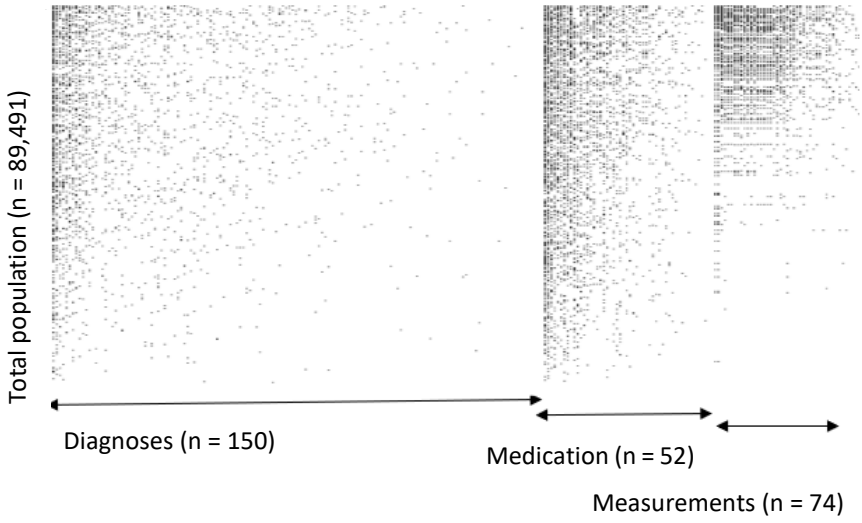
Models based on the derivation set variations were validated on the reference dataset (see schematic overview in Figure 1). Model performance was assessed via the concepts of discrimination (ability of the model to separate individuals who develop the event versus those who do not) and calibration (the agreement between the estimated and observed number of events). For evaluation of discrimination we used the concordance index (c-index), and calibration was assessed using the calibration curve slope and -intercept. For details on these metrics we refer to the literature.[24] We used bootstrap validation with 50 bootstraps for internal validation, and simple bootstrap resampling to derive empirical confidence intervals. Analyses were performed using Python version 3.7.

Results

For our example case study, we included 89,491 patients for analyses in whom 6,736 first-ever cardiovascular events occurred during a median follow-up of eight years. On average, patients were 51 years old, and 51% were women. (Table 1)

Figure 2 shows that for the majority of patients, of the total of 150 potential diagnoses no EHR-registrations were present. Although relatively more registrations among the 52 medication and 74 measurement codes were present, for a large part of the population no information was available. For variations in definition of outcome, the inclusion of acetylsalicylic acid in the definition resulted in a larger number of cases (Figure 3).

Figure 2. Visualization of data density in Dutch primary care EHR (n = 89,491)

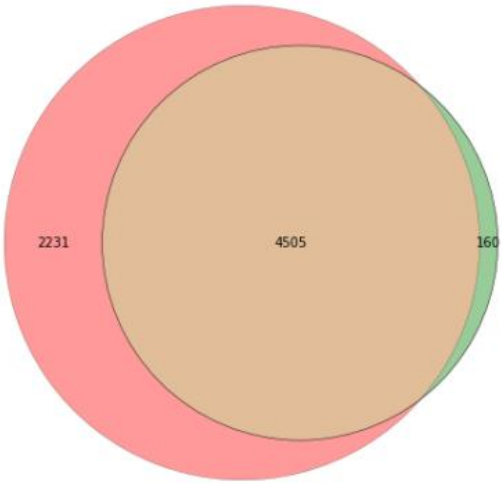


This figure shows the data density in the EHR for the first year of follow-up of all included patients. The x-axis is divided into three different predictor groups: diagnoses (any type of ICPC registration), medications (any type of ATC registration), and laboratory or vital parameter measurements (any type of registration), with each dot representing an EHR registration data point. The y-axis represents the entire research population ranked from patients with most data points and descending.

Differences were noted between the means in complete cases analysis, imputed by MICE and the estimated population mean. (Table 2) Testing the reference Cox PH model predicting cardiovascular events on the validation set resulted in a c-statistic of 0.67; 95% CI: 0.67–0.67), a calibration curve intercept of 0.00; 95% CI: -0.01–0.00), and -slope of 1.00; 95% CI: 0.99–1.00). Discrimination and calibration were similar for the models based on derivation sets with two- or three-year run-in variations. For the derivation sets with variations in outcome definition discrimination remained the same but calibration varied greatly, especially when outcome was based only on ICPC (calibration curve intercept: 0.84; 95% CI: 0.83–0.84, and -slope: 2.31; 95% CI: 2.29–2.32). In this derivation set variation the event rate was substantially lower compared with the validation set (3.4% versus 7.5%, respectively), and hence risk was underestimated at model validation. For models based on derivation set variations in missing data handling, again discrimination was similar to the reference model, but for complete case analysis calibration was substantially worse (calibration curve intercept: -0.52; 95% CI: -0.53—0.51, and -

slope: 0.60; 95% CI: 0.59–0.60). For this variation also the total sample size was substantially smaller (around 12% of the reference derivation set) and event rate was higher (11.4% versus 7.5% of the validation set), hence risk was overestimated at model validation (Table 3).

Figure 3. Venn diagram with three different operationalizations for the outcome definition



This Venn diagram shows the numbers of first-ever main adverse cardiovascular event cases resulting from the different outcome definitions: ICPC only (brown; 4505 cases), ICPC and ATC codes for event specific medication (clopidogrel, ticagrelor, dipyridamole) including acetylsalicylic acid (red; 4505 + 2231 cases) and ICPC and ATC codes for event specific medication excluding acetylsalicylic acid (brown + green; 4505 + 160 cases).

Table 1. Baseline characteristics of participants

Baseline characteristics	Cases (n = 6,736)	Controls (n = 82,755)
Age, mean *(± SD)*	54.8 (6.8)	51.3 (7.3)
Women, *n (%)*	2849 (42.3)	42867 (51.8)
Smoking, *n (%)*	494 (7.3)	3760 (4.5)
Presence of predictor measurement, *n (%)*		
Systolic blood pressure	2302 (34.2)	18992 (22.9)
Total serum cholesterol	1637 (24.3)	13254 (16.0)

Table 2. Imputation results of systolic blood pressure and total cholesterol in Dutch primary care EHR data (n=89,491)

	Systolic blood pressure (mmHg)	Total cholesterol (mmol/l)
Estimated population mean used for mean imputation (SD)	130 (16)	5.7 (1.1)
Sample mean of available measurements/complete case analysis (SD)	136 (17)	5.4 (1.1)
Sample mean after MICE imputation (SD)	132 (10)	5.4 (0.5)

Discussion

This study shows that for the prediction of first-ever cardiovascular event risk using Dutch primary care EHR data, different data preparation choices regarding the outcome definition (first-ever cardiovascular events) and methods used to address missing values in the derivation set can have a substantial impact on model calibration, while model discrimination remains essentially the same. The large changes in calibration curve intercept and -slope could be explained by the changes in percentage of events that resulted from the different data preparation choices in the derivation set variations. A drop of the proportion of events in derivation set variations compared with the reference derivation set (e.g. defining outcome using only ICPC codes) led to a decrease in the calibration curve intercept, and a rise of the proportion of events (e.g. in case of using complete case analysis to handle missing values) led to an increase. These deteriorations of calibration may be of substantial clinical significance when a prediction model is used in clinical practice, for example within a clinical decision support tool. To evaluate a model on its utility to support clinical decisions, calibration is a more relevant performance metric than model discrimination.[24, 25]

Table 3. Performance of the models based on derivation set variations compared with the reference model in Dutch primary care EHR data (n = 89,491)

		Derivation set characteristics**			Performance metrics **		
Data preparation challenge	Derivation set variation	Sample size (range)	Percentage events (range)	Median follow-up time (days; range)	C-statistic (95% CI)	Calibration curve intercept (95% CI)	Calibration curve slope (95% CI)
Reference derivation set*	NA	62644 (62557–62730)	7.5 (7.5–7.6)	2912 (2904–2920)	0.67 (0.67–0.67)	0.00 (-0.01–0.00)	1.00 (1.00–1.01)
Run-in variations	2 years run-in	58168 (58098–58236)	7.0 (7.0–7.1)	2832 (2832–2832)	0.67 (0.67–0.67)	0.00 (-0.01–0.00)	1.00 (0.99–1.00)
	3 years run-in	54958 (54884–55031)	6.4 (6.4–6.5)	2833 (2833–2833)	0.67 (0.67–0.67)	0.02 (0.01–0.03)	1.02 (1.01–1.03)
Variations in outcome definition	ATC (excl. ASA) or ICPC	63376 (63301–63448)	5.1 (5.1–5.2)	2933 (2925–2940)	0.67 (0.67–0.67)	-0.40 (-0.41–-0.40)	0.67 (0.66–0.67)
	ATC only	63518 (63436–63597)	7.5 (7.4–7.5)	2916 (2909–2922)	0.68 (0.68–0.68)	-0.01 (-0.02–0.00)	0.99 (0.99–1.00)
	ATC (excl. ASA) only	64739 (64662–64819)	4.6 (4.5–4.6)	2968 (2956–2979)	0.68 (0.68–0.68)	-0.52 (-0.53–-0.51)	0.59 (0.59–0.60)
	ICPC only	64089 (63998–64180)	3.4 (3.3–3.4)	3025 (3010–3040)	0.66 (0.66–0.66)	-0.84 (-0.85–-0.83)	0.43 (0.43–0.44)
Missing data method variations	Complete Case	7601 (7573–7629)	11.4 (11.3–11.5)	2425 (2409–2442)	0.62 (0.62–0.62)	0.53 (0.51–0.54)	1.69 (1.67–1.71)
	Mean imputation	62548 (62478–62618)	7.5 (7.5–7.6)	2910 (2901–2918)	0.66 (0.66–0.66)	0.01 (0.00–0.02)	1.01 (1.00–1.02)

ASA = acetylsalicylic acid; ICPC = International Classification of Primary Care diagnosis codes; ATC = Anatomical Therapeutic Chemical medication codes

**The reference derivation and validation set is defined by one year run-in, imputation using MICE, and outcome definition based on ICPC or ATC codes (including aspirin)*

***Derivation set characteristics and performance metrics are given as average across 50 bootstrap samples*

Previous research already identified numerous methodological challenges for development of clinical risk prediction models using EHR data. [6-8] To the best of our knowledge, this is the first study that quantifies the impact that different data preparation choices in an EHR data setting have on model performance. The three data preparation challenges that are treated in this paper do relate to previous studies that focus on EHR-based data. One study used multiple methods for aggregation of baseline measurements during a run-in period and found that simple aggregations such as the mean are sufficient to improve model performance.[26] Further, several studies illustrate the difficulty of choosing an outcome definition in an EHR data context, especially due to the substantial variations of misclassification for different types of EHR diagnosis codes. In one example the positive predictive value (PPV) of the diagnosis code for chronic sinusitis was 34%, versus 85% for nasal polyps. With the additional information of evaluation by an otorhinolaryngologist the PPV of the latter rose to 91%.[27, 28] One study quantified the effect on model performance of misclassification in predictors instead of the outcome, using the CHA_2DS_2-VASc prediction rule as a case study. The substantial misclassification of predictors did not affect overall model performance, but it did affect the risk of the outcome with a certain CHA_2DS_2-VASc score.[29] In this study we focussed on the influence of misclassification in outcome on model performance, but also misclassification in predictors should be taken into account when developing a clinical prediction model using EHR data. Regarding the imputation of EHR predictor values that are likely MNAR, studies found that there may still be options for imputation if missingness structure is explicitly modelled. Methodologies such as Bayesian analysis may be specifically suited for this purpose.[6, 30] However, further research into this topic is needed. One option is to discard a variable altogether, especially in case of large extent of missingness.[19] In the future, missingness in EHR data might be reduced by more systematic data capture, or through automated analysis of free text using natural language processing techniques.[31]

Strengths and limitations

Several methodological limitations need to be taken into account to interpret our study results. First, in our EHR data no reference standard for the definition of the outcome was present, complicating the interpretation of the model results. It should also be noted that for many EHR-derived diagnoses, available reference standards may a certain degree of misclassification.[32] Therefore, the researcher needs to work with the routine data that are available, often resulting in difficult or seemingly arbitrary choices regarding outcome definition. In this study we focused on the relative impact on model performance of different outcome definitions, instead of a comparison with a reference standard for outcome. We assumed that the definition

used in the reference derivation set (ATC including acetylsalicylic acid or ICPC) was most sensitive because of the broad inclusion of thrombocyte aggregation inhibitors that are prescribed after cardiovascular events. However, in the first years of our follow-up period acetylsalicylic acid was also prescribed in a primary prevention setting, thus outcome according to ATC excluding acetylsalicylic acid is considered as most specific. Second regarding the different choices in addressing missing data, in the reference derivation set systolic blood pressure and blood cholesterol were imputed using MICE despite the large extent of missingness in these predictors. As the predominant missingness mechanism is likely MNAR as has been argued in section 2.4.3, these imputation results are likely biased to some extent. The density of datapoints across all diagnosis, medication and measurement codes showed that for a large number of patients the lack of information often extended to the entire dataset, which also hampers reliable imputation. We compared imputation results with expected population means and indeed found a moderate difference. Although these likely biased estimates may not be a problem at internal validation, it may be at external or prospective validation when the missingness mechanism itself is not transportable to these new data environments. Third, although non-cardiovascular mortality could be considered as a competing event, we did not perform a competing risk analysis to limit the complexity of analyses in this paper. The number of non-cardiovascular deaths recorded during follow-up was 2838, which represents only 3% of the total study population. Therefore, the effect of non-cardiovascular mortality as competing event on potential overestimation of the cumulative incidence of cardiovascular events was likely limited. Finally, the discriminative performance of our models is relatively low. An explanation for the relatively poor discrimination is the limited number of predictors selected for the model and the limited age range of 40 to 65 years, based on our conformity with the SCORE model. Discriminative performance found in our study however is not uncommon for clinical prediction models used in practice, and is comparable with that of e.g. the CHA_2DS_2-VASc prediction rule.[33] In addition, compared with discrimination calibration is of more interest to compare model performance because of the future intended use of the models to support clinical decisions.[24] Strengths of this study include the very large sample size of our routine care dataset, and the large number of derivation set variations (eight) that we used to assess the impact of difficult or seemingly arbitrary choices in data preparation on model performance.

Future considerations

Our findings stress the importance of carefully considering differences data preparation choices between the population used for model derivation compared with the target population for model validation or deployment, because these differences may lead to substantial miscalibration. In essence this study's

methodology of including multiple derivation set variations could be seen as a form of sensitivity analysis to assess transportability of the model to a clinical setting in which different data preparation choices are made. However, all data used in this study were derived from the same EHR data source (ELAN). Therefore, we could not formally test transportability across different EHR data sources. Still, this study further illustrates the need for transparent reporting of choices in model development studies and model calibration in validation studies. This could be done using e.g. the RECORD statement for reporting on data preparation choices using routinely collected health data in EHR, and the TRIPOD statement for reporting on clinical prediction model development.[34, 35] The Python code used in this study has been made publicly available in an online repository ([link follows]).”

Conclusion

Our findings support that for developing clinical prediction models using EHR data, variations in data preparation choices regarding outcome definition and dealing with missing values may have substantial impact on model calibration, while discrimination remains essentially the same. It is, therefore, important to transparently report data preparation choices in model development studies and model calibration in validation studies.

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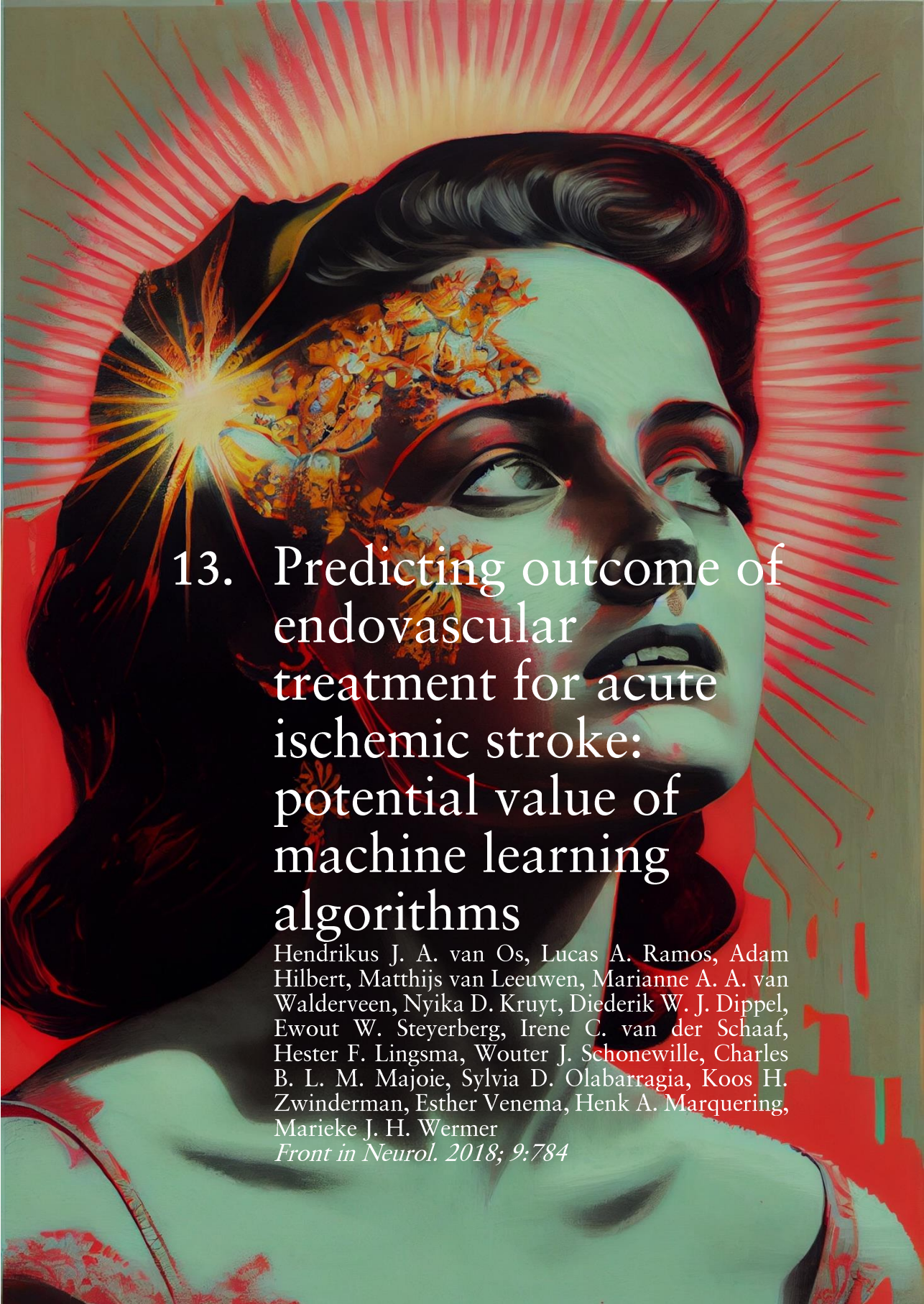

13. Predicting outcome of endovascular treatment for acute ischemic stroke: potential value of machine learning algorithms

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Abstract

Background and purpose: Endovascular treatment (EVT) is effective for stroke patients with a large vessel occlusion (LVO) of the anterior circulation. To further improve personalized stroke care, it is essential to accurately predict outcome after EVT. Machine learning might outperform classical prediction methods as it is capable of addressing complex interactions and non-linear relations between variables.

Methods: We included patients from the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) Registry, an observational cohort of LVO patients treated with EVT. We applied the following machine learning algorithms: Random Forests, Support Vector Machine, Neural Network, and Super Learner and compared their predictive value with classic logistic regression models using various variable selection methodologies. Outcome variables were good reperfusion (post-mTICI ≥2b) and functional independence (modified Rankin Scale ≤2) at 3 months using 1) only baseline variables and 2) baseline and treatment variables. Area under the ROC-curves (AUC) and difference of mean AUC between the models were assessed.

Results: We included 1383 EVT patients, with good reperfusion in 531 (38%) and functional independence in 525 (38%) patients. Machine learning and logistic regression models all performed poorly in predicting good reperfusion (range mean AUC:0.53–0.57), and moderately in predicting 3-month functional independence (range mean AUC:0.77–0.79) using only baseline variables. All models performed well in predicting 3-month functional independence using both baseline and treatment variables (range mean AUC:0.88–0.91) with a negligible difference of mean AUC (0.01;95%CI:0.00–0.01) between best performing machine learning algorithm (Random Forests) and best performing logistic regression model (based on prior knowledge).

Conclusion: In patients with LVO machine learning algorithms did not outperform logistic regression models in predicting reperfusion and 3-month functional independence after endovascular treatment. For all models at time of admission radiological outcome was more difficult to predict than clinical outcome.

Introduction

Endovascular treatment (EVT) is effective for ischemic stroke patients with a large vessel occlusion (LVO) of the anterior circulation. EVT results in a number needed to treat of 2.6 to reduce disability by at least one level on the modified Rankin Scale (mRS).[1] A recent meta-analysis showed a positive treatment effect of EVT across patient subgroups including different age groups, varying stroke severity, sex, and stroke localization.[1] However, many clinical and imaging predictors or their combinations were not considered in the subgroup analysis. Moreover, the RCTs that provided the data differed in their patient selection criteria. To further improve personalized stroke care, it is essential to accurately predict outcome and eventually differentiate between patients who will and will not benefit from EVT. Machine learning belongs to the domain of artificial intelligence and provides a promising tool in pursuing personalized outcome prediction, which is increasingly used in medicine.[2-7] The machine learning methodology allows discovering empirical patterns in data through automated algorithms. In some clinical settings machine learning algorithms outperform classical regression models such as logistic regression, possibly through more efficient processing of non-linear relationships and complex interactions between variables,[6, 8] although poorer performance has also been observed.[9]

In this study, we used multiple machine learning algorithms and logistic regression with multiple variable selection methods to predict radiological and clinical outcome after EVT in a cohort of well-characterized stroke patients. We hypothesized that machine learning algorithms outperform classic multivariable logistic regression models in terms of discrimination between good and poor radiological and clinical outcome.

Methods

Patients

We included patients registered between March 2014 and June 2016 in the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) Registry. The MR CLEAN Registry is an ongoing, national, prospective, open, multicenter, observational monitoring study covering all 18 stroke intervention centers that perform EVT in the Netherlands, of which 16 participated in the MR CLEAN trial.[10] The registry is a continuation of the MR CLEAN trial collaboration and includes all patients undergoing EVT (defined as entry into the angiography suite and receiving arterial puncture) for acute ischemic stroke in the anterior and posterior circulation. In the current analysis we included those patients who adhered to the following criteria:

age 18 years and older, treatment in a center that participated in the MR CLEAN trial, and LVO in the anterior circulation (internal carotid artery (ICA), internal carotid artery terminus (ICA-T), middle (M1/M2) cerebral artery, or anterior (A1/A2) cerebral artery), shown by CT angiography (CTA) or digital subtraction angiography (DSA).[11]

Clinical baseline characteristics

We assessed the following clinical characteristics at admission: National Institutes of Health Stroke Scale (NIHSS), Glasgow Coma Scale, medical history (TIA, ischemic stroke, intracranial hemorrhage, subarachnoid hemorrhage, myocardial infarction, peripheral artery disease, diabetes mellitus, hypertension, hypercholesterolemia), smoking, laboratory tests (blood glucose, INR, creatinine, thrombocyte count, CRP), blood pressure, medication (thrombocyte aggregation inhibitors, oral anticoagulant drugs, anti-hypertensive drugs, statins), modified Rankin Score (mRS) before stroke onset, administration of intravenous tPA (yes/no), stroke onset to groin time, transfer from another hospital, and whether the patient was admitted during weekend or off hours.

