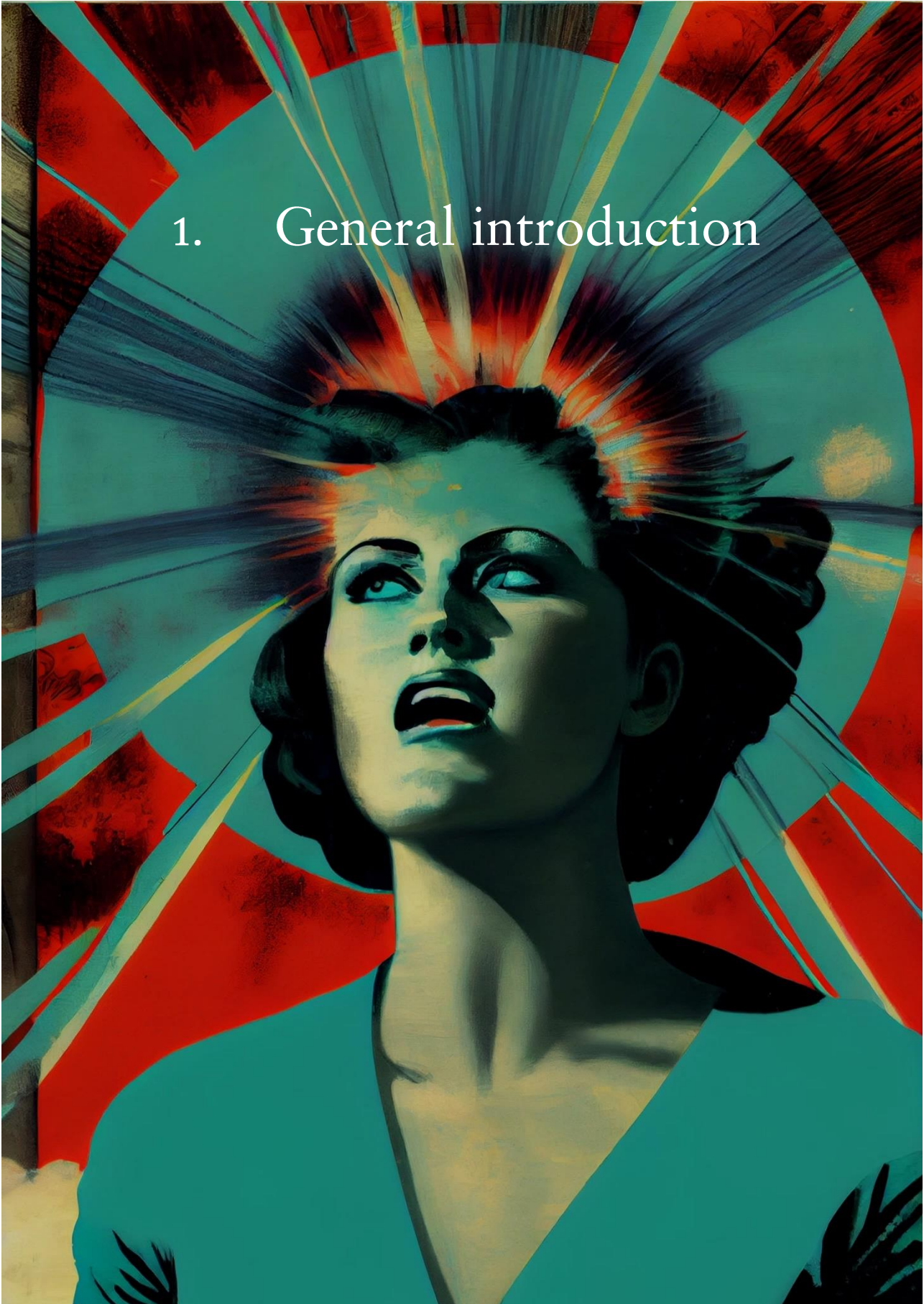
Hacking stroke in women: towards aetiology-driven precision prevention

Os, H.J.A. van

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]