Radiological baseline parameters

All imaging in the MR CLEAN Registry was assessed by an imaging core laboratory.[11] On non-contrast CT, the size of initial lesion in the anterior circulation was assessed by the Alberta Stroke Program Early CT Score (ASPECTS). ASPECTS is a 10 point quantitative topographic score representing early ischemic change in the middle cerebral artery territory, with a scan without ischemic changes receiving an ASPECTS of 10 points.[12] In addition, presence of leukoaraiosis and old infarctions, hyperdense vessel sign, and hemorrhagic transformation of the ischemic lesion were assessed on non-contrast CT.

On CTA, the core lab determined clot burden score, clot location, collaterals, and presence of intracranial atherosclerosis. The clot burden score evaluates the extent of thrombus in the anterior circulation by location scored on a 0–10 scale. A score of 10 is normal, implying clot absence; a score of 0 implies complete multi-segment vessel occlusion.[12] Presence of intracranial carotid artery stenosis, atherosclerotic occlusion, floating thrombus, pseudo-occlusion, and carotid dissection were scored on CTA of the carotid arteries. Collaterals were assessed using a 4 point scale, with 0 for absent collaterals (0% filling of the vascular territory downstream of the occlusion), 1 for poor collaterals (>0% and ≤50% filling of the vascular territory downstream of the occlusion), 2 for moderate collaterals (>50% and <100% filling of the vascular territory downstream of the occlusion), and 3 for excellent collaterals (100% filling of the vascular territory downstream of the occlusion).[13]

Treatment specific variables

Variables collected during EVT were type of sedation during the procedure (general or conscious), use of a balloon guiding catheter, carotid stent placement, performed procedure (DSA only or thrombectomy), and type of EVT-device (stent retriever, aspiration device, or a combination of both). In addition, data were collected on adverse events during the procedure (perforation, dissection, distal thrombosis on DSA). Interventional DSA parameters in our dataset were occluded vessel segment (ICA: origin, cervical, petrous, cavernous, supraclinoid, M1-M4, A1, A2), arterial occlusive lesion (AOL) recanalization score before and after EVT,[14] evidence of vascular injury (i.e. perforation, or dissection, vasospasm, new clot in different vascular territory or distal thrombus confirmed with imaging), and modified Thrombolysis in Cerebral Infarction (mTICI)-score before and after EVT. The mTICI-score grades the following categories of cerebral reperfusion: no reperfusion of the distal vascular territory (0), minimal flow past the occlusion but no reperfusion (1), minor partial reperfusion (2a), major partial reperfusion (2b), and complete reperfusion (3).[15] Further variables analyzed were time from stroke onset to recanalization, post-EVT stay on intensive care, high care or stroke care, NIHSS after EVT (<48h), delta NIHSS (pre-treatment NIHSS subtracted from NIHSS <48h after EVT) and hemicraniectomy or symptomatic intracranial hemorrhage <48h after EVT.

Outcome

The primary radiological outcome was good reperfusion defined as modified TICI-score directly post-procedure (post-mTICI) $\geq$ 2b.[15] The primary clinical outcome was functional independence at 3 months after stroke (mRS $\leq$ 2). We excluded patients in whom any of the main outcomes (3-month mRS and post-mTICI) were missing. To investigate the full potential of Machine learning compared with conventional methods in different settings after stroke we defined two prediction settings:

First, we assessed the probability of good reperfusion and good 3-month functional independence in our cohort of patients that underwent EVT based only on variables that were available on admission before entry into the angiography suite. With this baseline prediction setting we are able to investigate the added value of machine learning for models that could potentially support future clinical decision making regarding the performance of EVT yes or no.

Second, we tested the models for predicting 3-month functional independence in patients after EVT was performed. For this analysis we used all variables collected up to 48 hours after the end of the endovascular procedure (baseline and treatment variables).

Machine learning algorithms

The machine learning algorithms used in our study were Random Forests, Artificial Neural Network and Support Vector Machine, because they are among the algorithms that are currently most widely and successfully used for clinical data.[2-7] Each one of them represents a different algorithm 'family', each with radically different internal algorithm structures.[16] Since it was not known beforehand which kind of algorithm would perform best, we chose algorithms with different internal structures to increase the probability of good discriminative performance. We also used Super Learner, which is an ensemble method that finds the optimal weighted combination of predictions of the Random Forests, Artificial Neural Network and Support Vector Machine algorithms used in this study. Ensemble methods such as Super Learner have been shown to increase predictive performance by increasing model flexibility.[17] For the implementation of all machine learning algorithms we used off-the-shelf methods in the Python module Scikit-Learn.[18]

Super Learner

Super Learner is a stacking algorithm using cross-validated predictions of other models (i.e. a machine learning algorithm and logistic regression) and assigning weights to these predictions to optimize the final prediction. Super Learner's predictive performance has been found to surpass individual machine learning models in various clinical studies.[17, 19, 20]

Random Forests

Random Forests consists of a collection of decision tree classifiers that are fit on random subsamples of patients and variables in the dataset. The variation of the subsampled variables creates a robust classifier. In the decision trees, each node represents a variable and splits the input data into branches based on an objective function that determines the optimal threshold for separating the outcome classes. The predictions from each tree are used as 'votes', and the outcome with the most votes is considered the predicted outcome for that specific patient.[6, 21] From the Random Forests algorithm variable importances can be derived, which are the sum of weights of nodes of the trees containing a certain variable, averaged over all trees in the forest.[22]

Support Vector Machine

Support Vector Machine (SVM) is a kernel-based supervised machine learning classifier which can also be used to output probabilities. The SVM works by first mapping the input data into a high dimensional variable space. For binary

classification, a hyperplane is subsequently determined to separate two classes such that the distance between the hyperplane and the closest data points is maximized.[23]

Artificial Neural Network

In this study we use the multilayer perceptron, a popular class of artificial neural network architecture composed of one or more interconnected layers of neurons that process data from the input layer into predictions for the output layer. The algorithm computes a weight for each neuron based on input activation. These weights are updated by backpropagation and stochastic gradient descent.[24, 25]

Logistic regression

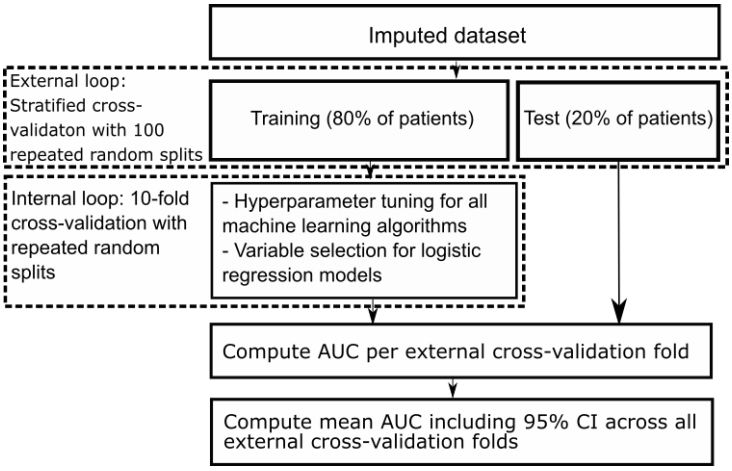
For logistic regression, generally a set of variables has to be selected to be included in the model. Since model performance can rely heavily on selecting the right variables, we tested five different variable selection methods prior to logistic regression. We first selected variables based on prior knowledge, a still widely used method that could be considered 'classical'.[26] We selected 13 variables available at baseline that were included in a previous study for a similar purpose.[27] (Supplementary Table Ia) In addition, from baseline and treatment variables we selected 15 variables based on expert opinions of vascular neurologists and radiologists. (Supplementary Table Ib).
We further considered four automated variable selection methods: i) backward elimination, which is also considered to be a more classical approach,[26] and three state-of-the-art variable selection methods: ii) least absolute shrinkage and selection operator (LASSO)[28], iii) Elastic Net, which is a modification of the LASSO found to outperform the former while still having the advantage of a similar sparsity of representation[29], and iv) selection based on Random Forests variable importance.

Analysis pipeline

We imputed missing values using multiple imputations by chained equations (MICE).[30] Variables with 25% missing values or more were discarded from further analysis. All remaining variables used in this study are listed in Supplementary Table II and III. In total, 53 baseline variables and 30 treatment variables were used as input for machine learning algorithms and automated variable selection methods for logistic regression. The ordinal clinical (NIHSS) and radiological (clot burden and ASPECTS) scores were presented as continuous scores in all models to increase model efficiency, and we assumed linear trends underlying the ordinal scores. We used nested cross-validation (CV), consisting of an outer and an inner CV loop. In the outer CV loop we used stratified CV with 100 repeated random splits resulting in a training set including 80% and a test set including 20% of all patients. Each

training set was used as input for the inner CV loop, consisting of ten-fold CV.[31, 32] In the inner CV loop we selected variables for the logistic regression models using the different variable selection methods, and optimized hyperparameters of all machine learning models. Hyperparameters are tuning parameters specific to each machine learning algorithm whose values have to be preset and cannot be directly learned from the data. We optimized hyperparameters with the random grid search module from Scikit-Learn.[18] We selected those with highest area under the receiver operating characteristic (AUC) across all internal CV folds to find the best set of selected variables and hyperparameters. Figure 1 shows a schematic representation of our nested CV methodology. For all Random Forests models of both prediction settings we ranked variables by decreasing variable importance. For each variable we assessed the frequency of being among the 15 most important variables in a Random Forests model for each of the 100 external CV folds.

Figure 1. Schematic representation of nested cross-validation methodology



Model performance

We assessed model discrimination (the ability to differentiate between patients with good and poor outcome) with receiver operating characteristic (ROC) analyses. Because of our outer CV loop with 100 repeated random splits, we obtained 100 different AUCs from every model. We computed the average ROC-curve and mean AUC with 95% confidence intervals (CI) for all models. We evaluated differences between mean AUCs of the best performing machine learning model and best performing logistic regression model by computing the difference of means including the associated 95% CI.

Results

Of the 1627 patients registered between March 2014 and June 2016, we excluded 244 patients for this analysis because of age < 18 (n = 2), posterior circulation stroke (n = 79), missing MR CLEAN trial center (n = 20), and missing mRS or post-mTICI (n = 143). Mean age was 69.8 years (SD ± 14.4) and 738 (54%) of the 1383 included patients were men. In total, 531 (38%) patients had good reperfusion after EVT and 525 (38%) were functionally independent (mRS ≤ 2) three months after stroke. Baseline characteristics are shown in Table 1.

Prediction of good reperfusion after EVT in patients at time of admission

Discrimination between good and poor reperfusion of the best machine learning algorithm (Support Vector Machine, mean AUC: 0.55) and the best logistic regression model (using backward elimination, mean AUC: 0.57) was similar (difference of mean AUCs: 0.02; 95% CI: 0.01–0.03). Discrimination was poor for all models, with a mean AUCs ranging from 0.53 to 0.57 (Table 2). Variable selection using LASSO or Elastic Net was not possible likely because the signal-to-noise ratio was insufficient.[18]

Prediction of 3-month functional independence in patients at time of admission

Discrimination of good functional outcome of the best machine learning algorithm (Super Learner, mean AUC: 0.79) and the best logistic regression model (using LASSO, mean AUC: 0.78) was similar (difference of mean AUCs: 0.01; 95% CI: 0.01 – 0.01). Discrimination was moderate for all models, with a mean AUCs ranging from 0.77 to 0.79.

Prediction of 3-month functional independence in patients after EVT

Discrimination of good functional outcome of the best machine learning algorithm (Random Forests, mean AUC: 0.91) and the best logistic regression model (using prior knowledge, mean AUC: 0.90) was similar (difference of mean AUCs: 0.01; 95% CI: 0.00 – 0.01). Discrimination was good for all models, with mean AUCs ranging from 0.88 to 0.91. We performed a post hoc analysis in patients with good reperfusion as defined by post-mTICI ≥ 2b, predicting 3-month functional outcome both at time of admission and after performance of EVT. We did not find significant differences in performance between machine learning algorithms and logistic regression models in this patient subset (data not shown).

In Table 3 we show the top 15 variables based on the frequency of being among the 15 most important variables in a Random Forests model for each of the 100 external CV folds.

Table 1. Baseline characteristics of participants

Characteristics	All patients (n = 1383)
Mean age ± SD *(years)*	69.8 ± 14.4
Men, *n (%)*	738 (53.5)
NIHSS score, *median (IQR)*	16 (11 - 20)
Mean systolic blood pressure ± SD *(mm Hg)*	150 ± 25
Medical history, *n (%)*	
Atrial fibrillation	411 (30.7)
Hypertension	697 (51.1)
Diabetes mellitus	235 (17.1)
Myocardial infarction	216 (15.9)
Peripheral artery disease	127 (9.4)
Ischaemic stroke	227 (16.5)
Hypercholesterolemia	411 (29.7)
Pre-stroke mRS > 2, *n (%)*	158 (11.6)
Smoking, *n (%)*	314 (22.9)
Medication use, *n (%)*	
DOAC**	35 (2.6)
Coumarine	179 (13.0)
Antiplatelet	461 (33.7)
Heparin	52 (3.8)
Blood pressure medication	707 (52.1)
Statin	490 (36.2)
Intravenous alteplase treatment, *n (%)*	1054 (76.2)
ASPECTS, *median (IQR)*	9 (7–10)
Time from stroke onset to groin in minutes, *median (IQR)*	210 (160–270)
Collateral score ≥ 2	764 (55)

**National Institutes of Health Stroke Scale score*

Table 2. Discrimination of machine learning algorithms and logistic regression models across the various prediction settings

Models, AUC (95% CI)*	Prediction setting (used variables: predicted outcome)		
	Baseline: post-mTICI	Baseline: mRS	All variables: mRS
Super Learner	0.55 (0.54–0.56)	0.79 (0.79–0.80)	0.90 (0.90–0.91)
Random Forests	0.55 (0.55–0.56)	0.79 (0.79–0.79)	0.91 (0.90–0.91)
Support Vector Machine	0.53 (0.53–0.54)	0.78 (0.77–0.78)	0.88 (0.88–0.89)
Neural Network	0.53 (0.53–0.54)	0.77 (0.76–0.77)	0.88 (0.88–0.89)
LR: automated selection**			
Random Forests	0.55 (0.55–0.56)	0.78 (0.78–0.78)	0.90 (0.90–0.90)
LASSO	NA¥	0.78 (0.78–0.79)	0.90 (0.89–0.90)
Elastic Net	NA¥	0.77 (0.77–0.78)	0.89 (0.88–0.89)
Backward elimination	0.57 (0.57–0.58)	0.78 (0.77–0.78)	0.90 (0.89–0.90)
LR: Prior knowledge‡	0.55 (0.55–0.58)	0.78 (0.78–0.79)	0.90 (0.90–0.90)

**Model discrimination is assessed by calculating mean Area Under the Curve (AUC) of the receiver operating characteristic across all outer cross-validation folds.*

***Logistic regression using automated variable selection methods*

¥Variable selection not possible, likely due to insufficient signal-to-noise ratio

‡Logistic regression using variables based on prior knowledge

Table 3. Variable importance of Random Forests for various prediction settings (used variables: predicted outcome)

Baseline: post-mTICI	Freq*	Baseline: mRS	Freq	All variables: mRS	Freq
RR systolic at admission	100	Age	100	NIHSS after 24-48 hours	100
Duration stroke onset to groin	100	NIHSS at baseline	100	Delta NIHSS: follow-up minus baseline	100
RR diastolic at admission	100	Duration stroke onset to groin	100	Age	100
Thrombocyte count	100	Glasgow Coma Scale	100	NIHSS at baseline	100
Age	100	RR systolic at admission	100	Duration from onset to recanalization	100
Creatinine	100	CRP	100	Duration of procedure	100
CRP	100	Creatinine	100	Delta NIHSS ≥ 4 points higher after EVT	100
NIHSS at baseline	100	Thrombocyte count	100	Duration stroke onset to groin	100
Clot burden score	100	RR diastolic at admission	100	Glasgow Coma Scale	100
Glasgow ComaScale	100	mRS prior to stroke	100	Creatinine	100
ASPECTS score at baseline	100	ASPECTS score at baseline	100	CRP	100
Glucose	100	Glucose	100	Thrombocyte count	100
Location: proximal M1**	74	Clot burden score	99	RR systolic at admission	100
Hyperdense artery sign NCCT	50	Presence of leukoaraiosis	96	mRS prior to stroke	91
History of atrial fibrillation	32	Collateral score	77	RR diastolic at admission	93

NCCT = non-contrast CT; CRP = C-Reactive Protein; RR = blood pressure; NIHSS = National Institutes of Health Stroke Scale score

**Frequency of being among the 15 most important variables in a Random Forests model for each of the 100 external CV folds*

***Location of intracranial occlusion on CTA*

Discussion

We found no difference in performance between best performing machine learning algorithms and best performing logistic regression models in predicting radiological or clinical outcome in stroke patients treated with EVT. For prediction of good reperfusion using variables available at baseline, all models showed a poor discriminative performance. This could indicate that reperfusion after EVT depends on characteristics not present in our variables available at time of admission, such as vascular anatomy or interventionalist related factors. Prediction of 3-month functional independence using variables known at baseline was moderate, predicting 3-month functional independence using baseline and treatment variables resulted in good performance.

We hypothesized that machine learning would outperform logistic regression models due to simultaneous assessment of a large number of variables, and more efficient processing of non-linear relations and interactions between them. Although a large number of variables (83 in total, see Supplementary Table II and III) were available for analysis in the MR CLEAN Registry database, performance of best machine learning algorithms and best logistic regression models were similar. This could indicate that interactions and non-linear relationships in our dataset were of limited importance.

To interpret our results, several methodological limitations have to be considered. First, due to their great flexibility machine learning algorithms are prone to overfitting, which results in optimistic prediction performance. To account for overfitting we used nested CV, which is considered to be an effective method for this aim.[33] Second, our outer CV loop resulted in 100 AUCs per model leading to relatively small confidence intervals of mean AUCs. Although this increases the probability of statistically significant differences between mean AUCs of various models, the clinical relevance of these mean AUC differences is difficult to interpret. Because in our study mean AUC differences between models are minimal, clinical relevance of these differences is also negligible. Third, we used data from a registry. Registries might be prone to selection bias. However, we expect that selection bias in our study was minimal because the MRCLEAN Registry in principle covers all patients treated with EVT in the Netherlands. In addition, in all centers patients were treated according to national guidelines, and registration of treatment was a prerequisite for reimbursement.[11]

Strong points of this study include the large sample size and standardized collection of patient data. Moreover, because of extensive hyperparameter tuning and state-of-the art variable selection methods, machine learning and logistic regression models were compared at their best performance. In several other studies that

compared machine learning algorithms with only logistic regression methods using variables based on prior knowledge, machine learning outperformed logistic regression.[6, 7, 34] Variable selection based on prior knowledge has the major drawback that predictive patterns in the data may be missed, as variable selection is strictly based on the literature and expert opinion.[26] In our study however, logistic regression using variables based on prior knowledge performed similarly to logistic regression using automated variable selection methods.

The distinction between machine learning and 'classical' regression methods is largely artificial. However, a clear distinction between various machine learning algorithms and logistic regression exists in terms of model transparency, which could be seen as the understanding of the mechanism by which the model works.[35] Logistic regression has the advantage of transparency at the level of individual variable coefficients, since from these coefficients odds ratios can be derived. However, variable importances derived from the Random Forests algorithm also offer insight in the importance of individual variables for prediction performance.[22] These variable importances take interaction between variables into account and have a similar interpretation for continuous and discrete variables, unlike odds ratios which constitute an effect per unit change of a predictor. Hence, Random Forests could be used as an efficient screening tool to pick up predictive patterns in the data that could potentially lead to further hypothesis-driven research. In Table 3 we show the top 15 variables from either the baseline or baseline and treatment variable set, based on Random Forests variable importance. The majority of variables in Table 3 do not overlap with the selection of variables based on prior knowledge, potentially providing researcher with additional information.

In this dataset we found no clinically relevant differences in prediction of reperfusion and 3-month functional independence across all models. However, since it is generally not known on beforehand which type of model will result in the best predictive performance in a new dataset, our methodology could be of importance in future studies. We present an analysis pipeline with both machine learning algorithms and logistic regression models including state-of-the-art variable selection methods. Assessing predictive performance of all models simultaneously enables the researcher to make the proper trade-off between predictive performance and model transparency. As our analysis pipeline is fully automated and input variables and outcome label can be altered at will, it is relatively easy to reuse in future studies. The Python code of our pipeline has been made publicly available in an online repository (https://github.com/L-Ramos/MrClean_Machine_Learning).

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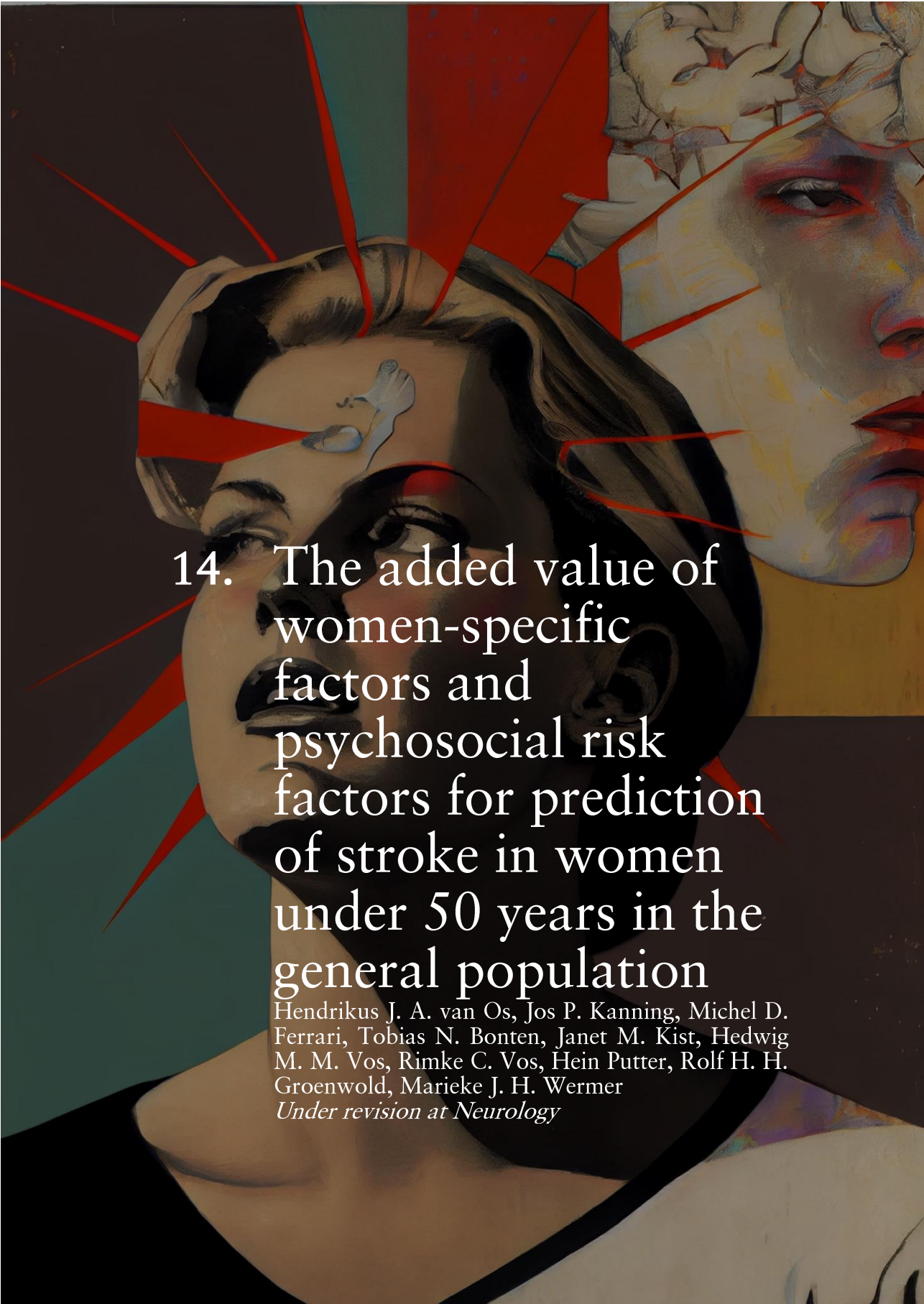

14. The added value of women-specific factors and psychosocial risk factors for prediction of stroke in women under 50 years in the general population

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Abstract

Background: Female-specific and psychosocial factors may be important in the prediction of stroke, but are not included in prediction models that are currently used. We investigated the added predictive value of these factors in women under 50.

Methods: We used data from the STIZON, population-based, primary care database of women aged 20–49 years without a history of cardiovascular disease. Analyses were stratified by 10-year age intervals at cohort entry. Cox proportional hazards models to predict stroke risk were developed, including traditional cardiovascular factors, and compared with models that additionally included female-specific and psychosocial factors. We compared the risk models using the C-statistic and the slope of the calibration curve at a follow-up of 10 years. We developed an age-specific stroke risk prediction tool that may help communicating the risk of stroke in clinical practice.

Results: We included 409,026 women with a total of 3,990,185 person years of follow-up. Stroke occurred in 2,751 women (incidence rate 6.9 [95%CI:6.6–7.2] per 10,000 person years). Models with only traditional cardiovascular factors performed poorly to moderately in all age groups: 20–29 years: C-statistic: 0.617 (95%CI:0.592–0.639); 30–39 years: C-statistic: 0.615 (95%CI:0.596–0.634); 40–49 years: C-statistic: 0.585 (95%CI:0.573–0.597). After adding the female-specific and psychosocial risk factors to the reference models, the model discrimination increased moderately, especially in the age groups 30–39 (ΔC-statistic: 0.023) and 40–49 years (ΔC-statistic: 0.029) compared to the reference models, respectively.

Conclusion: The addition of female-specific and psychosocial risk factors improves the discriminatory performance of prediction models for stroke in women under 50.

Introduction

Stroke is one of the leading causes of death and disability globally.[1] A decision to start preventive treatment depends first of all on the absolute risk of cardiovascular disease, including stroke and myocardial infarction, over a period of ten years. The current European guidelines recommend the use of the Systematic COronary Risk Evaluation 2 (SCORE2) for estimating cardiovascular risk in the general population.[2,3] This prediction model only includes traditional cardiovascular factors such as age, diabetes, hypertension, cholesterol, and smoking. However, there is increasing evidence that female-specific risk factors for stroke and other cardiovascular diseases, such as migraine, hormonal disorders and preeclampsia, are also important. In a systematic review of cardiovascular risk models in the general population, only two of 160 (1.3%) studies had used female-specific factors.[4] Both studies, and an additional one published a year later, concluded that inclusion of female-specific risk factors did not result in substantial improvement of model discrimination and reclassification.[5,6] However, the primary outcome measure of these studies was a combination of several major cardiovascular events, including myocardial infarction. Female-specific factors, however, primarily increase the risk of stroke.[7,8] Moreover, these studies included mainly postmenopausal women, while female-specific factors such as migraine and oral contraceptives increase the risk of stroke especially at reproductive age.[9,10] Psychosocial factors, such as low socioeconomic status and depression, have also been found to increase the risk of stroke in women to a greater extent in women compared with men.[11-14] However, their added value has hardly been assessed in prediction models for stroke.[4]
The aim of this study was therefore to assess the added value of female-specific and psychosocial factors, compared to traditional cardiovascular factors alone, in predicting the risk of stroke in women under 50 years.

Methods

Data source

We used data from the STIZON database, which directly retrieves data from electronic health records (EHRs) of a large number of primary care providers throughout the Netherlands and covers around 20% of the Dutch population.[15] From the STIZON dataset we only selected women from general practice centers which were situated in catchment areas of hospitals participating in the STIZON network. This allowed for linkage of hospital ICD-9 and ICD-10 diagnoses to primary care data. The STIZON dataset contains ICPC diagnosis codes for clinical entities and medication prescriptions according to the Anatomical Therapeutic Chemical (ATC) Classification System from primary care pharmacies.[16,17] ICD-9 and ICD-10 codes were present for all in-hospital diagnoses that occurred during

follow-up, while ICPC diagnosis codes were in principle available since birth. Inclusion criteria were female sex (as determined by registration in the primary care EHR), age of 20 to 49 years, and subscription to a STIZON general practice center between January 1st 2007 and December 31st 2020 for minimally one year. The first year of subscription was necessary as we defined this as a one year run-in period to assess predictor values such as prescribed medication or assessments of vital parameters. Exclusion criteria were a history of cardiovascular disease prior to baseline, including myocardial infarction, stroke, angina pectoris, peripheral artery disease, heart failure, and transient ischemic attack. Follow-up time started at the end of the one year run-in period, which was on January 1st 2008 or on the first general practice center subscription to the STIZON network after this date. Women were censored at the earliest date of the diagnosis of a major adverse cardiovascular event, death, deregistration with any practice connected to the STIZON network, or last upload of computerised data to the STIZON database (December 31st 2020). Medical ethical approval was not required for the utilization of data in this study.

Outcome definition

The primary outcome of our study was fatal and non-fatal stroke, defined as the presence of an ICD-9, ICD-10 or ICPC code for overall stroke or ischemic or hemorrhagic stroke subtypes specifically (Appendix I).

Traditional cardiovascular factors

Data on the following traditional cardiovascular factors were included for this study: age, smoking (defined as current or former tobacco use), and either an ICD-9, ICD-10 or ICPC diagnosis code or condition-specific ATC medication prescription code for hyperlipidemia, hypertension, and diabetes mellitus (Appendix I). We did not use biomarker measurements such as serum cholesterol, blood pressure and blood glucose because these measurements were missing in the vast majority (> 80%) of women in our research population. The measurement data are likely not missing at random, and in combination with the large extent of missingness, imputation would probably lead to biased imputations.[18] For binary factors such as smoking, in case of absence of the registration of smoking status in the EHR, it was not possible to distinguish between actual or unknown smoking status. Therefore, we considered the absence of the registration of smoking status as the absence of smoking, implying the imputation of zero. Risk factor information was assessed at the start of follow-up, and at the end of the one-year run-in period.

Female-specific factors

The following female-specific factors for stroke were included based on previous literature: migraine, gestational diabetes, preeclampsia, preterm birth (0 vs. ≥ 1),

miscarriage (0 vs. ≥ 1), stillbirth (0 vs. ≥ 1), menstrual irregularity or primary ovarian insufficiency, female infertility (unspecified), hysterectomy in medical history, poor fetal growth or small for gestational age of a women's child, complications during birth (postpartum hemorrhage, intrapartum hemorrhage, umbilical cord complications), hormonal replacement therapy, and combined hormonal contraceptive use.[19,20,21] A female-specific factor was considered present when either an ICD-10, ICD-9 or ICPC diagnosis code, or condition specific ATC medication prescription code was present. The female-specific factors menstrual irregularity and primary ovarian insufficiency were clustered into menstrual irregularity of any cause, since primary ovarian insufficiency is a main cause for menstrual irregularity.[22] The definition of female-specific factors based on these codes can be found in Appendix I.

Psychosocial factors

Based on the literature we selected the following psychosocial factors.[11-14] Socioeconomic status score was derived from the first four postal code digits, using data from the Netherlands Institute for Social Research (SCP) as a standardized measure based on income, education and occupation of the inhabitants.[23] An history of depression or psychotic disorders was defined by either an ICD-10, ICD-9 or ICPC diagnosis code, or ATC code for antidepressant or antipsychotic drug prescriptions.

Statistical analysis

We developed multivariable Cox proportional hazard (PH) regression models for prediction of the risk of stroke. Because previous literature showed significant age-dependent effects of female-specific factors on risk of stroke,[24,25] we stratified all analyses by three 10-year intervals between the ages of 20–49 at baseline (20–29, 30–39, and 40–49 years) to study potential age-dependent effects of female-specific and psychosocial factors. Women from each age interval at baseline could have follow-up extending the 10-year interval, and could therefore potentially contribute to more than one interval. We assessed the potential added value of female-specific factors with respect to the prediction of risk of stroke using a step-wise approach. First, female-specific factors with a prevalence of less than 0.5% in the overall research cohort were excluded. Second, we assessed both the univariate association of each female-specific factor with risk of stroke, and the association between female-specific factors and risk of stroke independent of traditional cardiovascular factors by developing different models with one female-specific factor together with the five traditional cardiovascular factors. For all three age-based strata, we reported both the hazard ratio (HR), adjusted HR (aHR), and 95% confidence interval (CI) of each female-specific factor, and model discrimination and change in model

discrimination that resulted from including each female-specific factor separately. Third, all female-specific and psychosocial factors that occurred in more than 0.5% of the overall research cohort were included in final models per age stratum (Table 2).

We compared model performance using the selection of traditional cardiovascular, female-specific, and psychosocial factors from step three, compared with reference models with traditional cardiovascular factors alone. Model performance was assessed via both model discrimination (C-statistic) and calibration (calibration curve slope, assessed at 10-years of follow-up). Further, we expressed change in C-statistic between reference models and models including female-specific, and psychosocial factors as difference with the reference model relative to the full scale, which follows from the equation below.

$$\frac{C\text{–}statistic\ (new\ model)\ -\ C\text{–}statistic\ (reference\ model)\ -\ 0.5\ (C\text{–}statistic\ base\ value)}{C\text{–}statistic\ (reference\ model)}$$

Performance metrics were internally validated using 100 bootstraps and corrected for optimism using a previously validated method (Harrell's bias correction).[26] We derived empirical confidence intervals by repeating the bootstrap procedure 50 times. We did not take non-cardiovascular death into account as a competing risk because we assessed a cohort of young women at a maximum of 49 years at baseline. In this population, the cumulative incidence of non-cardiovascular death will be very small compared with the entire population, limiting the competing risk effect on the estimation of the risk of stroke. Because our cohort consists of relatively young women, the absolute 10-year risk of stroke will be predominantly under 1%, which is the lower bound of the moderate risk category according to the European Society of Cardiology Prevention guideline for cardiovascular disease.[2] Consequently, no meaningful absolute risk cut-off is available to use for the assessment of model performance using for example the categorical net reclassification index.[27]

To facilitate the interpretation of the absolute 10-year risk predictions of (non-)fatal stroke from our models, we have developed a novel tool based on the previously published cardiovascular risk age tool.[28] The principle of this tool is that i) as a reference, for each age, the absolute risk of stroke is calculated for women without any traditional cardiovascular, female-specific and psychosocial risk factors; ii) For women at a certain age and one or more risk factors, the absolute 10-year risk is compared with the reference to find the corresponding 'stroke risk age', which may be substantially higher than the actual age. We will present two clinical vignettes to illustrate the clinical utility of our stroke risk age tool.

Results

We included 409,026 women, aged 20–49 years, with no history of cardiovascular disease at baseline with a total of 3,990,185 person-years of follow-up. Stroke occurred in 2,751 women over a median of 11 years. The overall incidence rate of stroke was 6.9 (95% CI: 6.6–7.2) per 10,000 person-years, increasing exponentially in the three age groups (Table 1).

Table 1. Incidence rate of stroke per age group

Age group (years at baseline)	Patients (n)	Total follow-up (years)	Events (n)	Incidence rate per 10,000 person years (95% CI)
20–29	128,885	1,145,403	254	2.2 (1.9–2.5)
30–39	136,708	1,340,917	705	5.3 (4.9–5.6)
40–49	143,433	1,503,865	1,792	12 (11–13)
Total	409,026	3,990,185	2,751	6.9 (6.6–7.2)

The prevalence of traditional cardiovascular factors at baseline increased significantly by age group. Hypertension was the most common traditional cardiovascular risk factor (12% in women aged 40–49 years at baseline) and complications during childbirth the most frequent female-specific risk factor (11% in women aged 30–39 years at baseline). Female-specific factors that occurred in less than 0.5% of the entire population were PCOS, gestational diabetes, and history of hysterectomy (Table 2).

The female-specific and psychosocial factors that were independently associated with stroke as traditional cardiovascular factors were, in women aged 20–29 years: irregular menstruation for any cause and complications during childbirth, and hormonal replacement therapy; In women aged 30–39 years: migraine, preeclampsia, complications during childbirth, combined hormonal contraceptive use, socioeconomic status score, and depression; and in women aged 40–49 years: combined hormonal contraceptive use, socioeconomic status score, depression, and psychotic disorder (Table 3).

Model performance of models including only traditional cardiovascular factors was poor to moderate in all age groups: 20–29 years: C-statistic: 0.617 (95% CI: 0.592–0.639); 30–39 years: C-statistic: 0.615 (95% CI: 0.596–0.634); 40–49 years: C-statistic of 0.585 (95% CI: 0.0.573–0.597). The slopes of the calibration curves of the reference models in the three age groups were good: 20–29 years: 0.949 (95% CI: 0.894 - 0.978); 30–39 years: 0.977 (95% CI: 0.952–1.000); 40–49 years: 0.984 (95% CI: 0.962–1.000; Table 4). The addition of female-specific risk factors to the

reference models led to a moderate improvement of model discrimination, especially in the 40–49 year age group (Δ C-statistic: 0.018 compared to reference model, 18.8% difference with the reference model relative to full scale). The addition of psychosocial factors social status score and history of depression further increased the discriminatory performance (Δ C-statistic: 0.019 and 0.029, respectively, compared with reference models, 16.8% and 34.5% difference, respectively, with the reference model compared with the full scale C-statistic, Table 4). The absolute 10-year risks of stroke predicted by the models combining traditional cardiovascular, female-specific and psychosocial factors were generally low, but increased substantially in all age strata (Figure 1).

Figure 2 shows calibration curves of the three models containing traditional cardiovascular, female-specific, and psychosocial risk factors.

Finally, we present two illustrative clinical vignettes based on the prediction models from this study. First, a 33-year-old woman with a history of migraine, who smokes and uses combined hormonal contraceptives, has a mean predicted absolute 10-year risk of stroke of 0.7% (95% CI: 0.4%–1.1%) according to our model. According to our stroke risk age tool, this risk is comparable to that of a 43-year-old woman without any predefined risk factors other than age. Second, a 40-years-old woman with a history of depression and hypertension using combined hormonal contraceptives has a mean predicted absolute 10-year risk of stroke of 1.1% (95% CI: 0.8%–1.4%) in our model, which is similar to the risk of stroke of a 48-year-old woman without any predefined risk factors according to the stroke risk age tool (Figure 3).

Table 2. Baseline characteristics for women in three age groups between 20 and 49 years at baseline with and without stroke

Groups	Baseline characteristic	20–29 years* Stroke (n = 254)	20–29 years* No stroke (n = 128,631)	30–39 years Stroke (n = 705)	30–39 years No stroke (n = 136,003)	40–49 years Stroke (n = 1,792)	40–49 years No stroke (n = 141,641)
	Age, mean (± SD)	25.6 (2.6)	24.6 (2.9)	36.4 (3.0)	35.1 (3.2)	45.5 (3.1)	44.9 (3.1)
Cardiovascular risk factors, *n*	Smoking (ever)	<10 (<3.9)	1345 (1.0)	22 (3.1)	2000 (1.5)	87 (4.9)	3304 (2.3)
	Hyperlipidemia	<10 (<3.9)	346 (0.3)	22 (3.1)	1022 (0.8)	108 (6.0)	3666 (2.6)
	Hypertension	13 (5.1)	3997 (3.1)	73 (10.4)	5893 (4.3)	355 (19.8)	15044 (10.6)
	Diabetes mellitus	<10 (<3.9)	556 (0.4)	15 (2.1)	1176 (0.9)	67 (3.7)	2478 (1.7)
Women-pecific risk factors, *n (%)*	Migraine	<10 (<3.9)	3678 (2.9)	47 (6.7)	5116 (3.8)	106 (5.9)	7316 (5.2)
	Gestational diabetes	<10 (<3.9)	216 (0.2)	<10 (1.4)	734 (0.5)	<10 (0.6)	285 (0.2)
	Preeclampsia	<10 (<3.9)	556 (0.4)	20 (2.8)	1933 (1.4)	<10 (0.6)	645 (0.5)
	Preterm birth ≥ 1	<10 (<3.9)	743 (0.6)	21 (2.9)	2574 (1.9)	10 (0.6)	1214 (0.9)
	Abortion ≥ 1	<10 (<3.9)	2356 (1.8)	32 (4.5)	5617 (4.1)	34 (1.9)	2518 (1.8)
	Menstrual irregularity	12 (4.7)	3182 (2.5)	28 (3.9)	4159 (3.1)	85 (4.7)	5859 (4.1)
	Infertility	<10 (<3.9)	996 (0.8)	11 (1.6)	3459 (2.5)	16 (0.9)	1376 (1.0)
	Hysterectomy	<10 (<3.9)	215 (0.2)	<10 (1.4)	221 (0.2)	<10 (0.6)	239 (0.2)
	Poor fetal growth	<10 (<3.9)	434 (0.3)	<10 (1.4)	1221 (0.9)	10 (0.6)	525 (0.4)
	Complications during birth	22 (8.7)	4858 (3.8)	93 (13.2)	14878 (10.9)	56 (3.1)	5349 (3.8)
	Hormonal replacement therapy	<10 (<3.9)	283 (0.2)	<10 (1.4)	670 (0.5)	33 (1.8)	1658 (1.2)
	Combined hormonal contraceptive use	120 (47.2)	59471 (46.2)	297 (42.1)	46287 (34.0)	606 (33.8)	35950 (25.4)
Psychosocial risk factors	Socioeconomic status score, *mean (± SD)***	0.18 (0.77)	0.19 (0.76)	0.21 (0.77)	0.29 (0.74)	0.24 (0.72)	0.32 (0.68)
	Depression, *n (%)*	19 (7.5)	6056 (4.7)	83 (11.8)	10534 (7.7)	327 (16.3)	15844 (10.2)
	Psychotic disorder, *n (%)*	<10 (<3.9)	1145 (0.9)	<10 (1.4)	1795 (1.3)	57 (3.2)	2189 (1.5)

**Age at baseline*

***Mean socioeconomic status score based on principal component analysis, with higher scores indicating higher socioeconomic status*

Table 3. Univariate association between women-specific risk factors and stroke per age group, and association independent of traditional cardiovascular risk factors

Risk factors		20–29 years		30–39 years		40–49 years	
		HR (95% CI)	aHR* (95% CI)	HR (95% CI)	aHR* (95% CI)	HR (95% CI)	aHR* (95% CI)
Traditional cardiovascular (reference model)	Age	1.13 (1.08–1.18)	NA	1.12 (1.09–1.15)	NA	1.06 (1.04–1.07)	NA
	Hyperlipidemia	6.81 (2.81–16.5)	NA	4.04 (2.64–6.18)	NA	2.40 (1.97–2.91)	NA
	Diabetes mellitus	4.80 (1.98–11.6)	NA	2.54 (1.52–4.23)	NA	2.23 (1.74–2.84)	NA
	Hypertension	1.48 (0.84–2.58)	NA	2.34 (1.83–2.98)	NA	1.99 (1.77–2.24)	NA
	Smoking	2.90 (1.37–6.14)	NA	2.23 (1.46–3.40)	NA	2.12 (1.71–2.64)	NA
Women-specific	Migraine	0.90 (0.42–1.91)	0.79 (0.37–1.69)	1.69 (1.26–2.28)	1.48 (1.10–2.01)	1.11 (0.91–1.35)	0.98 (0.81–1.20)
	Preeclampsia	NA	NA	1.97 (1.26–3.08)	1.83 (1.17–2.85)	1.09 (0.55–2.19)	1.15 (0.57–2.30)
	Preterm birth ≥ 1	0.74 (0.10–5.29)	0.58 (0.08–4.14)	1.54 (0.99–2.40)	1.50 (0.96–2.34)	0.72 (0.39–1.34)	0.79 (0.43–1.48)
	Abortion ≥ 1	1.28 (0.57–2.88)	1.11 (0.49–2.50)	1.06 (0.74–1.51)	1.05 (0.74–1.50)	1.14 (0.81–1.60)	1.26 (0.90–1.78)
	Irregular menstruation	2.14 (1.17–3.91)	1.98 (1.08–3.63)	1.23 (0.83–1.84)	1.14 (0.77–1.71)	1.15 (0.93–1.43)	1.06 (0.85–1.32)
	Infertility	1.58 (0.50–4.92)	1.21 (0.39–3.79)	0.62 (0.34–1.12)	0.61 (0.34–1.10)	1.01 (0.62–1.66)	1.11 (0.68–1.82)
	Complication during birth	2.69 (1.74–4.16)	2.14 (1.37–3.34)	1.29 (1.04–1.61)	1.27 (1.02–1.58)	0.91 (0.70–1.19)	1.00 (0.76–1.30)
	Poor fetal growth	1.33 (0.19–9.48)	1.10 (0.15–7.82)	1.34 (0.67–2.69)	1.30 (0.65–2.60)	1.61 (0.87–3.00)	1.82 (0.98–3.39)
	Hormonal replacement therapy	5.22 (1.67–16.3)	4.48 (1.43–14.1)	0.80 (0.26–2.50)	0.72 (0.23–2.25)	1.49 (1.06–2.10)	1.30 (0.92–1.84)
	Combined hormonal contraceptive use	0.90 (0.70–1.15)	0.92 (0.72–1.18)	1.20 (1.03–1.39)	1.20 (1.03–1.40)	1.37 (1.24–1.51)	1.35 (1.22–1.49)
Psychosocial	Socioeconomic status score	0.93 (0.79–1.09)	0.92 (0.79–1.08)	0.80 (0.73–0.88)	0.80 (0.73–0.88)	0.82 (0.77–0.87)	0.83 (0.78–0.89)
	Depression	1.58 (0.99–2.52)	1.38 (0.86–2.21)	1.51 (1.20–1.90)	1.32 (1.04–1.66)	1.69 (1.49–1.91)	1.52 (1.34–1.72)
	Psychotic disorder	1.40 (0.45–4.38)	1.20 (0.38–3.77)	1.05 (0.54 - 2.03)	0.89 (0.46–1.73)	2.21 (1.70–2.88)	1.96 (1.50–2.55)

**HR = Hazard Ratios; aHR = Hazard Ratios adjusted for age, hyperlipidemia, diabetes mellitus, hypertension and smoking*

Table 4. Performance of female-specific Cox PH models with different risk factor selections across the three age groups