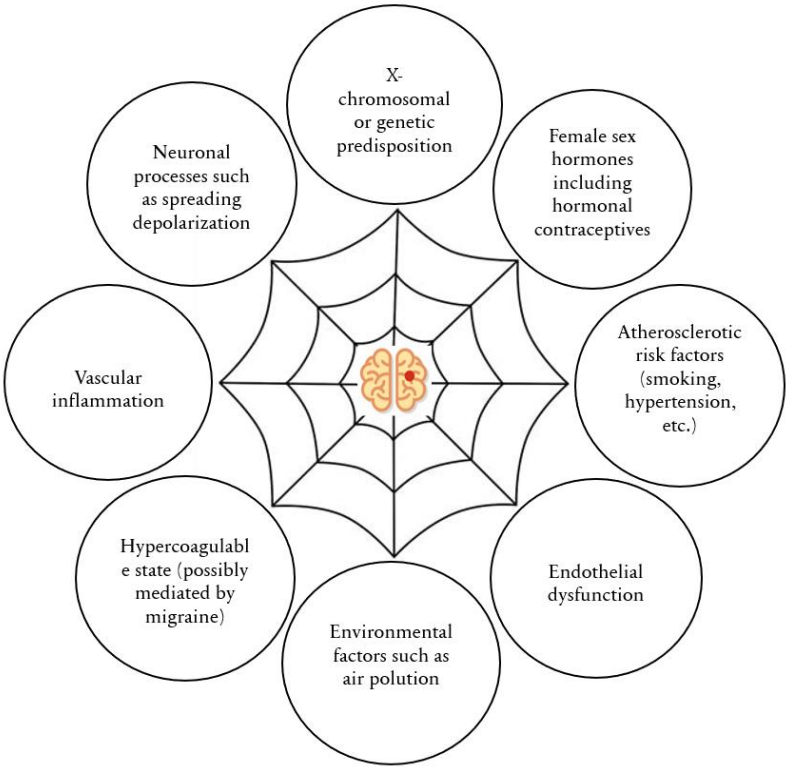
Haemorrhagic stroke represents around 15% of all strokes, and is subdivided into intracerebral and subarachnoid haemorrhage (SAH). Intracerebral haemorrhage is caused by bleeding into the brain tissue, and in case of SAH bleeding occurs into the subarachnoid space around the brain. SAH accounts for approximately 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

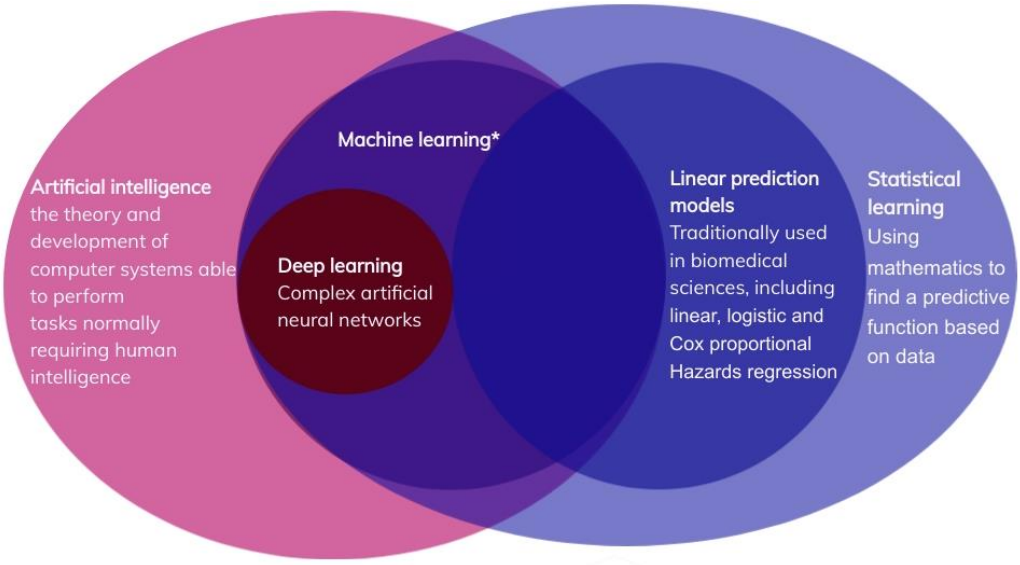
information can be retrieved among the enormous quantities of routine care data. After all, EHRs are not designed for research but to support the clinical workflow, generally within a limited timeframe. Therefore, besides the three 'V's of volume, variety and velocity, a fourth and perhaps most important '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

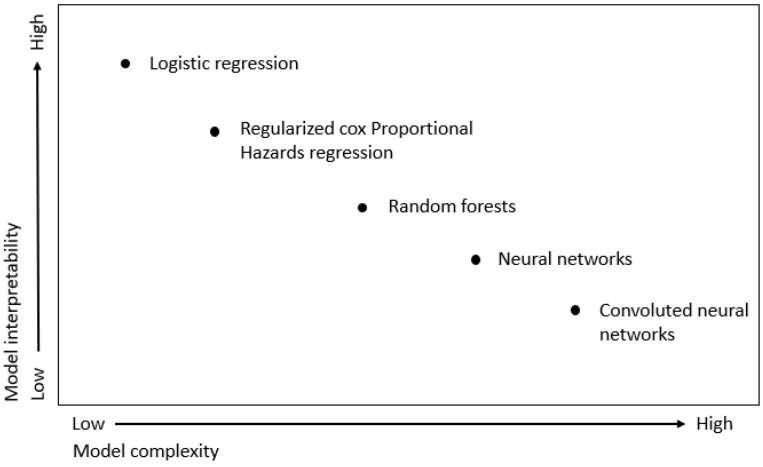
is also called deep learning, and has specific applications such as the direct analysis of raw image data. The machine learning subgroup of statistical models is less well demarcated.[75] I will therefore not use the term machine learning in this thesis, as it underpins a false dichotomy between machine 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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