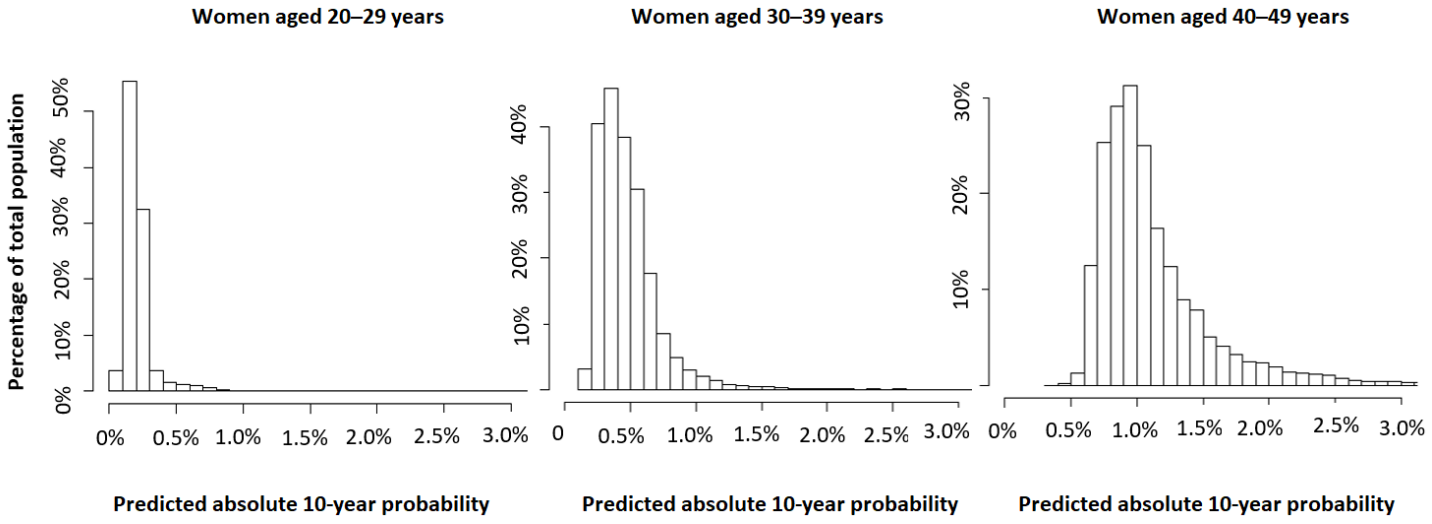
Age range	Risk factor selections	C-statistic (95% CI)	Δ C-statistic*	Calibration curve slope (95% CI)
20–29 years	Traditional cardiovascular	0.616 (0.592–0.639)	ref.	0.949 (0.894–0.978)
	Traditional + female-specific	0.625 (0.590–0.652)	0.009	0.871 (0.801–0.939)
	Traditional + female-specific + psychosocial	0.632 (0.606–0.660)	0.016	0.868 (0.808–0.920)
30–39 years	Traditional cardiovascular	0.613 (0.595–0.630)	ref.	0.977 (0.952–1.000)
	Traditional + female-specific	0.626 (0.604–0.649)	0.013	0.930 (0.905–0.955)
	Traditional + female-specific + psychosocial	0.636 (0.619–0.663)	0.023	0.937 (0.894–0.960)
40–49 years	Traditional cardiovascular	0.584 (0.573–0.597)	ref.	0.984 (0.962–1.000)
	Traditional + female-specific	0.602 (0.592–0.610)	0.018	0.957 (0.941–0.975)
	Traditional + female-specific + psychosocial	0.613 (0.602–0.625)	0.029	0.959 (0.943–0.970)

**Difference between c-statistices of reference models (traditional cardiovascular risk factors) and models including female-specific and psychosocial risk factors*

***Difference between C-statistices expressed as difference with the reference model relative to full scale (C-statistic range of 0.5–1.0)*

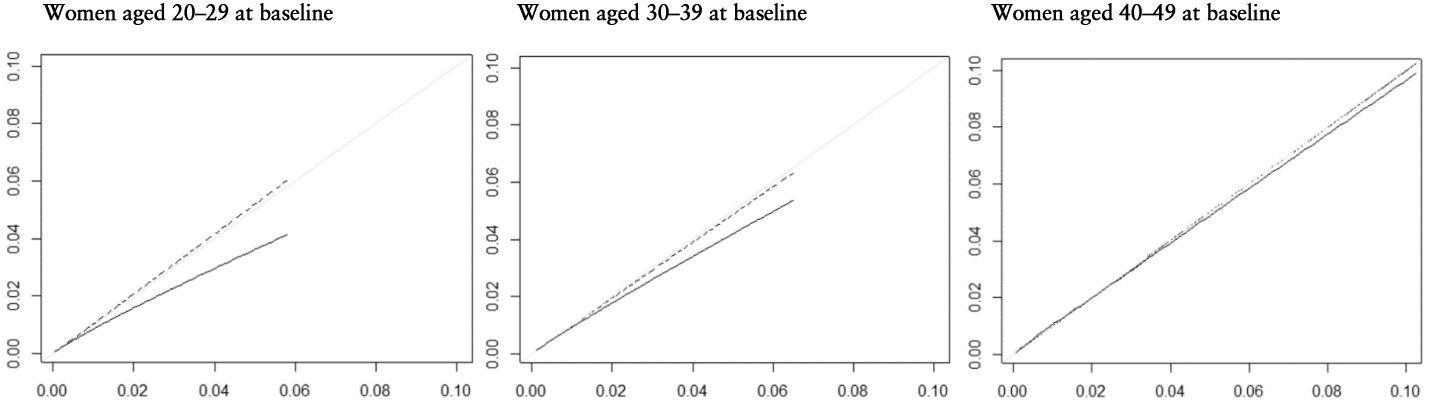
Model performance metrics were optimism-corrected using 100 boorstraps and empirical confidence intervals were derived by repeating the bootstrapping procedure 50 times

Figure 1. Absolute ten-year risk predictions of female-specific prediction models across the three age ranges



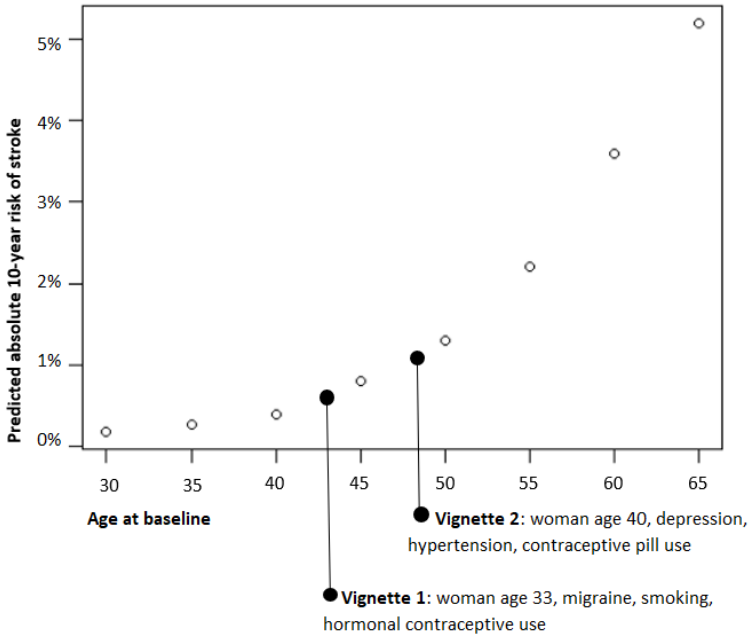
On the X-axis predicted probabilities from optimism-corrected prediction models including traditional cardiovascular, female-specific, and psychosocial risk factors. Predicted probabilities are divided into bins based on increments 0.1%, and on the Y-axis the fraction of the population within each bin is plotted.

Figure 2. Calibration plots of female-specific prediction models across three age ranges



Calibration plots with on the Y-axis the observed, and on the X-axis the predicted probabilities at 10 years of follow-up, for the three models containing traditional cardiovascular, female-specific, and psychosocial risk factors. For each model, two calibration curves are constructed using restricted cubic splines with a Cox proportional hazards model (10 knots): the original model (continuous line) and the optimism-corrected model (dashed line).

Figure 3. Visualization of the stroke risk age tool



This figure shows the graph of predicted absolute ten-year risk of stroke for women without any traditional cardiovascular, female-specific, and psychosocial risk factor levels and age increasing from 30 to 65, and the absolute ten-year risks of women from vignettes 1 and 2 plotted in the same graph.

Discussion

In this study we show (i) that female-specific factors such as migraine, irregular menstruation, complications during childbirth, preeclampsia, hormonal replacement therapy, and combined hormonal contraceptive use, as well as psychosocial risk factors such as social status score and a history of depression or psychotic disorders, are associated with an increased risk of stroke in women aged 20–49 years, (ii) that this association is independent of that caused by traditional cardiovascular risk factors, and (iii) that associations change across the three ten-year age strata. Moreover, addition of these risk factors to prediction models that include only traditional cardiovascular risk factors, substantially increase the predictive performance of models for the prediction of stroke in women aged 20–49 years.

Three studies previously investigated the added value of female-specific risk factors in cardiovascular risk models.[5,6,29] In the Women's Health Initiative Observational Study, pregnancy loss, absence of breastfeeding for ≥ 1 month, and irregular menstruation were independently associated with an increased future risk of cardiovascular events in post-menopausal women.[6] However, adding these factors to the model only modestly improved the c-statistic from 0.726 to 0.730. In a Norwegian study, only preeclampsia remained associated with the risk of cardiovascular events after adjustment for established risk factors (HR: 1.60; 95% CI: 1.16–2.17).[5] The addition of pregnancy complication history to the established prediction model led to small improvements in discrimination (c-statistic difference 0.004, 95% CI 0.002–0.006) and correct reclassification of events (net reclassification improvement 0.02, 95% CI 0.002–0.05). A Swedish study found that low birth weight of a woman's child was associated with cardiovascular events (aHR: 1.68; 95% CI: 1.19–2.37).[29] The addition of a history of hypertensive disorders during pregnancy or low birth weight of the offspring to the traditional cardiovascular risk factors did not meaningfully improve the ten-year prediction of cardiovascular risk in women aged 50 years or older.

Importantly, all of these studies were conducted mainly or exclusively in peri- or postmenopausal women, whereas the stroke risk increasing effect of female-specific risk factors appears to be mainly or only present in young woman. In contrast, our study was conducted in pre-menopausal women and aimed to determine whether female-specific factors had a potential added predictive value for stroke and whether this differed in different age groups. For example, in the study of Kurth et al, [24] migraine only increased the risk of stroke in women aged 45–49 years, but not in older age. In our study, migraine was an independent risk factor in women aged 30–39 years at baseline. However, as the median follow-up time was 11 years, this probably corresponds to a relative risk increase for stroke in the mid-40s age range.

Also for preeclampsia, there is mainly evidence for an increased risk of stroke during the reproductive age (RR: 1.81; 95% CI: 1.45–2.27), which is consistent with our findings in the age group between 30–39 years. However, another study found an increased risk of stroke in women with a history of preeclampsia up to the sixth life decade.[25] This finding contrasts with our study which found no increased risk in women aged 40–49 years. Interestingly, we found a strongly increased risk of stroke in women aged 20–29 who used hormonal replacement therapy. This finding may be confounded by premature ovarian insufficiency, which itself may be underreported in the EHR.[30]

In contrast to these earlier studies, we found a substantial improvement in the discrimination of the stroke prediction models in women aged 30–39 years after adding female-specific and psychosocial factors. This may be explained by a differential effect of female-specific factors on stroke specifically versus general cardiovascular outcomes, the selection of other female-specific factors, the addition of psychosocial factors to our prediction models, or the stratification into three ten-year age groups.

Limitations and strengths

Our study also has limitations. First, there are a number of quality problems with EHR-derived data, in particular the underreporting of clinical conditions.[31,32] For example, the lifetime prevalence of migraine in women is estimated to be around 33%.[33] However, in the Dutch primary care EHR data, on average migraine is only recorded in 2.5% of the general population.[34] In our study, we found an EHR registration for migraine in 4.0% of women younger than 50 years. There are several reasons for the underreporting of migraine. Many patients with migraine do not visit the general practitioner for their migraine[35], and if they do, migraine is probably not always accurately reported in the EHR by the general practitioner.[32] It is probable that patients who do visit the general practitioner have a more severe migraine phenotype, which is more likely to be recorded in the EHR. Because migraine with a high attack frequency has a relatively stronger relation with the risk of ischemic stroke, in our study the association between migraine and stroke could be overestimated.[34] Not only migraine, but also other factors such as smoking (only 3% of women) were underreported in our data. Moreover, although primary care EHR systems have already been widely used since 1990, the quality of the records has increased in recent decades due to improvements in quality control.[35] Therefore, the reporting of female-specific factors related to pregnancy and childbirth may be less accurate in the 40–49 age group than in younger age groups. For the derivation of our prediction models, however, the underreporting of traditional cardiovascular, female-specific and psychosocial factors do not necessarily pose a problem. After all, measurement error (including underreporting) in predictors is unlikely to affect

the generalizability and transportability of our prediction models, if the measurement error is similar in the deployment setting of the models.[36] Second, our reference models included predictors based on the ICPC, ICD-9, ICD-10 or ATC codes for hypertension, hyperlipidemia and diabetes, instead of continuous measurements of blood pressure, cholesterol or serum glucose which are used in most cardiovascular risk prediction models.[36] Not including continuous measurement data in our reference models may have reduced the predictive performance. However, more than 90% of our population lacked measurement data, and the values were probably not missing at random. Therefore, imputation would likely have resulted in biased imputed values.[18] Third, the discriminatory performance of the prediction models in this study is moderate (C-statistics of around 0.61–0.63), but is comparable to prediction models that have been implemented in clinical practice such as CHA_2DS_2-VASc.[37] In addition, because age is by far the most important predictor for the risk of stroke, the restriction of age at baseline to a ten year range also reduces the C-statistic. Further, good model calibration around the absolute risks that are relevant for clinical decisions may be a better indicator for the clinical use of a model compared with discrimination.[38] Fourth, the clinical outcome in our study included both ischemic and hemorrhagic stroke subtypes. Female-specific risk factors may have a differential effect on these two subtypes. In a meta-analysis, migraine had a larger effect on hemorrhagic (aHR: 1.43; 95% CI: 1.03–1.99) than on ischemic stroke (aHR: 1.29; 95% CI: 1.08–1.54.[39] From a clinical utility perspective however, the overall stroke outcome of prediction models may be more practical because in the context of primary prevention no distinction is made between ischemic and hemorrhagic stroke.[2] Fifth, the registration of non-cardiovascular death outside of the hospital in the primary care EHR is known to be relatively incomplete. However, this problem is likely to be limited due to the relatively small fraction of non-cardiovascular deaths in our young population. Sixth, the EHR data on which our study is based do not contain specific information regarding gender. Therefore, we could not discern between cis- and transgender, and gender expansive individuals, and it is unclear whether results can be generalized to transgender and gender expansive individuals

Strengths of our study include the use of the largest dataset to date to study female-specific risk factors in women under 50 and to develop female-specific prediction models. Moreover, in our cohort study, primary care and hospital diagnosis codes were linked. This allowed for a more valid determination of the clinical outcome compared with the use of primary care data alone. Furthermore, by stratifying our population into ten-year age groups, we were able to account for variation in the associations between female-specific risk factors and risk of stroke across the lifespan.

Clinical implications

Although many different prediction models for the risk of cardiovascular events have been developed, female-specific factors or women under 40 years are rarely included.[40] Our study is the first to develop prediction models for stroke risk, including female-specific risk factors specifically in a young population. A challenge in using prediction models for risk of cardiovascular events and stroke in individuals under 50 years is that the predicted absolute ten-year risks are generally very low. In our population these risks were generally lower than 2.5%. The European Society of Cardiology guideline for prevention of cardiovascular disease recommends preventive medication from an absolute ten-year SCORE2 risk of 2.5% and onwards in individuals under 50 years.[2] This, however, does not mean that predicted ten-year risks under 2.5% are irrelevant. The stroke risk age tool developed in this study can help select young women with an absolute risk of stroke that is relatively high due to combinations of female-specific, psychosocial and modifiable cardiovascular risk factors, compared with women without these factors. Currently, a lack of risk awareness is a major factor contributing to the lack of preventive measures and healthy lifestyle choices among women.[41] These women could be proactively advised to eliminate modifiable risk factors early in life to prevent cardiovascular events and other diseases such as dementia.[28] [42,43] Moreover, in younger women, female-specific risk factors often precede the occurrence of traditional cardiovascular risk factors – for example, preeclampsia preceding the occurrence of hypertension.[44] After successful external validation, the stroke risk age tool can be used to counsel women in clinical practice. Moreover, all risk factors used in our models are based solely on medical history present in the primary care EHR. Therefore simple, non-invasive, relatively inexpensive, and even fully automated population stratification procedures can be performed to proactively identify and screen at-risk women. Based on our results, we advise healthcare professionals – and especially general practitioners – to take female-specific and psychosocial factors into account for the estimation of the risk of stroke, and to invest in the quality of registrations of these factors in the EHR. Importantly, it is likely that psychosocial factors 'depression' and 'psychotic disorders' are indicators for social determinants of health, which could practically not have been retrieved from the EHR. Therefore, in the implementation phase of prediction models that utilize these factors, we should invest in education of all end users to prevent any form of stigmatization.

Conclusion

The addition of female-specific and psychosocial risk factors to traditional cardiovascular predictors improves the discriminatory performance of prediction models for women under age 50. Our newly developed stroke risk age tool can help discuss stroke risk in clinical practice.

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15. First-ever cardiovascular event prediction in patients under 50 years using complex data-driven models on routine care data

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Abstract

Background: Prediction models for risk of cardiovascular events generally do not include young adults, and cardiovascular risk factors differ between women and men. Therefore, this study aimed to develop a prediction model for first-ever cardiovascular event risk in men and women aged 30–49, using a large Dutch electronic health record (EHR)-derived primary care population-based cohort and comparing complex data-driven models with Cox regression models.

Methods: We included patients from the Dutch STIZON routine care database. Patients aged 30–49 years without cardiovascular disease, or prescription of statins or thrombocyte aggregation inhibitors prior to baseline were included. Outcome was defined as first-ever cardiovascular event. Our reference models were sex-specific Cox proportional hazards models based on traditional cardiovascular predictors. In addition, we developed Cox elastic net and random survival forests models, and used two other predictor subsets with the 20 or 50 most important predictors from all information available in the EHR, based on the Cox elastic net model regularization coefficients. For all models we assessed the C-index and calibration curve slopes at ten years of follow-up. We stratified our analyses based on the 30–39 and 40–49 years age groups at baseline.

Results: We included 542,141 patients (mean age 39.7 years, 51% women). During follow-up, 10,767 first-ever cardiovascular events occurred (incidence rate: 19.7 [95%CI: 19.3–20.1] per 10,000 person years). Cox elastic net predictor selection resulted in several non-traditional cardiovascular predictors that were ranked as important, including socioeconomic status score and hormonal contraceptive use in women specifically. Discrimination of reference models including traditional cardiovascular predictors for both women and men was moderate (women: C-index: 0.648; 95%CI: 0.645–0.652; men: C-index: 0.661; 95%CI: 0.658–0.664). In women and men, the Cox PH model including 50 most important predictors resulted in an increase in C-index (0.030 in women and 0.012 in men), and a net correct reclassification of 3.7% of the events in women and 1.2% in men compared with the reference model. After stratification of the 30–39 and 40–49 years age groups at baseline, discriminatory performance was attenuated for all Cox PH models in both women and men.

Conclusions: Sex-specific EHR-derived prediction models for first-ever cardiovascular events in the general population under 50 have moderate discriminatory performance. Data-driven predictor selection leads to identification of non-traditional cardiovascular predictors which modestly increase discriminatory performance of models and correct reclassification of events, particularly in women.

Introduction

Cardiovascular events are a leading cause of disability and death worldwide.[1] In the last half century cardiovascular event-related mortality decreased continually. However, opportunities in primary prevention of cardiovascular events are still being missed.[2] Currently in Europe, decisions on preventive interventions in adults without prior cardiovascular disease aged 40–69 years are based on the absolute ten-year risk of cardiovascular events, resulting from the SCORE2 prediction model.[3] Early identification of individuals at high risk of cardiovascular events is beneficial, because atherosclerosis is a chronic process that starts early in life.[4] Therefore, early treatment of risk factors is beneficial, and accurate risk estimates applicable to younger persons are required.[5]

Evidence on sex differences between cardiovascular risk factors is mounting, which pleads for including sex-specific risk factors such as preeclampsia and combined oral contraceptive pill use in prediction models.[6] Derivation of sex-specific models for the prediction of cardiovascular risk in young individuals requires a large sample size. Pooling electronic health record (EHR) data results in large prospective cohorts, offering a great opportunity for the derivation of prediction models.[7] The QRISK3 prediction model for the risk of cardiovascular events is an example of leveraging information from the EHR, and has been successfully externally validated in the general population in the United Kingdom.[8] QRISK3 is a traditional regression model using predictors which are selected based on prior knowledge. However, because EHR-derived cohorts are constituted by both a large sample size and a very high number of potentially relevant predictors, complex data-driven modelling techniques may outperform traditional regression models in predicting the risk of cardiovascular event.[9-11]

This study aimed to develop sex-specific prediction models for first-ever cardiovascular event risk in patients aged 30–49 in a primary care setting, using data from a large Dutch EHR-derived population-based cohort. We assessed whether the data-driven selection of predictors and the use of complex prediction models offer an increase in predictive performance, compared with a Cox regression model using only traditional cardiovascular predictors.

Methods

Data source

The research cohort in this study was derived from the STIZON database. STIZON directly receives data from EHRs of a large number of primary care providers throughout the Netherlands.[12] We only selected patients from general practice centers which were localized in catchment areas of hospitals participating in the

STIZON network. This enabled us to link hospital ICD-9 and ICD-10 diagnoses to primary care data. The STIZON dataset contains ATC medication prescriptions from primary care pharmacies during follow-up time, and ICPC diagnosis codes for clinical entities in principle starting from birth.[13,14] ICD-9 and ICD-10 codes were available for all in-hospital diagnoses that occurred during follow-up. Inclusion criteria were an age of 30–49 at baseline, and subscription to a STIZON general practice center between January 1st 2007 and December 31st 2020 for at least one year, which was required because we defined the one-year as a run-in period. This run-in period was used for averaging the predictor values of laboratory or vital parameter assessments, if multiple of such measurements were present within this period. Exclusion criteria were cardiovascular disease, and use of statins or cardiovascular event-specific thrombocyte aggregation inhibitors at baseline. Follow-up time started at the end of the one year run-in period (January 1st 2008) or on the first general practice center subscription date after January 1st 2008. Patients were censored at the earliest date of the diagnosis of a first-ever fatal or non-fatal cardiovascular event, non-cardiovascular death, deregistration with any practice connected to the STIZON network, or the last upload of computerised data to the STIZON database (December 31st 2020). The ethics review board has provided a statement that this study was not subject to ethics review according to the Medical Research Involving Human Subjects Act (WMO). Because of the sensitive nature of the data collected for this study, data will need to be requested from a third party (STIZON).

Outcome definition

First-ever cardiovascular events were defined using ICD-9, ICD-10 or ICPC codes for fatal and non-fatal acute myocardial infarction and stroke (including ischemic, hemorrhagic and unspecified stroke, Table S1)

Predictors

All predictors which were used for analyses can be found in Table S1. Predictors included demographics, symptoms and diagnoses other than fatal and non-fatal cardiovascular events, and were based on ICPC, ICD-9, and ICD-10 codes, prescribed medication coded according to the ATC classification, laboratory test results performed in primary care, consultation dates and frequency.[13, 14] In addition, the four-digit postal code area data was transformed into a socioeconomic status score based on income, education and occupation of the inhabitants.[15] ICPC, ICD-9, and ICD-10 codes and condition-specific ATC-codes were clustered based on clinical knowledge by two domain experts (HvO & MR) if multiple codes constituted the same clinical entity. An example is the grouping of different types of malignancy diagnoses into an overall malignancy predictor. For computational

purposes, we only selected predictors that occurred in at least 0.1% of the total study population across the entire follow-up time, after clustering. All continuous predictors were standardized before analysis. Baseline information was assessed at the end of the one-year run-in period.

Missing value handling

With respect to missing predictor values, we made a distinction between binary predictors – such as registration of a certain diagnosis or prescription of medication – and continuous predictors such as measurements of laboratory parameters or blood pressure. For all binary predictors, we assumed that the absence of an EHR registration meant the absence of the clinical entity itself, and therefore no imputation was performed. However, for continuous predictors such as vital parameter or laboratory assessments, imputation of missing values was required for inclusion in the prediction models. Because in routine healthcare data the majority of such assessments is only performed in a small subset of the population, the extent of missingness may be large and the underlying mechanism of missingness is likely missing not at random. Because in our dataset for all continuous laboratory or vital parameter assessments missingness exceeded 25%, we chose not to impute the missing values to limit the risk of biased predictor value imputations. We only used binary indicators in the analyses, which indicated whether the assessment had been performed or not.

Predictor selection

We used two methods for the selection of predictors which were used to develop prediction models. First, for the reference models we chose the traditional cardiovascular risk factors age, sex, smoking (ever), and either an ICD-9, ICD-10 or ICPC diagnosis code or condition-specific ATC medication prescription code for hyperlipidemia, hypertension, and diabetes mellitus, based on prior evidence.[16] Since we excluded patients who received statin treatment at baseline, hyperlipidemia was based on diagnosis codes only. Second, we used data-driven predictor selection based on a Cox elastic net model (α of 0.00058 for women, α of 0.00072 for men; L1 to L2 regularization penalty ratio: 0.5) to select the most important 20 and 50 predictors based on the absolute regularized coefficients of a sex-specific Cox elastic net model.

Model development

The three different selections of predictors (traditional cardiovascular risk factors for the reference model, and the 20 and 50 most important predictors based on a Cox elastic net model) were used to develop Cox proportional hazards (PH) models, Cox elastic net models, and random survival forests. Models were developed for

women and men separately. Cox elastic net models and random survival forests are more flexible than Cox PH models, because they include hyperparameters. Hyperparameters of Cox elastic net and random survival forests were optimized using predefined hyperparameter grids (Table S2). To account for overfitting and internally validate our findings, we used a nested validation approach. First, the data was randomly split into a derivation and validation set, of respectively 80% and 20% of the population. Hyperparameter optimization was then performed on the derivation set, using 10-fold cross validation. Overall model performance was assessed using the hold-out validation set. We repeated this process 50 times using bootstrap resampling to assess variability in outcomes and to report empirical 95% confidence intervals. We did not take non-cardiovascular death into account as a competing event, since our population was young and non-cardiovascular mortality was expected to be very low. Model performance was defined by both model discrimination (concordance index or C-index) and calibration (calibration curve slope at ten years of follow-up). We expressed change in C-index between reference and other prediction models as difference relative to the full scale of the C-index, which is from 0.5 to 1. Further, we assessed net reclassification using the categorical net reclassification index (NRI). We chose a 2.5% ten-year absolute risk of first-ever cardiovascular events as threshold for high cardiovascular risk. This is in line with the European Society of Cardiology (ESC) guideline for prevention of CVD in individuals under 50 years, and implies that risk factor treatment should be considered. Our predefined absolute risk threshold of 2.5% is therefore of clinical importance.[17] In addition, we stratified our analyses based on two age groups (30–39 and 40–49 years at baseline). The 30–39 years age group is of particular interest, because the SCORE2 model starts at an age of 40. For all performance metrics we calculated empirical 95% confidence intervals (CI) by fitting a new model in each of the 50 bootstrap samples, and basing the CI on the standard deviation of the distribution of the performance metrics. Python version 3.10 was used for pre-processing and analysis of data. Our study adhered to the TRIPOD (Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis) statement for reporting.[18]

Results

We included 542,141 patients aged 30–49 years without prior CVD or statin use at baseline in this study, of whom 51% were women. During 5,461,316 person years of follow-up, a total of 10,767 first-ever cardiovascular events occurred. This resulted in an incidence rate of 19.7 (19.3–20.1) per 10,000 person years in the total population, 13.6 (13.2–14.0) in women and 26.2 (25.5–26.8) in men. Table 1 shows the baseline characteristics of men and women in the total study population. The average age was 39.7 years (SD ± 5.7). Systolic blood pressure was assessed in 6.6%,

and total serum cholesterol in 2.4% of the total population. We, therefore, discarded continuous measurements and only included indicators of whether tests were performed.

Subsequently, after the data-driven selection of predictors using Cox elastic net models, the 20 most important predictors are shown in Table 2. The 50 most important predictors can be found in Table S3. Substantial differences in predictor importances were observed between women and men. For example, for women two female-specific risk factors (combined oral contraceptive use and intrauterine contraceptive use) are ranked in the top 20. The top 20 most important predictors for women and men, stratified based on the 30–39 and 40–49 years age groups, are shown in Table S4.

Discrimination of Cox PH reference models including traditional cardiovascular predictors for both women and men was moderate (women: C-index: 0.648; 95% CI: 0.645–0.652; men: C-index: 0.661; 95% CI: 0.658–0.664) and calibration was good (calibration curve slope in women: 0.999; 95% CI: 0.998–1.001; and in men: 1.001; 95% CI: 0.998–1.004; Table 3). In women, the Cox PH model including 50 most important predictors resulted in an increase in C-index of 0.030 compared with the reference model (20% difference with the reference model relative to the full scale of the C-index). In men, Cox PH model including 50 most important predictors also resulted in the relatively largest increase in C-index, although to a lesser extent compared with women (0.012 increase in C-index; 7% difference with the reference model relative to the full scale of the C-index). The more flexible modelling approaches (Cox elastic net and random survival forests) did not perform better than the Cox PH models across any of the different predictor subsets (Table S5).

For women and men, the categorical NRI was assessed for the Cox PH model with 50 most important predictors versus the reference Cox PH model. For women, net correct reclassification was for events 3.7% (95% CI: 3.2%–4.2%), and for non-events 0.0% (-0.1%–0.1%); and for men, net correct reclassification for events was 1.2% (0.8%–1.6%), and for non-events was -0.8% (-1.1%–-0.4%). Absolute risks for the Cox PH model with 50 most important predictors is shown for women and men (Figure).

After stratification of the 30–39 and 40–49 years age groups at baseline, discriminatory performance was attenuated in the 30–39 years age group, and further decreased in the 40–49 years age group, for all Cox PH models in both women and men (Table 3).

Table 1. Baseline characteristics for women and men

Baseline characteristics	Women (n = 276,113)		Men (n = 266,028)	
	Cases (n = 3,800)	Controls (n = 272,313)	Cases (n = 6,915)	Controls (n = 259,113)
Demographic features				
Age *(mean +- SD)*	42.4 (5.0)	39.5 (5.7)	42.9 (4.8)	39.6 (5.6)
Socioeconomic status score *(mean ± SD)*	0.23 (0.75)	0.31 (0.71)	0.25 (0.74)	0.30 (0.72)
Follow-up time *(median years ± IQR)*	6.6 (3.8–9.4)	11.0 (8.3–13.0)	6.9 (4.0–9.6)	11.0 (8.0–13.0)
Cardiovascular risk factors, *n (%)*				
Smoking (current)	154 (4.1)	4897 (1.8)	264 (3.8)	5087 (2.0)
Hyperlipidemida	32 (0.8)	761 (0.3)	69 (1.0)	1261 (0.5)
Hypertension	157 (4.1)	3896 (1.4)	168 (2.4)	3339 (1.3)
Diabetes mellitus	43 (1.1)	1163 (0.4)	67 (1.0)	1295 (0.5)
Measurements, *n (%)**				
Systolic blood pressure	485 (12.8)	20823 (7.6)	526 (7.6)	13907 (5.4)
Serum glucose	133 (3.5)	8245 (3.0)	171 (2.5)	4463 (1.7)
Total serum cholesterol	318 (8.4)	13585 (5.0)	468 (6.8)	12150 (4.7)

Cases: patients who suffered a first ever cardiovascular disease event during follow-up; controls: all other patients

**Any laboratory or vital parameter measurement during the one-year run-in period*

Table 2. Top 20 most important predictors for women and men separately

Women (n = 276,113)		Men (n = 266,028)	
Predictor	**Coef.***	**Predictor**	**Coef.***
Age	0.416	Age	0.533
Socioeconomic status score	0.115	Socioeconomic status score	0.101
Combined oral contraceptive use	0.070	Smoking: current	0.069
NSAID use	0.060	NSAID use	0.067
Gastroesophageal reflux medication	0.053	Diabetes mellitus	0.039
Smoking: current	0.052	Practice nurse contact for somatic complaints	0.035
Acetylsalicyc acid use	0.052	RAAS inhibitors	0.033
Comorbidity count	0.049	Psoriasis	0.031
RAAS inhibitors	0.045	Gastroesophageal reflux medication	0.027
Betablockers	0.043	Comorbidity count	0.026
Calcium channel blockers	0.040	Hyperlipidemia	0.019
Blood pressure measured last year	0.032	Epilepsia	0.019
Dermatological complaints	0.031	Calcium channel blockers	0.018
Intrauterine contraceptive use	0.030	Oral anticoagulant drugs	0.016
Hyperlipidemia	0.029	Esophageal disorders	0.014
Antibiotic use	0.028	Allergic rhinitis	0.014
Depression	0.027	Antibiotic use	0.014
HIV/AIDS	0.024	Alcohol use	0.014
Female sex organ complaints and symptoms	0.023	Kidney failure	0.014
Diabetes mellitus	0.023	Male sex organ complaints	0.014

**Absolute, regularized coefficient of Cox elastic net models (women: alpha = 0.00058; men: alpha = 0.00062)*

***Comorbidity count: simple count of chronic conditions per patient, enlisted in Supplementary Table II*

Table 3. Discrimination and calibration of sex-specific prediction models for different predictor subsets, stratified by age groups

		Women (n = 276,113) Performance metrics (95% CI)				Men (n = 266,028) Performance metrics (95% CI)			
Age range	Predictors	C-index	Δ C-stat.*	Δ C-stat.**	Calibration curve slope at 10 years	C-index	Δ C-stat*	Δ C-stat.**	Calibration curve slope at 10 years
30–49	Baseline	0.648 (0.645–0.652)	Ref.	Ref.	0.999 (0.998–1.001)	0.661 (0.658–0.664)	Ref.	Ref.	1.001 (0.998–1.004)
	20	0.674 (0.671–0.677)	0.026	18%	1.000 (0.998–1.003)	0.673 (0.670–0.676)	0.012	7%	1.000 (0.998–1.002)
	50	0.678 (0.675–0.681)	0.03	20%	1.000 (0.997–1.002)	0.673 (0.671–0.675)	0.012	7%	1.001 (0.998–1.004)
30–39	Baseline	0.605 (0.601–0.609)	Ref.	Ref.	1.000 (0.998–1.003)	0.608 (0.604–0.612)	Ref.	Ref.	1.000 (0.998–1.003)
	20	0.651 (0.646–0.654)	0.049	47%	1.000 (0.997–1.003)	0.629 (0.625–0.633)	0.021	19%	1.001 (0.998–1.004)
	50	0.658 (0.654–0.663)	0.053	50%	0.999 (0.998–1.002)	0.629 (0.626–0.633)	0.021	19%	0.999 (0.996–1.002)
40–49	Baseline	0.572 (0.568–0.576)	Ref.	Ref.	0.999 (0.998–1.002)	0.578 (0.574–0.583)	Ref.	Ref.	1.001 (0.998–1.004)
	20	0.619 (0.615–0.623)	0.047	65%	1.000 (0.997–1.003)	0.600 (0.596–0.605)	0.022	28%	1.000 (0.997–1.003)
	50	0.624 (0.619–0.628)	0.052	72%	1.000 (0.997–1.002)	0.601 (0.597–0.605)	0.023	29%	1.001 (0.998–1.004)

Baseline traditional cardiovascular predictors: age, hypertension, antihypertensive medication, diabetes mellitus, hyperlipidemia, with Cox PH model using baseline predictors as reference model

**Difference in C-statistic compared with the reference model; **Difference in C-statistic compared with the reference model relative to full scale*

Discussion

We found that in an EHR-derived population-based cohort of primary care patients aged between 30–49, sex-specific prediction models for first-ever cardiovascular events had moderate discriminatory performance and were well calibrated. Compared with the reference Cox PH models, the Cox PH models based on the 50 most important predictors had better discriminatory performance in both women and men, and were well calibrated. In women the improvement in discrimination was more substantial as compared with men, and the net correct reclassification of events was 3.7%. The more complex modelling methods Cox elastic net and random survival forests did not result in improvements in discrimination or calibration compared with the reference model, regardless of the predictor subset that was chosen. After stratification of the age groups at baseline, we found that discriminatory performance was attenuated in the 30–39 years age group, and further decreased in the 40–49 years age group. This was as expected, because we restricted the range of age, which is the most important predictor for cardiovascular events.

Several previous studies reported on the prediction of cardiovascular events using large EHR-derived datasets and complex data-driven models. One study which used data from the CPRD database (n = 378,256 patients between 30–84 years at baseline) found that a neural network substantially outperformed a reference logistic regression model (C-index: 0.764 versus 0.728), and correctly reclassified 7.6% of events. However, no survival models were used which limits the possibilities for valid clinical implementation. Another study included 423,604 UK Biobank participants, and deployed an automated machine learning pipeline named AutoPrognosis. Compared with a Cox PH reference model which included only traditional cardiovascular predictors, a machine learning ensemble method including all 473 predictors resulted in a C-index of 0.774 versus 0.734 of the reference model, and a net correct reclassification of events of 12.5%. An important difference with our study is that the UK Biobank contained relatively complete information on continuous predictors such as systolic blood pressure and total cholesterol.

In general, improvement in model performance may be due to (i) information gain resulting from including more predictors, or (ii) modelling gain which is the ability of models to capture non-linear associations or interactions among predictors.[19] In our study, the gain of complex (random survival forests) versus simple (Cox PH) models appeared to be limited. Random survival forests performed slightly more poorly compared with Cox regression models, potentially because of random forests methods are prone to overfitting.[20] We do seem to find information gain by including predictors which are ranked as most important according to Cox elastic

net models. This indicates that data-driven predictor selection results in the identification of valuable non-traditional cardiovascular predictors which increase predictive performance, such as socioeconomic statusscore and hormonal contraceptive use in women specifically. Because Cox PH and Cox elastic net models have a similar performance, Cox PH models would be preferred for clinical use since they can be interpreted more easily.[21]

Limitations and strengths

Our study has several limitations. First, EHRs are designed to record data that are routinely collected during the clinical workflow to streamlining patient care, and not for the purpose of research.[22] Despite standardization using universal ICPC, ICD and ATC coding, previous research shows substantial underreporting in clinical diagnosis codes and large variability in inter-practice data quality.[23] Underreporting leads to misclassification in predictors and outcome. Misclassification is not a problem in prediction research if the measurement error is similar in development compared with the deployment setting. Misclassification of the outcome may, however, lead to a biased estimation of absolute risk.[24] Fatal cardiovascular events could only be identified if they occurred in-hospital using ICD-9 or ICD-10 codes. It is possible that in our study incidence of these events has been underestimated. Cardiovascular mortality comprises a quarter of all total CVD events. Prior research shows that the discriminating ability of prediction models did not differ between the fatal and non-fatal cardiovascular events.[25] Further, to optimally exclude patients with a history of cardiovascular events at baseline, we excluded patients with prescriptions of thrombocyte aggregation inhibitors which were specific for cardiovascular events (clopidogrel, dipyridamole, ticagrelor) at baseline. We did not include acetylsalicylic acid in this definition because of its prescription as analgesic in the study period, hence specificity for cardiovascular events was low.[26] In addition, we did not develop lifetime risk models in this cohort of young patients, because of the risk of misclassification in predictors and outcome may aggravate cohort effects. Second, we did not take non-cardiovascular death into account as a competing risk because we assessed a young patient cohort at a maximum of 49 years at baseline. In this population, the cumulative incidence of non-cardiovascular death was very small (0.6%) compared with the entire population, limiting the competing risk effect on the estimation of stroke risk. It should however be noted that registration of mortality in our EHR data is of suboptimal quality. Third, the reference Cox PH model did not include continuous laboratory or vital parameter measurements such as systolic blood pressure and total serum cholesterol, which limits the head to head comparison with commonly used models such as SCORE2.[3] However, such a comparison was not the purpose of this study. In addition, because we use data-driven selection of predictors, we identified predictor representations other than continuous measurements of blood pressure and cholesterol that did not

require imputation. This is an advantage because of the often very high extent of missingness of measurement data in the EHR. Fourth, our study population excluded patients receiving statin at baseline, which limits its use in patients already receiving statin treatment. However, our prediction models are specifically suited to support preventive interventions such as initiation of statin treatment, similar to the QRISK3 study in the United Kingdom, which is also based on EHR data.[8] We did not choose to exclude patients who received antihypertensive but not statin treatment at baseline, since in these patients the clinical decision on the initiation of statin treatment is also relevant and our models could be used for this decision. Fifth, although the continuous NRI is a more sensitive measure to assess model reclassification, we chose the categorical NRI because the 10-year risk threshold of 2.5% represents a clinically relevant threshold.

Strengths of this study includes the very large sample size of a cohort of patients under 50 years at baseline which is to our best knowledge among the largest to date. This offered a unique possibility to study data driven methods for the prediction of cardiovascular events in young patients. Further, all predictors used in our models are directly available in the EHR, which facilitates implementation of the models directly into the EHR. In addition, the linking of primary care and hospital diagnosis codes in the STIZON cohort enables validation of the cardiovascular outcome. Further, the data-driven predictor selection procedure results in that our models leverage predictive information from predictors other than continuous measurements of traditional cardiovascular predictors. Therefore, it is not necessary to impute these continuous measurements, which were missing in the vast majority of patients in our population.

Clinical implications

Our EHR-derived models will not replace traditional models such as SCORE2, but could be used in a two-step population health approach. First, at any given time point our models can automatically identify patient subgroups at increased risk for first-ever cardiovascular events above the absolute ten-year risk cut-off as specified by the ESC prevention guideline. Second, these patients subgroups could be invited to the primary care practice center for further cardiovascular risk assessment including measurement of systolic blood pressure and total- and HDL-cholesterol, after which traditional models such as SCORE2 could be used to estimate individualised risk. A previous modelling study found that such stepped strategy may result in more cost-effective cardiovascular risk management than the current opportunistic screening.[27] The ESC guideline states 2.5% ten-year risk of cardiovascular events as the threshold between moderate and high risk for women and men under 50 years, high risk being an indication for preventive pharmacotherapeutics. Although for patients under 50 years in our cohort absolute

ten-year risks are generally low, our data-driven models can be used to automatically identify patients whose absolute risk reaches the 2.5% risk cut-off. In women, we found that the Cox PH model with 50 most important predictors resulted in a net correct reclassification of events (3.7%) around this risk cut-off compared with the reference model. Although this percentage is low, application on a large scale could lead to sufficient clinical impact to justify the use of a relatively more complex model. After stratification based on the 30–39 and 40–49 year age groups, we found that men and women between the age of 30–39 years at baseline had substantially lower absolute risks of cardiovascular events compared with those aged between 40–49 years. However, since the ESC guideline uses the SCORE2 model which does not include patients under 40 years, the absolute risk threshold of 2.5% likely is too high for individuals between the age of 30–39 years. Therefore, to define meaningful thresholds that can guide preventive therapy, we call for further research into the age group of 30–39 years. The focus may in this context not be pharmacotherapeutic, but rather on lifestyle interventions for prevention of cardiovascular disease. In addition, for the 30–39 years age group lifetime risk estimation may further help in risk communication and interpretation. However, we should first invest in the creation of higher quality longitudinal data sources to derive valid lifetime risk prediction models. In addition, data-driven predictor selection has led to the identification of important non-traditional cardiovascular predictors such as socioeconomic status score and NSAID use. After stratifying for age subgroups, we found differences in the ranking of the 20 predictors that were most important in our prediction models. For example, in both women and men aged 30–39 years at baseline, the relative importance of NSAID use further increased compared with the 40-49 years age group.

Conclusion

Sex-specific EHR-derived prediction models for first-ever cardiovascular events in the general population under 50 have moderate discriminatory performance and are well calibrated. Data-driven predictor selection leads to identification of non-traditional cardiovascular predictors, which modestly increase discriminatory performance of models and correct reclassification of events, mostly in women.

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16. General discussion

In **part I** of this thesis, I conducted aetiological research on sex differences in the pathophysiology and clinical presentation of stroke. In **part II**, the aim was to develop female-specific prediction models of the risk of stroke that can be implemented in clinical workflows.{Steyerberg, 2014 #2435} In the current chapter, I will discuss the overarching challenges addressed in part I and part II. Because the overarching goal of this thesis is to lay the foundation for precision prevention of stroke in women, this chapter seeks to show what future research and policy steps are needed to move from this foundation to large-scale implementation of precision prevention in clinical practice.

Pathophysiology of sex differences in stroke – what should the next steps be?

The modulating effect of age on the risk of stroke

Age is the most important predictor for the risk of cardiovascular events, and substantially modulates the relationship between other traditional cardiovascular factors and cardiovascular risk.[2,3] Much is still unknown about whether – and if so, how – age modulates the effect of female-specific risk factors on the risk of stroke. In women with migraine aged 45–49 years, the risk of ischaemic stroke is substantial (aHR: 5.35, 95% CI: 2.08–13.79) compared to women without migraine, while there appears to be no increased risk in women with migraine older than 65.[4] Also in women with a history of preeclampsia, the increased risk of stroke is evident during reproductive age, although some studies suggest that the risk increase is also present later in life.[5,6]

High-quality data on the associations between female-specific risk factors and stroke in women under 50 years are scarce, which is a recurrent limitation in part I of this thesis. In **chapter 2,** we used DUST study data to evaluate the hypothesis that the association between migraine and stroke is caused by an increased burden of cerebrovascular atherosclerosis in people younger than 50 years. However, this was complicated by the fact that only 86/656 (13%) patients were younger than 50 years. We did, however, see a trend of fewer cerebrovascular calcifications in patients with versus without migraine (aRR: 0.82; 95% CI: 0.64–1.05), which decreases the likelihood that macrovascular atherosclerosis is the main pathophysiology underlying the migraine–stroke relationship. In **chapter 5**, I studied the potential association between migraine and delayed cerebral ischaemia in patients with aSAH. Although in the overall population no association was present, I found a statistically significant interaction ($p = 0.075$, at an alpha of 0.10 for interaction terms) between age and migraine with respect to risk of delayed cerebral ischaemia. This suggested an association between migraine and delayed cerebral ischaemia exclusively in young patients. However, after including additional aSAH

patients in the cohort to perform an analysis in patients under 50 years **(chapter 6)**, we also did not find an association between migraine and the risk of delayed cerebral ischaemia. This contradicts an earlier matched case-control study, which found an odds ratio of 2.68 (95% CI: 0.99–7.29; p-value < 0.05) for the association between delayed cerebral ischaemia and a history of migraine in young women.[7] The point estimate from this case-control study could be an overestimation because it was derived from a small dataset of matched pairs, further illustrating the importance of replicating observational association studies with cohorts of sufficient sample size.[8] In the String-of-Pearls Stroke Study cohort presented in **chapter 9**, only 65 (7%) of the 997 included women with a history of migraine were younger than 50 years. This sample size did not allow for the assessment of multiple associations between traditional cardiovascular risk factors or ischaemic stroke aetiology and migraine. I did, however, demonstrate that female stroke patients with migraine were at increased risk of stroke onset at an age under 50 years (RR: 1.7; 95% CI: 1.3–2.3). Since no sex differences in the occurrence of traditional cardiovascular risk factors were found in women with- versus without migraine, this suggests that mechanisms other than traditional macrovascular atherosclerotic aetiologies play a role in the higher risk of stroke in migraine.[4]

Large, population-based cohorts may help solve questions regarding stroke pathophysiology in women under 50 years. In **chapter 7,** I assessed the potential interaction between combined oral contraceptive use and migraine leading to ischaemic stroke in women aged 18–50 years. In the large EHR-derived population-based STIZON cohort (n = 1,404,681 adult patients), a total of 617 women under 50 years at baseline suffered from stroke during follow-up, which resulted in a sufficient sample size to answer my research question. In **chapter 14**, the STIZON cohort enabled me to assess associations between several female-specific risk factors and ischaemic stroke risk factors in three subcohorts of women aged 20–29, 30–39, and 40–49 years. I found that migraine (aHR: 1.48; 95% CI: 1.1–2.01) and preeclampsia (aHR: 1.83; 95% CI: 1.17–2.85) were only significantly associated with risk of stroke in women aged 30–39 at baseline, while hormonal contraceptive use was associated in both women aged 30–39 (aHR: 1.20; 95% CI: 1.03–1.40) and aged 40–49 (aHR: 1.35; 95% CI: 1.22–1.49). These findings corroborate the hypothesis that the causal relationship between female-specific risk factors and ischaemic stroke is substantially modulated by age.

<u>Data quality regarding exposure to female-specific risk factors – migraine as an example</u>

For aetiological studies on the migraine–stroke association, another frequent limitation is the quality of the data on migraine. Migraine is a clinical diagnosis, and the gold standard is an interview performed by a headache specialist, based on the

International Classification of Headache Disorders criteria.[9] However, such interviews are not structurally performed in routine care, and are not feasible in an acute stroke research setting. Therefore, in **chapters 2, 3, 5, 6, and 9,** history of migraine was assessed using the previously validated five-question Migraine Screener for Stroke (MISS). The MISS has a high positive predictive value for migraine with and without aura combined (0.80; 95% CI: 0.59–0.93), but a poor positive predictive value for migraine with aura (0.38; 95% CI: 0.24–0.53).[10] Consequently, I could not sufficiently discriminate between migraine with and without aura in the aforementioned five studies in **part I** of this thesis. This distinction is important because a systematic review of cohort studies found that migraineurs with aura (aHR 1.56, 95% CI: 1.30–1.87) but not those without aura (aHR 1.11, 95% CI: 0.94–1.31) had an increased risk of stroke.[11] In contrast, one large Danish cohort study that was published later showed a significant association between migraine without aura and ischaemic stroke. However, this study only included migraine patients who were diagnosed in an emergency department, inpatient, or outpatient hospital setting, which may have resulted in a selection of migraine patients that suffer from relatively frequent migraine attacks. A high attack frequency has been associated with a relatively stronger increase in the risk of ischaemic stroke.[12] Further, in our studies using the MISS we cannot exclude the possibility that it is mainly or exclusively the subset of migraine patients with aura that is responsible for the associations found between migraine and radiological characteristics of stroke, or of stroke itself. This could result in an overestimation of the risk of stroke in patients with migraine.

In **chapters 7, 14 and 15**, migraine history was defined based on routine care data, using a combination of primary care and hospital diagnosis codes and medication prescription data for specific antimigraine drugs. **Chapter 14** shows that in the population-based STIZON cohort of women under 50 years (n = 409,026) migraine according to my definition was present in 4% of individuals. This is much lower compared with the results from large population-based migraine studies, which report a one-year prevalence of migraine of around 18–25% in women and 6–8% in men. [13-16] The underreporting of migraine prevalence in routine care data sources may have different causes. One study from 2002 estimated that only two-thirds of migraine patients visit a physician for their headache.[17] If a patient visits the GP and migraine is diagnosed, there still is a substantial probability that the diagnosis is not registered in primary care, since underreporting in the EHR is generally high.[18] A less error-prone source of routine data in the Netherlands is the out-patient pharmacy prescription database which is linked with the STIZON primary care and hospital data.[19] By using medication prescription codes, it is possible to accurately identify the subgroup of migraine patients who use migraine-specific drugs. This subgroup of migraine patients likely has more severe migraine attacks. However, no

conclusive evidence exists that the severity of migraine attacks modulates the risk of ischaemic stroke.[20] Another important drawback of the EHR as data source for definition of migraine is that the distinction between migraine with and without aura is rarely made in clinical practice.

The bias-variance trade-off, and the role of the EHR in aetiological research

For unbiased estimates of associations between female-specific risk factors and stroke, the collection of high quality data on both exposure and outcome is essential. Simultaneously, a sufficient sample size is required, which is challenging because stroke in women under 50 years is rare. In practice, however, the larger the sample size, the poorer the quality of exposure and outcome assessment, generally due to the practical and financial constraints of large-scale data collection. Therefore, most studies – including those in this thesis – suffer from a data quality-quantity trade-off. Statistically speaking, this is the trade-off between bias and variance, and this trade-off is one of the most important factors in choosing the right research design.[21] Because stroke in women under 50 years is rare, a case-control design is relatively efficient. If controls are sampled in an optimal way, a case-control study should result in the same estimation of an exposure–outcome relationship as a cohort study.[22] However, in practice multiple co-occurring sources of bias often limit causal inference from case-control data. A prospective cohort study design could eliminate problems such as recall bias. An example of a traditional prospective cohort study in which the association between female-specific risk factors and stroke is assessed, is the Nurses' Health Study II (115,541 women aged 25–42 years at baseline). However, these large-scale studies are logistically challenging, and the assessments of exposures are limited. In the Nurses' Health Study II, information on migraine aura or migraine frequency were not available, which eliminated the possibility for clinically relevant subanalyses.[23]

In the search for very large, richly phenotyped cohorts, pooled routine health data collections may offer a part of the solution, at a relatively low cost. Therefore, we use the STIZON cohort in **chapters 7 and 13–15**, which has the important advantage that it consists of multiple linked routine data sources including the primary care EHR, hospital ICD-9 and ICD-10 registrations, and outpatient pharmacy data.[90] For female-specific risk factors, the primary care EHR is the primary source of interest. However, a major drawback is that the data entry into the EHR has almost no quality assurance measures, which results in lower quality of outcome and exposure data.[18,24,25] Underreporting of exposures in the EHR is a common problem, which may result in biased estimates of outcome-exposure relationships. At the same time, the confidence interval around such biased estimates may be very small because of the large sample size. It is therefore important to not fall victim to the so-called big data paradox, which has been described as 'the more

the data, the surer we fool ourselves'.[21] Which directions should we take to answer the most urgent aetiological questions on the associations between female-specific risk factors and stroke in women? And which (observational) research strategy offers the most optimal trade-off between bias and variance? There lies a complementary value in both (i) EHR-based cohorts with large sample sizes and ascertainment of a very wide range of exposures but low data quality; and (ii) traditional cohort or case-control studies with a higher quality of ascertainment of outcome and exposures but often with limited sample sizes, depending on the aetiological research question. Therefore, there is a role for EHR-based cohort studies in aetiological research.

Prediction models for the risk of stroke in women – external generalisability, transportability, and the role of causality

The bias-variance trade-off in prediction research

In **chapters 12, 14 and 15**, I used EHR-based cohorts to develop prediction models, for the estimation the risk of cardiovascular events and stroke specifically. In prediction research, the bias-variance trade-off also plays a key role in research methodology, although the concept is applied in a fundamentally different way compared with aetiological research. Bias in prediction does not mean the unbiased estimation of exposure–outcome associations, but constitutes a difference between predicted and observed risks in a target population of interest. Important flaws in EHR-based cohorts – such as measurement error in exposures – may lead to a biased estimation of an exposure–outcome relationship, but do not necessarily lead to biased predictions. That is, if the measurement error of the derivation population is similar to that of the target population.[26] Bias in predicted risks result from limited generalisability or transportability of a prediction model to a new setting, and restricts the clinical usefulness and -safety of a prediction model. Therefore, the careful reporting of discrimination and calibration after internal and external validation is key. The calibration of the model is particularly important for clinical decision making, because a model needs to be well calibrated around the absolute predicted risk that constitutes the decision threshold.[27] In **chapter 12**, I assessed the impact of different choices in data preparation on model discrimination and calibration. This study essentially simtulates external validation scenarios in which a clinical prediction model is derived from EHR data, and then transported to another context in which different data preparation choices are made. The conclusion is that differences in data preparation can have a large impact on model calibration. However, model calibration is not consistently reported in clinical research practice. Of 363 cardiovascular risk models that have been identified up until 2018, for as few as 21% calibration is reported after external validation.[28]

Consequently, the lack of reporting of calibration has previously been described as the Achilles heel of current predictive analytics.[29]

Another decisive factor that relates to the bias-variance trade-off in prediction modelling is overfitting, also known as model optimism. Overfitting means that a model performs well on the study data but predictions are not valid for new subjects.[30] The extent of overfitting can be reduced by increasing the number of events per each predictor included in the prediction model. For linear regression models, a widely accepted rule of thumb is a minimum of 10 events per predictor.[31] However, for complex data-driven models, more than 200 events per variable may be needed to limit overfitting.[32] Because complex data-driven models can be notoriously 'data-hungry', it is important to reduce risk of overfitting as much as possible. Therefore, in **chapter 13,** I presented a modelling pipeline to limit the risk of overfitting. I did this by preventing so-called information leakage between the optimisation of hyperparameters (inner cross-validation loop) and internal validation of the optimised models (outer cross-validation loop).[33] I reused this code for **chapters 14 and 15,** and made it publicly available online (*https://github.com/L-Ramos/MrClean_Machine_Learning*).

The trade-off between model complexity and interpretability

Complex data-driven models have the advantage of capturing non-linear predictor-outcome relationships and high-dimensional interactions among predictors, which could lead to additional explained variance of the outcome but may also result in overfitting.[34] Recently, a systematic review of 71 studies that compared model performance between complex data-driven- and traditional linear regression models based on traditional research cohorts, showed that in the majority of studies there is no additional value of complex data-driven models.[35] In **chapter 13** I, too, did not find an added value of complex data-driven models compared with logistic regression for the prediction of functional outcome in patients after endovascular treatment for an ischaemic stroke. Interestingly, another study which compared complex data-driven models with traditional regression models for prediction of the same outcome in a similar population did find a significantly higher performance for complex data-driven models (C-statistic: 0.86; 95% CI: 0.85–0.86) compared with traditional statistical methods (C-Statistic: 0.79; 95% CI: 0.77–0.81). Of note, in this study multimodal imaging predictors such as CT perfusion parameters were included in complex data-driven models, which may have resulted in a more complex data environment compared with the study in **chapter 13.**[36] Is this difference in discriminatory performance (C-statistifc of 0.86 versus 0.79) clinically relevant, and does it justify the increase in model complexity? To answer this question, discrimination is not the most relevant performance indicator that should be used. Rather, difference in clinical utility of two models needs to be compared,

for example by showing reclassification around the absolute risk that constitutes a relevant threshold for a decision in clinical practice.[27] In **chapter 15**, complex data-driven methods for predictor selection and for prediction of first-ever cardiovascular events in the general population under 50 years were compared with a Cox PH reference model including only traditional cardiovascular predictors. The best performing model was a Cox PH model including most important 50 predictors resulting from a Cox ElasticNet predictor selection procedure, which resulted in a correct reclassification of 3.7% of events around a relevant decision threshold (2.5% absolute 10-year risk of cardiovascular events) compared with the reference model. The benefits of the large scale implementation of this model may justify the increase in model complexity compared with the reference model. Importantly, **chapter 15** shows that the added value of complex data-driven may not arise from the increased flexibility of the model, but of selection of predictors other than those based on prior knowledge.

Importance of aetiological knowledge to support model transportability

The aim of statistical modelling is traditionally distinguished in (i) explanatory analysis, i.e. assessing causal relationships between exposures and outcomes, and (ii) predictive analysis, which aims to accurately predict individual risk on an outcome based on input data.[37] All causal factors are per definition predictors of the outcome, but predictors are not necessarily causally related to the outcome and can also be a proxy for causal factors.[38] Having yellow fingers is an example of such a predictor; highly predictive for the risk of cardiovascular events, but its association with the outcome is confounded by smoking.[39] Causal knowledge of predictor–outcome associations may be important to ensure model transportability. Transportability requires that the prevalence of the outcome, distribution of the predictors and predictor–outcome associations must be conserved.[1] Not meeting these requirements leads to a deterioration in model calibration, called calibration drift.[40,41] Therefore, for the development of prediction models it is preferred to choose predictors that pose a limited risk of calibration drift. In **chapter 15**, I included binary missing indicators of the presence or absence of a vital parameter or laboratory measurement, such as systolic blood pressure or total serum cholesterol. I did this because the measurements themselves are only present in a small proportion of the general population. Because in EHR data the missingness mechanism is often missing not at random, and the imputation of predictor values may lead to biased predictions.[42] The presence of such measurements are a result of GP behaviour and can be informative. However, to use a missing indicator for presence or absence to improve the predictive performance of models can be dangerous, because a change in GP behaviour may affect the predictor–outcome association over time, causing calibration drift. [43,44] An example is the 2019 update of the cardiovascular risk management guideline from the Dutch College of General

Practitioners. In the update it was recommended to start the screening of high blood pressure in women ≥ 45 years with a history of preeclampsia or gestational hypertension.[45] As a result, GP behaviour will likely have changed over the last years, together with the association between presence of a blood pressure measurement and cardiovascular outcomes. A model developed before the update, but applied to patients afterwards, may have suffered from calibration drift. To prevent calibration drift, we should quantify model performance over time, and may need to periodically update prediction models that have been implemented in clinical practice.[46]

Knowledge discovery through data-driven analysis

Identification of novel, strong predictors, or interaction among different predictors of the risk of cardiovascular events may lead to new directions for aetiological research – so-called knowledge discovery. Complex data-driven models can be used to identify strong predictor-outcome associations, and could be the first step to develop causal hypotheses. For example in **chapter 15,** I used sex-specific, EHR-derived Cox elastic net models to rank predictors according to their importance. In this ranking, substantial differences between men and women could be seen, including two female-specific risk factors which were ranked in the top 20 (combined oral contraceptive and intrauterine contraceptive use). Interestingly in men, psoriasis was ranked among the most important predictors. Previous studies indicate a potential causal relationship between psoriasis and cardiovascular disease, potentially because of a systemic inflammatory component of the condition.[47] Epilepsy is another non-traditional cardiovascular predictor that is ranked within the top 20 of most important predictors for men. However, the association between epilepsy and the risk of cardiovascular events may be confounded by health behaviours, which illustrates the need of replication of the exposure–outcome associations in aetiological research.[48]

Implications, and future research and policy steps

Do we need yet another cardiovascular risk prediction model?

A systematic review in 2016 identified 363 models that predict the risk of cardiovascular events, of which 70 (19%) have been externally validated. In general, it is advisable to reuse already validated models, or perhaps tailor them to local settings using recalibration.[28] However, in **chapters 14 and 15** I chose to build new EHR-based prediction models for the risk of cardiovascular events and stroke specifically, because of the following reasons.

First, the SCORE2 model for the estimation of cardiovascular risk in the general population does not include patients under 40 years, and no female-specific

predictors are used. Therefore, in **chapter 14** I derived three prediction models from populations of women aged 20–29, 30–39, and 40–49 years, which included several female-specific and psychosocial factors. These models may help select young women with an absolute risk of stroke that is relatively high compared with women of the same age that have ideal risk factor levels. To this purpose I developed a novel 'stroke risk age' tool. Currently, a lack of risk awareness represents a major restriction on the implementation of preventive measures and healthy lifestyle choices in the female population.[49] Although for adults under 50 absolute risks rarely warrant the prescription of preventive medication according to the ESC guideline[50], the stroke risk age tool may help to identify women who could benefit from lifestyle interventions that target modifiable risk factors.[50,51]

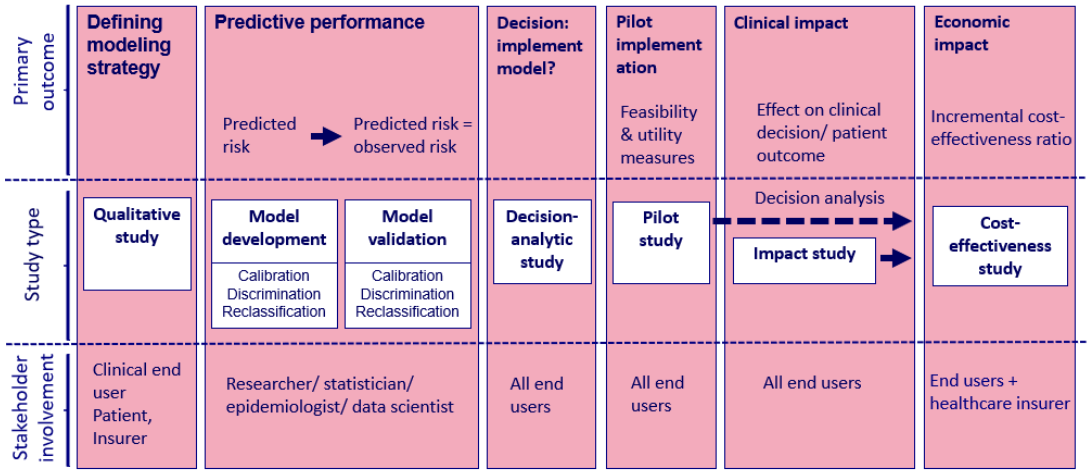
Second, we should distinguish between the use of a prediction model on the individual patient level and on the population level.[52] Regarding the individual patient level, predicted cardiovascular risk may for example be used to prescribe preventive statin therapy, in which case the cost of over- or underestimating risk for such an impactful clinical decisions is high.[18] Choosing a model that has been externally validated multiple times, such as the SCORE2 model, may therefore be the optimal choice.[53] In addition, treatment benefit based on the reduction of lifetime risk of cardiovascular events may be of added value, using for example the LIFE-CVD model.[57] The predictor values that are required as the input for SCORE2 or LIFE-CVD – such as systolic blood pressure or total serum cholesterol – can be collected directly from the patient during a consultation in the primary care practice centre. On the population level, prediction models can be used to generate a distribution of absolute cardiovascular risks of an entire primary care practice population. This enables the GP to proactively invite the patients with the highest risk, who may currently be undertreated.[54] However, for more than 80% of the Dutch adult primary care population no information on important cardiovascular predictors such as systolic blood pressure and total serum cholesterol is present in the EHR in a one-year time period. It is not feasible to invite all of these patients to the primary care practice centre for laboratory or vital parameter assessments. Imputing missing values in the EHR data is also problematic, as was discussed previously. Therefore in **chapter 15,** the sex-specific prediction models for the risk of cardiovascular events used predictive information from predictors other than continuous measurements of traditional cardiovascular predictors, which means there was no need to impute missing values. Instead of using continuous measurements such as systolic blood pressure as predictors, missing indicators were used. Therefore, despite inherent quality issues of EHR data, new EHR-based models can complement existing cardiovascular risk models that are based on traditional cohorts. Both EHR-derived and traditional cohort-derived models could be used in a two-step approach, at the population and individual level. First, the

primary care EHR is automatically screened for women with a potentially high risk of cardiovascular disease or stroke (population level) using models as presented in **chapter 15**. Second, the women identified in step one are invited for a cardiovascular risk (re)assessment at the primary care practice (individual level). During this patient visit, relevant predictor data, such as systolic blood pressure, can be collected to use as input for models that are extensively validated such as the SCORE2 or LIFE-CVD model.[53,55]

Towards the wide-scale implementation of clinical decision support systems

In **chapters 14 and 15**, the development and internal validation of several EHR-based models have been described. However, a long 'valley of death' lies ahead before these model could be implemented in clinical practice on a wide scale. Next steps include external validation,[1] and the assessment of the impact of the model implementation on health outcomes, for example via a clinical (cluster-)randomised trial.[52] Impact assessment is a complex and costly step. Therefore, a decision analytic study may be carried out as step in between model validation and implementation, to investigate the potential impact on health and economic outcomes by modelling the likely effect of its implementation on clinical decision making.[52] When one decides to perform an impact assessment of the model, the impact can only be validly estimated when the prediction model is successfully implemented in clinical practice, often in the form of a clinical decision support system (CDSS).[56] The implementation of a CDSS is a multifaceted challenge, which requires automated integration with the IT infrastructure and therefore clinician's workflow, interpretability of prediction model outputs by the end user, and more.[57]

Figure 4. The roadmap of a clinical prediction from model conception towards the wide-scale implementation in the clinical workflow as a CDSS product



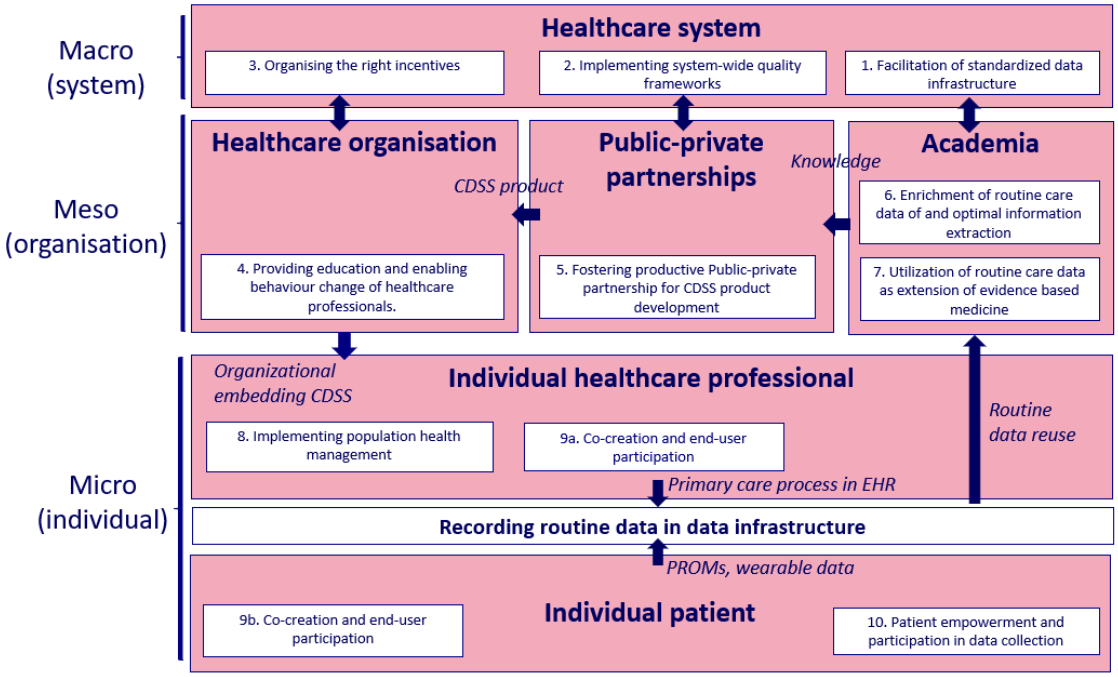
Precision prevention of stroke in women - towards a learning population health management system

The Lancet International Commission on Women and Cardiovascular Disease recently set the goal of significantly reducing the global burden of cardiovascular disease, including stroke, in women by 2030.[58] To improve the clinical outcome of stroke in women, stroke management including timely diagnostics should be improved, including an increase in awareness of differences in stroke symptoms as presented in **chapter 10**. But to make a substantial impact, the focus must shift from treatment to prevention of stroke, because approximately 70% of cardiovascular disease cases and cardiovascular disease-related deaths in the general population can be attributed to modifiable risk factors.[59] The lack of control of modifiable risk factors in the general population is persistent across Europe.[60,61] An additional complicating factor is the growing number of complex multimorbid patients, and the fact that to date little to no attention has been paid to social determinants of health in the prevention of cardiovascular disease.[62]

A paradigm shift in the organisation of healthcare is needed to successfully reduce the burden of cardiovascular disease, and stroke in particular, in women on a population-wide scale. Population health management is a concept that could drive this paradigm shift, since it defines healthcare models along the individuals' continuum of health and well-being, integrating services in health care, prevention, social care and welfare.[63] Tailoring appropriate preventive policies to subgroups in whom care gaps have been identified and the highest potential gains are expected – also known as panel management – enables precision prevention of cardiovascular disease and stroke in particular.[64] The leading analytic framework for population health management identifies population-based risk stratification as one of the essential steps.[63] The EHR-derived risk prediction models presented in **chapters 15** can support population health management in primary care through the automated identification patient subgroups at high risk of cardiovascular events or stroke in particular. An important limitation of the clinical usefulness of EHR-based prediction models is the relatively low quality of the data from which they are derived.[1] Improving EHR data quality may enable us to base more impactful clinical decisions on the predictions of EHR-derived models, such as prescription of preventive medication. A structural improvement of routine data capture is therefore necessary. This, however, will only occur when the right incentives for healthcare organizations and -professionals are in place, which requires reorganization of the healthcare system. In the last decade, the United States National Academy of Medicine proposed the 'learning healthcare system' as the solution. Its principle is that routinely captured health data can be used for feedback for real time improvement of care processes, through personalization of treatment and diagnosis.[65] This requires the alignment of science, informatics and healthcare

organisations (Figure 5). Large scale examples of learning healthcare systems in the United States such as the Veterans Health Administration Quality Enhancement Research Initiative have shown an acceleration of clinical impact from research in a learning healthcare system.[66] A recent example from the Utrecht Cardiovascular Cohort in the Netherlands shows that an investment in the integration of primary care, hospital care services and data registration has led to improved cardiovascular risk factor registration in about one-third of participants.[67] A learning healthcare system could substantially reduce the 'valley of death' between development and implementation of clinical prediction models. Because of the real time availability of EHR data, prediction model performance and predictor- and outcome distributions could be continuously monitored to detect potential calibration drift.[46]

Figure 5. Schematic overview of a learning healthcare system



The learning healthcare system adapted from Lessard et al.[68], combined with the integration levels of the rainbow model (macro, meso, and micro) for population health management.[69] The blue arrows indicate the flow of data and resources that are necessary for the creation and implementation of a CDSS product for precision prevention of stroke in women.

Not only prediction but also causal inference research may benefit from a learning healthcare system. By increasing the quality of the routinely registered outcome and exposure data in the EHR until it approaches that of traditional cohort research, we could assess outcome-exposure relationships while limiting bias and confounding.[70] It may become the most realistic way to investigate the association between (interactions among) women-specific risk factors and stroke in young women, given the enormous resources (including time) that are needed for traditional prospective cohort research. It currently takes 17 years on average before new knowledge generated by randomised controlled trials is implemented in clinical practice.[71] By embedding pragmatic randomised controlled trials in a learning healthcare system we could potentially validate the effectiveness of preventive policies tailored to subgroups of women at high risk of stroke, to further realise precision prevention while curtailing the costs and total implementation time.

Finally, I present ten recommendations on the system-, organisation- and individual integration level according to the learning population health management concept. These steps may help realise precision prevention of stroke in women in the coming decade. (Table)

Table. Ten recommendations for moving towards a learning healthcare system for precision prevention of stroke in women

Integration level	Recommendation
Macro (system) level E.g. ministry of health, financial bodies, healthcare insurers	1. Organising the right incentives in the healthcare system that reward positive health outcomes instead of financing care based on price per volume.
	2. Implementing healthcare system-wide quality frameworks and -standards ensuring the valid development and implementation of prediction models.
	3. Facilitation of a national data infrastructure which facilitates pooling or joint analysis of data sources.
Meso (organisation) level E.g. healthcare, public-private partnerships, academia	4. Providing education and enabling behaviour change of healthcare professionals.
	5. Fostering productive Public-private partnership for building CDSS products that enable population-based use of clinical prediction models.
	6. Enrichment of routine care data of and optimal information extraction from EHR data.
	7. Increased utilisation of routine care data as extension of evidence based medicine.
Micro (professional) level E.g. [data]scientist, healthcare professional	8. Implementing population health management and empanelment in organisations in healthcare and the social domain.
	9. Co-creation with and behavioural change in the patient and healthcare professional as end-users.
Micro (patient) level	10. Patient empowerment and -participation in data collection.

Ad 1. Value-based healthcare – a healthcare delivery model in which health care providers receive payment based on patient health outcomes – is an essential requirement for population health management, because steering for population health outcomes rather than production can reward the integration of services across healthcare, prevention, and social care services, and the organisation of care across the echelons of primary, secondary and tertiary care.[72] To move towards a learning population health management system, it is also important to incentivise the capture and management of high quality routine care data.

Ad 2. As of 2021, in Europe clinical prediction models for diagnosis or prognosis are classified as medical devices according to the Medical Devices Regulation.

However, this legal framework does not require the methodological rigour that is needed for peer-reviewed validation studies. Therefore, it is important to introduce additional complementary methodological frameworks, which has led to a Dutch field standard for the development and implementation of clinical AI prediction models.[73] Next steps include embedding this field norm in the healthcare system to prevent harmful results of invalid prediction model results.

Ad 3. Pooling or joint analysis of different data sources allows for better phenotyping of patient subgroups, which could lead to precision prevention. For example, socioeconomic and ethnicity data are important predictors for cardiovascular risk and can explain sex differences to some extent.[74] However, the highest possible standards for privacy should be maintained. An alternative to pooling data sources is federated learning, which is based on algorithms that 'visit' data sources and are updated by information without the need of actually pooling of data.[75]

Ad 4. The successful implementation of a CDSS requires education of all end users in the correct use of such systems, and in on underlying epidemiological assumptions and the probabilistic nature of the CDSS, and the relevant legal framework.[73] A learning population health system would also require all end users to know the importance of a high quality routine data collection, and accordingly education of end users is needed on data standardisation and other quality standards.

Ad 5. In public-private partnerships, academic knowledge and access to clinical care can be combined with resources from the private sector, increasing the likelihood of successful implementation and upscaling of CDSS in clinical care.[76] A key driver of a successful public-private partnership is a good business model.[77] Both academic and healthcare organisations, and digital health manufacturing companies should therefore invest in joint business cases for CDSS implementations that enable precision prevention in clinical practice.

Ad 6. A major challenge in using EHR data to derive prediction models for women under 50 years is the extent of missing values in predictors such as systolic blood pressure and smoking. Several studies show that coded routine data can be further enriched by extracting clinical concepts from free text entered into the EHR for example during consultations[78], or by extracting ICD-10 diagnosis codes from discharge letters.[79] For example, smoking can be identified from text in the EHR with 88% sensitivity and 92% specificity.[80]

Ad 7. More should be invested in methodological guidelines about how EHR-derived cohorts can complement traditional (registry-based) research cohorts in answering aetiological questions or developing prediction models.[81] In particular, guidelines should further specify how to deal with the limited quality of routine care

data in aetiological or prediction research. The RECORD statement already provides a first step for this.[82] Further development of methodologies for quantitative bias assessment could help us interpret EHR-based model predictions in the context of the many data quality issues.[83]

Ad 8. Healthcare organisations should organise care paths along the continuum of health and well-being of the individual, which implies the optimisation of care across the echelons of primary, secondary and tertiary care. Panel management may also allow for more efficient task differentiation in primary care, which could increase effectiveness of care and help manage workload.[84]

Ad 9. The primary end users of a CDSS for the risk of cardiovascular events or stroke specifically will be healthcare professionals and patients, and a real impact on health outcomes will only be achieved through behaviour change among these end users. Their involvement from the beginning of the developmental process is a critical factor in the success of the implementation of the CDSS.[73] Around 70% of cardiovascular risk is caused by modifiable risk factors.[59] Therefore, improving healthy behaviour in patients who are at high risk of cardiovascular disease is paramount.

Ad 10. Empowerment of patients – helping them to discover the inherent capacity to be responsible for one's own health – may be a critical modifying factor for the effect of the implementation of a CDSS in clinical practice on lifestyle change.[85] It is, however, important to take cultural and (health) literacy barriers to empowerment into account.[86] Patient empowerment may also result in patients taking a more active role in data collection, either via digital questionnaires with patient-reported outcomes, or via wearable data streams such as digital blood pressure monitors.[87]

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17. Summary

In this thesis I aimed to lay the foundation for the precision prevention of stroke in women. In **part I,** the pathophysiology underlying female-specific risk factors for stroke and sex differences in clinical presentation of stroke were discussed. In **part II,** I described how health data – routinely collected in electronic health records (EHR) – can be used to develop prediction models for risk of cardiovascular events and stroke specifically. For this purpose, I used a variety of statistical learning approaches, ranging from traditional regression to complex data driven models.

Summary of part I. Pathophysiology of stroke in women

In **chapter 2,** I tested the hypothesis that increased risk of ischaemic stroke in migraine patients is caused by a higher atherosclerotic burden in the cerebral vasculature, in a cohort (n = 656) derived from the Dutch Acute Stroke Study (DUST). I found no differences in the occurrence of atherosclerosis or stenosis in intracranial in intracranial (51% versus 74%; adjusted risk ratio [aRR]: 0.82; 95% CI: 0.64–1.05) or extracranial vessels (62% versus 79%; aRR: 0.93; 95% CI: 0.77–1.12) between patients with versus without migraine. These findings are important, because they support the hypothesis that the increased risk of ischaemic stroke in migraine patients is, at least for a substantial part, caused by mechanisms other than traditional atherosclerotic processes.

In **chapter 3** the potential association between sex and intra- and extracranial calcifications was shown, using a prospective cohort (n = 1,397) included from the DUST. My results confirm that in the extracranial circulation atherosclerosis is less prevalent in women compared with men (adjusted prevalence ratio [aPR]: 0.86; 95% CI: 0.81–0.92). This suggests that the prevalence of intracranial atherosclerosis is similar in women and in men (aPR: 0.95; 95% CI 0.89–1.01), indicating that the protective effect of oestrogen in women affects the intracranial arteries to a lesser extent compared with the extracranial arteries.

In **chapter 4,** the potential causal role of a history of headache and intrinsic coagulation protein levels in the serum on the risk of ischaemic stroke was investigated. I did this using a case-control study, including 113 women with ischaemic stroke and 598 healthy controls from the RATIO case-control study. My results suggest that a supra-additive effect may exist of the combination of a history of headache and intrinsic coagulation protein antigen levels and -activation on the risk of ischaemic stroke. This effect was most pronounced for kallikrein C1 inhibitor (adjusted odds ratio [aOR] protein alone: 2.2, 95% CI, 1.3–3.8; headache alone: 2.3, 95% CI: 1.3–4.1; in combination: 7.4, 95% CI: 2.9–19) and Factor XI antigen level (aOR protein alone: 1.7, 95% CI: 1.0–2.9; aOR headache alone: 2.0, 95% CI: 1.1–3.7; in combination: 5.2, 95% CI, 2.3–12). Previous research of our group and others gives rise to the hypothesis that sex differences in haemostatic factors can

increase the risk of stroke in women, potentially because of the modulating effect of female sex hormones.[154-156] Interestingly, findings in this chapter may indicate that an interaction exists between intrinsic coagulation factors and headache including migraine. This hypothesis is an alternative to traditional atherosclerotic mechanisms of cerebral infarctions in women.

In **chapters 5.** I assessed the hypothesis that delayed cerebral ischaemia occurs more frequently in aSAH patients with versus without migraine, in a cohort of 582 men and women. The rationale was that the migraine brain is more sensitive to spreading depolarization, which may in a pathological context such as aSAH lead to spreading ischaemia. My results showed that patients with a history of migraine are in general not at increased risk of developing delayed cerebral ischaemia compared with aSAH patients without migraine (adjusted hazards ratio [aHR]: 0.89; 95% CI: 0.56–1.43). However, I could not exclude a possible association in the subgroup of patients under 50 years, because a statistically significant interaction was identified between migraine and age (p-value = 0.075, at an alpha of 0.10 for interaction terms). In addition, younger patients with migraine are presumed to be more sensitive to spreading depolarisation, and, therefore, the association between migraine and delayed cerebral ischaemia may exist exclusively in this subgroup.

Therefore, in **chapter 6**, a follow-up study in patients under 50 years (n = 251) was conducted after additional patients in this age category were included. However, also in this population I did not find an association between a history of migraine and delayed cerebral ischaemia. I, therefore, conclude that a positive history of migraine is not a factor to take into account in treating patients with aSAH at risk of delayed cerebral ischaemia.

In **Chapter 7**, I present the design of the stroke cohort that is part of the Dutch String-of-Pearls Stroke Study cohort, which has resulted in a dataset with uniform and standardised storage of detailed clinical data of all Dutch University Medical Centres. This publication illustrates the potential value of registry-based research, and aids in the comparison between traditional cohort-, registry-, and EHR-based cohorts regarding the research on pathophysiology of stroke in women in this thesis.

In **chapter 8** I offer an overview of the associations between migraine, traditional cardiovascular risk factors and ischaemic stroke aetiologies, stratified for sex. Patients were included from the Dutch String-of-Pearls Stroke Study cohort (n = 2,492). I did not find any associations between a history of migraine and the prevalence of traditional cardiovascular risk factors. I did, however, find that women with a history of migraine had an increased risk of stroke with an onset occurring under 50 years of age, compared with women without migraine. This result confirms previous reports on a younger age at stroke onset in patients with

migraine. Since in these women traditional cardiovascular risk factors did not occur more frequently, results point towards mechanisms other than those mediated by atherosclerosis.

In **chapter 9,** I assessed the joint effect of migraine and combined oral contraceptive (COC) use on the risk of ischaemic stroke. I defined a nested case-control study using data from a population-based cohort, including 617 cases and 6,170 age-matched controls. Next, I integrated these data with previously published evidence using a systematic review and meta-analysis. In my case-control study, I found a significant increase in risk of ischaemic stroke (aOR: 6.83; 95% CI: 3.95–11.7) for both migraine and COC use combined versus neither factor. In migraine patients who both smoked and used COC versus women without migraine who did not smoke or use COC, the risk of stroke was increased substantially (aOR: 30.2; 95% CI: 4.22–610). After the synthesis of these new data with previously published data, I found that in young women with migraine who use COC compared with women without migraine and COC use, the increase in the risk of ischaemic stroke may be supra-additive, also in those using COCs with a low estrogen dose. I also showed that interactions between female-specific (COC use, migraine) and traditional cardiovascular (smoking) may lead to substantially increased risks for ischaemic stroke.

In **chapter 10,** I performed a meta-analysis to investigate whether there are sex differences in the clinical presentation of acute stroke or transient ischaemic attack (TIA). My meta-analysis shows, for the first time, substantial differences in women versus men with respect to both focal symptoms (facial weakness; OR 1.12; 95% CI: 1.02–1.24; based on 6 studies) and non-focal symptoms (for example minor change in level of consciousness or mental status change: OR 1.29, 95% CI 1.08–1.54; based on 13 studies; coma or stupor: OR 1.31; 95% CI: 1.16–1.49; 15 studies). I advise that clinicians should be aware of these differences, because the more frequently occurring non-focal stroke symptoms in women could result in an increased risk of misdiagnosis and possible undertreatment of stroke in women.

In **chapter 11,** the pathophysiology of headache as a presenting symptom of acute ischaemic stroke is investigated in the DUST population (n = 284). I found that headache occurred less frequently in patients with versus patients without atherosclerosis in the extracranial anterior circulation (35% versus 48%; RR 0.72; 95% CI: 0.54–0.97). This finding supports the hypothesis that vascular wall elasticity is a necessary contributing factor for the occurrence of headache during acute ischaemic stroke. I found no sex differences in the incidence of headache in this population. However, because this study helps in better characterising headache as a presenting symptom of ischaemic stroke, the results contribute the recognition

of ischaemic stroke based on non-focal symptoms. As such, this chapter ties in with the conclusions from Chapter 10.

Summary of part II. Prediction of stroke in women

My aim in **chapter 12** was to quantify the impact of different choices regarding the preparation of EHR-derived data on the predictive performance of models. As a case study, we focussed on the estimation of cardiovascular risk in the Dutch ELAN primary care cohort. In total, 89,491 patients were included, of whom 6,736 suffered from a first-ever cardiovascular event during a median follow-up of eight years. The definition of the outcome that was solely based on diagnosis codes resulted in a systematic underestimation of the risk of cardiovascular events (calibration curve intercept: 0.84; 95% CI: 0.83–0.84). Contrarily, complete case analysis led to overestimation of the risk (calibration curve intercept: -0.52; 95% CI: -0.53–-0.51). With these results, I showed that data preparation choices regarding the definition of the outcome or methods to handle missing values can substantially impact model calibration. This in turn may hamper reliable clinical decision support. It is, therefore, essential that methodological choices are transparently presented in prediction research and are motivated to safeguard model transportability from one EHR context to another clinical setting.

In **chapter 13,** I compared the predictive performance between multiple complex data-driven and simple regression models, with respect to functional and reperfusion outcome after ischaemic stroke. For this purpose, I included 1,383 patients of the MR CLEAN Registry cohort, which consists of ischaemic stroke patients who underwent endovascular treatment. I hypothesised that complex data-driven models would outperform logistic regression models with respect to discrimination between good and poor radiological or functional outcome, potentially because of more efficient processing of non-linear relationships and complex interactions between variables. No clinically relevant differences were found between all model, irrespective of the method used for predictor selection. The added value of this chapter is the publication of a fully automated analysis data preparation and model analysis pipeline, with models covering much of the statistical learning spectrum, and a nested validation procedure to account for overfitting. This pipeline was reused in Chapters 14 and 15.

In **chapter 14,** the potential added value of female-specific and psychosocial factors compared with only traditional cardiovascular factors for the prediction of risk of stroke was assessed in the Dutch population-based STIZON cohort of women under 50 years (n = 409,026). Analyses were stratified by three age groups of 20–29, 30–39 and 40–49 years at baseline. Stroke occurred in 2,751 women during a median of 11 years of follow-up. The incidence rate of stroke was 6.9 (6.6–7.2) per 10,000

person years. Adding female-specific and psychosocial risk factors to traditional cardiovascular predictors improved discriminatory performance of prediction models for women under 50 years, notably in 30–39 and 40–49 year age groups (Δ C-statistic: 0.023 and 0.029) compared with the reference models. The 'stroke risk age' tool I developed and presented in this chapter can be used to support risk communication in primary care, which – after validation and implementation research – could lead to motivation for a healthier lifestyle.

In **chapter 15,** the aim was to develop a prediction model for first-ever cardiovascular event risk in primary care patients aged 30–49 years, for which I also used the STIZON cohort. In total, 542,147 patients without cardiovascular disease or prescription of statins prior to baseline were included. Sex-specific EHR-derived prediction models for first-ever cardiovascular events were found to have moderate discriminatory performance and are well calibrated. Data-driven predictor selection leads to identification of non-traditional cardiovascular predictors which increase discriminatory performance of models and correct reclassification of events, mostly in women. In women, the Cox PH model including 50 most important predictors resulted in an increase in C-statistic compared with the reference model of 0.03, and a net correct reclassification of events of 3.7%. These models can be used to identify women within the primary care practice population, whose absolute risk reaches the 2.5% risk cut-off, which could lead to an early initiation of preventive treatment.

18. Nederlandse samenvatting

Achtergrond

Bij een beroerte krijgt een deel van de hersenen geen zuurstof en voeding meer, waardoor schade aan het brein ontstaat. Dit kan komen door de afsluiting van een bloedvat in de hersenen (herseninfarct) of een hersenbloeding. Beroerte is wereldwijd een van de belangrijkste oorzaken van invaliditeit en overlijden. Preventie van beroerte is daarom essentieel. Effectieve preventie dient afgestemd te worden op onder andere de klinische kenmerken, de levensstijl, en de omgeving van het individu. Dit wordt ook wel precisie preventie genoemd. Een belangrijk voorbeeld dat de noodzaak van precisiepreventie illustreert, is het bestaan van geslachtsverschillen in de mechanismen van het ontstaan van beroerte. Tot nu toe zijn vrouwen ondervertegenwoordigd in klinische studies voor beroertes en andere hart- en vaatziekten, terwijl onderzoek in toenemende mate uitwijst dat een geslachtsspecifieke aanpak van (de preventie van) beroerte van belang is. Daarnaast is de klinische uitkomst van een beroerte op lange termijn slechter bij vrouwen dan bij mannen, wat slechts ten dele kan worden verklaard door de langere levensverwachting van vrouwen. Deze slechtere uitkomst bij vrouwen kan verband houden met verschillen tussen vrouwen en mannen in de klinische presentatie van een beroerte, waarbij dit voor vrouwen kan leiden tot onderdiagnose en -behandeling van een beroerte.

Ook in de mechanismen voor het ontstaan van een beroerte bestaan belangrijke geslachtsverschillen. Vrouwen worden enerzijds beschermd voor hart- en vaatziekten – en dus beroerte – door oestrogeen tijdens de vruchtbare levensfase. Anderzijds zijn er risicofactoren die uitsluitend of met name bij vrouwen een rol spelen, zoals migraine, een hoge bloeddruk tijdens de zwangerschap (pre-eclampsie), en het gebruik van de contraceptiepil. Deze vrouwspecifieke risicofactoren komen relatief vaak voor, en zijn dus relevant. Het is echter nog onbekend via welke mechanismen deze factoren het risico op een beroerte verhogen, en daarom is meer onderzoek nodig. Daarnaast worden voor het voorspellen van het risico op een beroerte in de praktijk alleen traditionele risicofactoren (zoals roken, een hoge bloeddruk, een verhoogd gehalte van de bloedvetten) meegenomen, en worden vrouwspecifieke risicofactoren nog niet standaard meegenomen. Hierdoor worden mogelijk vrouwen gemist met een verhoogd risico op een beroerte, waardoor ook de preventieve behandelingen niet op tijd worden gestart.

Vrouwspecifieke risicofactoren spelen met name bij vrouwen van vruchtbare leeftijd een rol; een groep waarin het risico op een beroerte over het algemeen laag is. Daarom is een grote steekproefomvang nodig om mechanismen van deze factoren te onderzoeken. De komst van zogenoemde ‘big data’ bronnen in de gezondheidszorg kan hiervoor een oplossing zijn. Dit zijn bijvoorbeeld databases die bestaan uit gegevens uit elektronische patiëntendossiers (EPDs) van miljoenen

Nederlandse patiënten, die verzameld zijn tijdens routine zorgprocessen. Dergelijke grote hoeveelheden patiëntengegevens zijn doorgaans niet realistisch in traditioneel wetenschappelijk onderzoek. De vraag blijft echter of de kwaliteit van de gegevens voldoende is om wetenschappelijke conclusies op te baseren. EPDs zijn immers niet ontworpen voor onderzoek, maar ter ondersteuning van de klinische workflow, doorgaans binnen een beperkt tijdsbestek. Daarnaast kunnen in deze 'big data' omgevingen meer geavanceerde analysemethoden nodig zijn om alle nuttige informatie te extraheren. Methodologieën binnen het domein van de kunstmatige intelligentie (AI), machine learning in het bijzonder, worden algemeen beschouwd als een mogelijke oplossing voor dit probleem. Machine learning wordt ook wel gedefinieerd als: 'het proces waarbij computers de manier waarop ze taken uitvoeren veranderen door te leren van nieuwe gegevens, zonder dat een mens nodig is om instructies te geven in de vorm van een programma'. In de praktijk is er echter geen goed onderscheid te maken tussen machine learning en 'traditionele' statistische modellen. Daarom gebruik ik in mijn onderzoek het meer pragmatische onderscheid tussen complexe data-gedreven, en eenvoudige mens-gestuurde modellen.

In dit proefschrift heb ik getracht de basis te leggen voor de precisiepreventie van beroerte bij vrouwen. In **deel I** werden de pathofysiologie die ten grondslag ligt aan vrouwspecifieke risicofactoren voor beroerte, en geslachtsverschillen in de klinische presentatie van beroerte besproken. In **deel II** beschreef ik hoe gezondheidsgegevens uit het EPD kunnen worden gebruikt om voorspellingsmodellen te ontwikkelen voor het risico op een myocardinfarct of beroerte. Dit liet ik zien aan de hand van een verscheidenheid aan statistische modellen, variërend van traditionele regressie tot complexe data-gedreven modellen.

Deel I: Pathofysiologie van beroerte bij vrouwen

Migraine, met name met aura, verhoogt het risico op beroerte met name bij vrouwen in vruchtbare leeftijd. Er is echter nog onbekend via welke mechanismen. In **hoofdstuk 2** testte ik de hypothese dat dit verhoogde risico veroorzaakt werd door een verhoogde mate van aderverkalking (atherosclerose) in de hersenvaten van migrainepatiënten, bij 656 beroertepatiënten uit het Nederlandse DUST cohort. Ik vond echter geen verschil tussen mate van atherosclerose in patiënten met en patiënten zonder migraine, waaruit ik concludeerde dat er waarschijnlijk een ander mechanisme dan atherosclerose ten grondslag ligt aan het verhoogde risico op beroerte in migrainepatiënten. Vervolgens werd in **hoofdstuk 3** de mogelijke associatie onderzocht tussen geslacht, en verkalking in de slagaderen in de hals en in het brein. Hierbij maakte ik gebruik van een prospectief cohort van 1,397 patiënten uit de DUST. Mijn resultaten bevestigden dat in de halsslagaders atherosclerose minder vaak voorkomt bij vrouwen dan bij mannen, en lieten zien dat de prevalentie van atherosclerose van de slagaders in het brein bij vrouwen en

bij mannen ongeveer gelijk is. Deze laatste bevinding wijst erop dat ofwel het beschermende effect van oestrogeen bij vrouwen beperkt invloed heeft op de slagaders in het brein, ofwel dat het effect van traditionele vasculaire risicofactoren bij vrouwen anders is in de halsslagaders versus de slagaders in het brein.

Dit roept de vraag op wat dan wel het mechanisme is dat ervoor zorgt dat patiënten (en met name vrouwen) met migraine vaker een beroerte krijgen. Karakteristieken van bloedstolling zijn uit eerder onderzoek aangewezen als potentiële oorzaak. In **hoofdstuk 4** onderzocht ik de mogelijke associatie tussen een voorgeschiedenis van hoofdpijn en intrinsieke stollingseiwitgehalten in het serum met het risico op een herseninfarct onderzocht in de RATIO studie (113 vrouwen met een herseninfarct en 598 gezonde controles,). Omdat migraine niet direct uitgevraagd was bij de patiënten, gebruikten we hoofdpijn als surrogaat. Mijn resultaten suggereren dat er een supra-additief effect is van de combinatie van een voorgeschiedenis van hoofdpijn en intrinsieke stollingseiwit-antigeenniveaus en -activering op het risico van een herseninfarct. Dit wil zeggen dat het uiteindelijke risico op beroerte van deze stollingseiwitten en hoofdpijn samen hoger was dan te verwachten was van het effect van deze factoren afzonderlijk. Interessant is dat de bevindingen in dit hoofdstuk kunnen betekenen dat er een interactie bestaat tussen intrinsieke stollingsfactoren en hoofdpijn, inclusief migraine. Deze hypothese is een alternatief voor traditionele atherosclerotische mechanismen onderliggend aan herseninfarcten bij vrouwen.

Een ander fenomeen dat mogelijk ten grondslag ligt aan de relatie tussen migraine en beroerte is 'spreading depolarisation'. Dit zijn zich langzaam verspreidende ontladingen van hersencellen, die tevens de migraine aura's in ongeveer een derde van de patiënten met migraine veroorzaken. Een hypothese is dat deze ontladingen in het geval van bepaalde hersenaandoeningen – zoals een type hersenbloeding genaamd aneurysmale subarachnoïdale bloedingen (aSAB) – kunnen leiden tot sterfte van hersenweefsel door zuurstoftekort (secundaire ischaemie). Migrainepatiënten lijken gevoeliger te zijn voor spreading depolarisation. Daarom onderzocht ik in **hoofdstuk 5** in een cohort van 582 mannen en vrouwen of patiënten met een voorgeschiedenis van migraine vaker secundaire ischaemie kregen in vergelijking met patiënten zonder migraine. Mijn resultaten toonden deze relatie niet aan. Echter kon ik een mogelijke associatie in de subgroep van patiënten jonger dan 50 jaar niet uitsluiten, omdat een statistisch verband werd gevonden tussen migraine en leeftijd. Daarnaast wordt vanuit proefdieronderzoek verondersteld dat het brein van migrainepatiënten vooral op jonge leeftijd gevoeliger is voor spreading depolarisation. Daarom werd in **hoofdstuk 6** een vervolgstudie uitgevoerd waarbij het cohort uit hoofdstuk 5 werd uitgebreid met patiënten jonger dan 50 jaar tot een totaal aantal van 251. Echter vond ik ook in deze populatie geen associatie tussen een voorgeschiedenis van migraine en secundaire ischemie. Ik concludeer dus dat

migraine geen factor is om rekening mee te houden bij de behandeling van patiënten met aSAH met een verhoogd risico op secundaire ischemie.

In de wetenschappelijke literatuur is meermaals gevonden dat in patiënten met migraine mogelijk andere traditionele risicofactoren voor beroerte vaker voorkomen. Om dit te kunnen onderzoeken presenteerde ik in **hoofdstuk 7** de methodologische opzet van het beroerte cohort (het zogenaamde Parelsnoer beroertecohort) dat deel uitmaakt van het Nederlandse Parelsnoer initiatief. Dit is een dataset met uniforme en gestandaardiseerde opslag van gedetailleerde klinische gegevens van alle Nederlandse Universitair Medische Centra. Deze publicatie illustreert de potentiële waarde van onderzoek gebaseerd op patiëntenregistraties. In **hoofdstuk 8** gebruikte ik dit Parelsnoer beroertecohort met in totaal 2,492 mannen en vrouwen om een overzicht te krijgen van de associaties tussen migraine en traditionele risicofactoren voor beroerte en de etiologie van herseninfarcten, gestratificeerd voor geslacht. Een voorgeschiedenis van migraine was niet geassocieerd met geslachtsverschillen in de prevalentie van traditionele cardiovasculaire risicofactoren. Wel werd bevestigd dat vrouwen met migraine een verhoogd risico hadden op een beroerte op jonge leeftijd (jonger dan 50 jaar), in vergelijking met vrouwen zonder migraine. Aangezien bij deze vrouwen traditionele cardiovasculaire risicofactoren niet vaker voorkwamen in mijn studie, wijzen de resultaten erop dat mogelijk andere mechanismen dan atherosclerotische processen een rol spelen in het ontslaan van beroerten in deze groep mensen.

Een ander belangrijk vraagstuk is of het veilig is om de contraceptiepil voor te schrijven aan vrouwen met migraine, omdat uit eerder onderzoek blijkt dat deze twee risicofactoren voor een herseninfarct elkaar mogelijk kunnen versterken. In **hoofdstuk 9** bestudeerde ik dit gecombineerde effect in een groep van 617 vrouwen met een herseninfarct onder de 50 jaar, die waren geïncludeerd vanuit het op het EPD-gebaseerde STIZON cohort. Deze vrouwen werden vergeleken met 6,170 vrouwen die op dezelfde leeftijd geen herseninfarct kregen. Ik vond dat de combinatie van migraine en het gebruik van de contraceptiepil gebruik het risico op een herseninfarct sterker verhoogde dan kon worden verwacht van deze afzonderlijke risicofactoren bij elkaar opgeteld. Dit zou kunnen duiden op een biologische interactie is tussen beide factoren. Indien vrouwen met migraine die de contraceptiepil gebruikten ook rookten, werd het risico op een herseninfarct nog verder verhoogd. Daarom raden we sterk af om contraceptiepillen voor te schrijven in migrainepatiënten die roken, zowel in het geval van migraine met en zonder aura.

In **hoofdstuk 10** onderzocht ik potentiële geslachtsverschillen in de symptomen van een beroerte, door het systematisch analyseren van de gegevens uit eerdere publicaties op dit onderwerp (meta-analyse). Deze meta-analyse is de eerste die significante verschillen laat zien tussen vrouwen en mannen, waarbij vrouwen vaker

zogenoemde niet-focale symptomen (niet duidelijk passend bij een probleem op één specifieke plek in het brein) hebben zoals verandering in het bewustzijnsniveau. Ik adviseer dat clinici zich bewust worden van deze verschillen, omdat de vaker voorkomende niet-focale beroerte symptomen bij vrouwen mogelijk kunnen leiden tot een verhoogd risico op een verkeerde diagnose, en daarop volgende onderbehandeling van beroerte bij vrouwen.

In **hoofdstuk 11** ging ik verder in op hoofdpijn als symptoom van het herseninfarct, en onderzocht ik mogelijke mechanismen die hieraan ten grondslag liggen in 284 mannen en vrouwen vanuit de DUST populatie. Ik vond dat hoofdpijn minder vaak voorkwam bij patiënten met, dan bij patiënten zonder atherosclerose in de extracraniële voorste circulatie. Deze bevinding ondersteunt de hypothese dat vaatwandelasticiteit een noodzakelijke bijdragende factor is voor het optreden van hoofdpijn tijdens een herseninfarct. Ik vond geen geslachtsverschillen in de mate van optreden van hoofdpijn in deze populatie. Echter, omdat deze studie helpt in het beter karakteriseren van hoofdpijn als presenterend symptoom van een herseninfarct, dragen resultaten bij aan het beter herkennen van herseninfarcten aan de hand van niet-focale symptomen. Als zodanig sluit dit hoofdstuk aan op de conclusies uit hoofdstuk 10.

Deel II: het voorspellen van beroerte bij vrouwen

Dit deel van mijn proefschrift had als doel om voorspelmodellen te ontwikkelen voor het risico op beroerte bij vrouwen, en om benodigde methodologie te ontwikkelen voor dergelijke voorspelmodellen. In **hoofdstuk 12** onderzocht ik de impact van het maken van methodologische beslissingen over het voorbereiden van grote hoeveelheden data uit het EPD van huisartsen, bijvoorbeeld rondom metingen die ontbraken in een deel van de populatie maar wel nodig waren voor een voorspelling van het risico op beroerte. Voor dit onderzoek gebruikte ik gegevens van 89,491 patiënten uit het Nederlandse ELAN eerstelijns zorg cohort. Ik vond dat wanneer andere keuzes in data voorbereiding werden gemaakt voor het ontwikkelen van modellen vergeleken met de testomgeving (het valideren), de kwaliteit van de modellen substantieel achteruit kan gaan. Het is dus erg belangrijk dat voor voorspelmodellen die in de praktijk gebruikt worden goed wordt aangegeven hoe keuzes zijn gemaakt in voorbereiding van data, omdat de nieuwe data uit de klinische praktijk op dezelfde manier moet worden aangeboden aan het model.

Vervolgens onderzocht ik in **hoofdstuk 13** de meerwaarde van complexe, data-gedreven analysemethoden in vergelijking met traditionele (logistische regressie) modellen om de klinische uitkomst drie maanden na een endovasculaire behandeling voor een herseninfarct te voorspellen. Dit deed ik in 1,383 patiënten uit het MR CLEAN Registry cohort. De hypothese was dat er in deze data eventuele complexe

relaties tussen variabelen in deze data bestaan, waardoor complexe data-gedreven methoden mogelijk beter presteren. Dit bleek echter niet het geval te zijn, hetgeen mogelijk te wijten is aan het gebrek van relaties tussen factoren in deze data, die dermate complex zijn dat ze ook complexere analysemethoden rechtvaardigen. De toegevoegde waarde van dit hoofdstuk is de validatie en publicatie van een volledig geautomatiseerde analyse data voorbereidings- en modelanalyse pijplijn, met een groot aantal modellen variërend van complex data-gedreven tot traditionele regressie. Deze pijplijn werd hergebruikt in hoofdstukken 14 en 15.

In **hoofdstuk 14** ontwikkelde ik voorspelmodellen voor het risico op beroerte in vrouwen, in drie leeftijdsgroepen van 20–29, 30–39 en 40–49 jaar. De data die gebruikt werden waren afkomstig van 409,026 vrouwen uit het op het EPD-gebaseerde STIZON cohort. Een beroerte deed zich voor bij 2,751 vrouwen. Ik onderzocht de meerwaarde van vrouwspecifieke en psychosociale risicofactoren versus alleen traditionele cardiovasculaire factoren in voorspelmodellen door de prestaties van de modellen met deze verschillende samenstellingen van factoren te vergelijken. Ik vond dat het toevoegen van factoren als migraine, pre-eclampsie, gebruik van de contraceptiepil, sociaaleconomische status de modelprestaties licht verbeterden, met name in de leeftijdsgroepen van 30–39 en 40–49 jaar. Middels een zogenoemde 'beroerte leeftijd' instrument kan risicocommunicatie met jonge vrouwen met een verhoogd risico op beroerte mogelijk ondersteund worden. De modellen moeten echter eerst gevalideerd worden in een andere databron.

In **hoofdstuk 15** was het doel om een voorspellingsmodel te ontwikkelen voor het risico op een eerste myocardinfarct of beroerte voor patiënten in de eerstelijns gezondheidszorg, met een leeftijd van 30–49 jaar. Hiervoor maakte ik wederom gebruik van het STIZON cohort. In totaal werden 542,147 patiënten geïncludeerd zonder cardiovasculaire ziekte of statine gebruik bij baseline. Geslachtsspecifieke voorspellingsmodellen gebaseerd op data uit het EPD voor eerste myocardinfarct of beroerte bleken een matig tot redelijk te presteren. Wanneer factoren uit de EPD data werden geselecteerd met complexe, data-gedreven methoden, vond ik dat er meerdere niet-traditionele factoren naar boven kwamen, waardoor de modellen met deze factoren beter voorspelden dan modellen die alleen op traditionele factoren waren gebaseerd. Deze modellen kunnen worden gebruikt om vrouwen binnen de praktijkpopulatie van de eerstelijns gezondheidszorg te identificeren die een extra verhoogd risico op beroerte hebben. Dit kan vervolgens weer leiden tot een vroegtijdige start van een preventieve behandeling.

Wat zijn de implicaties van dit onderzoek, en hoe nu verder?

Mijn onderzoek naar de mechanismen onderliggend aan de relatie tussen vrouwspecifieke risicofactoren en beroerte, in het bijzonder de relatie tussen migraine en herseninfarcten, laten zien dat leeftijd een grote invloed heeft op deze relaties. Vooral bij vrouwen in de vruchtbare levensfase lijken vrouwspecifieke risicofactoren een rol van belang te spelen. Het gaat in dit onderzoek naar mechanismen primair over een verhoging van het relatieve risico op een beroerte, wat wil zeggen dat het risico van vrouwen met bepaalde (combinaties van) vrouwspecifieke factoren verhoogd is vergeleken met vrouwen zonder deze factoren. Belangrijk om te beseffen is dat het absolute risico in deze leeftijdscategorie laag is; dat wil zeggen de kans dat vrouwen überhaupt een beroerte krijgen. Echter heeft een beroerte op jonge leeftijd mogelijk nog grotere gevolgen op de kwaliteit van leven. Daarnaast kan het effect van de aanwezigheid van meerdere vrouwspecifieke factoren en bijvoorbeeld traditionele factoren tegelijk leiden tot verhoging van het absolute risico in deze jonge patiënten. Dit zou bijvoorbeeld zo kunnen zijn in het geval van vrouwen met migraine met aura die roken en de contraceptiepil gebruiken.

Uiteindelijk is het van belang dat de kennis over mechanismen van het ontstaan van beroerte bij vrouwen wordt omgezet in strategieën voor preventie. In de literatuur is al een groot aantal (meer dan 350) modellen voor cardiovasculaire ziekten – waaronder beroerte – te vinden. Waarom ontwikkel ik dan nieuwe modellen in dit proefschrift? De modellen in hoofdstukken 14 en 15 zijn de eerste van hun soort die zich specifiek richten op het risico van beroerte in vrouwen onder de 50 jaar, en in het bijzonder ook onder de 40 jaar, terwijl de huidige richtlijnen doorgaans gemaakt zijn voor volwassenen vanaf 40 jaar. Juist in deze jongere vrouwen vonden we een relatief grote impact van vrouwspecifieke factoren op het risico van een beroerte. Echter is er nog een lange weg te gaan om deze modellen daadwerkelijk te implementeren in de praktijk, zoals het toetsen van deze modellen op nieuwe datasets, en het voldoen aan de huidige wet- en regelgeving voor een veilige toepassing.

Het ontwikkelen en implementeren van voorspelmodellen voor vroegherkenning van risico op beroerte is niet genoeg. Er is een paradigmaverschuiving in de organisatie van de gezondheidszorg nodig, waarbij de aandacht wordt verlegd van behandeling naar preventie van beroerte. Ongeveer 70% van de gevallen van hart- en vaatziekten in de algemene bevolking kan worden toegeschreven aan risicofactoren waar de patiënt zelf invloed op heeft. 'Population health management' is een concept dat deze paradigmaverschuiving zou kunnen faciliteren, door zorg als continuüm te definiëren van specialist, huisarts, en thuissituatie van de patiënt, waarbij diensten op het gebied van gezondheidszorg, preventie, sociale zorg en welzijn worden geïntegreerd. Voor population health management is het nodig om

subpopulaties te definiëren aan de hand van risico of zorgvraag, bijvoorbeeld door het toepassen van de modellen die ik heb gepresenteerd in **hoofdstuk 15**. Omdat modellen zijn gebaseerd op het EPD, kunnen ze ook automatisch worden geïntegreerd in het EPD om overzichten van patiënten te genereren, waarna proactief preventieve zorg op maat kan worden aangeboden. Echter is de kwaliteit van gegevens uit het EPD momenteel nog een beperking voor de bruikbaarheid van deze gegevens in de praktijk. Een structurele verbetering van de routinematige gegevensvastlegging is daarom noodzakelijk. Dit zal echter alleen gebeuren wanneer de juiste prikkels voor zorgorganisaties en -professionals aanwezig zijn. In een 'lerend gezondheidssysteem' kunnen gegevens uit het EPD worden gebruikt voor een continue verbetering van zorgprocessen, en het personaliseren van behandeling en diagnose. De toepassing van population health management in een lerend gezondheidssysteem stelt ons in staat om binnen 10 jaar de precisiepreventie van beroerte voor vrouwen mogelijk te maken, en via een soortgelijke aanpak het verbeteren van de preventie van beroerte voor de hele populatie.

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Appendices to all chapters

The appendices to all chapters in this thesis can be found on:
https://bit.ly/thesis_vanos_appendices.

Curriculum Vitae

Hendrikus (Hine) van Os was born on July 12th 1992 in Nieuwkoop, the Netherlands. He attended the Groene Hart Lyceum secondary school in Alphen aan den Rijn, of which the last two years he also participated in the Pre-University College of Leiden University. In 2010, he continued at Leiden University, studying astrophysics. After one year, he switched to a Bachelor's degree in medicine at the Leiden University Medical Center (LUMC), which he combined with an extracurricular programme at the department of Clinical Epidemiology, and a pre-Master's degree in biomedical sciences. In 2012, the MD-PhD programme at the LUMC allowed him to start his research at the department of Neurology, under supervision of prof. dr. M. J. H. Wermer and prof. dr. M. D. Ferrari. During these first years, Hendrikus also graduated cum laude from his classical piano studies at the Royal Conservatory in The Hague. Hendrikus visited the Charité in Berlin, Germany, multiple times in 2015 and 2016 for the study on headache and intrinsic coagulation parameters using the RATIO cohort data, for which he was supervised by dr. B. S. Siegerink. In the summer of 2016 he also visited the Yang Ming Hospital in Taipei, Taiwan, for a study on MRI data of white matter hyperintensities from migraine patients under supervision of prof. S. J. Wang. After finishing his Masters of medicine in 2017, Hendrikus was selected for the MD-PhD grant, which funded the first two years of his PhD program. Under supervision of prof. dr. M. J. H. Wermer, he laid the groundwork for the Hacking Women's Stroke study, for which he later received a Dekker Junior Researcher Grant from the Dutch Heart Foundation in 2020. Also in that year, Hendrikus was awarded the Innovation Grant from the Dutch Heart Foundation after a four-month crowdfunding campaign, during which he collected a total of € 67.000 for the development and implementation of prediction models for stroke. In 2021 he received the ZonMw Gender & Prevention grant for epidemiological research on female-specific risk factors in routine data.

During his PhD research, Hendrikus followed several epidemiology oriented courses to attain his degree in Epidemiologist B after he receives his PhD. From 2020 until now, he also combined his PhD research with the role of general manager at the National eHealth Living Lab (NeLL), under the guidance of prof. dr. N. H. Chavannes. NeLL is part of Public Health and Primary Care department at the LUMC, and its mission is to build future-proof healthcare models through the scientific validation, implementation and upscaling of digital health tools and infrastructures. During his role of general manager, Hendrikus has coordinated multiple consortia including healthcare insurers, software companies, data- and behavioral scientists, doctors, and patients; multidisciplinary collaborations that are urgently needed to realise precision prevention of stroke in women in our healthcare system.

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