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Delirium in Ischemic Stroke and Biological Sex Differences within: A Reproducible Research Using Bayesian Methodology from the Heidelberg Rekanalisation Therapy Registry (1998—2022)

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Table of contents

Chapter 1

Chapter 2

Introduction

Stroke is a significant, global challenge, because it is one of the top causes of death and disability worldwide. The World Health Organization (WHO) states that stroke accounts for about 11% of all global deaths. It is the second leading cause of death in non-communicable diseases and the third leading cause of death overall in 2024 (after ischemic heart disease and COVID-19 (Feigin et al. 2021; Feigin et al. 2024).

According to the Global Burden of Disease (GBD) study from 2024 there were 11.9 million new stroke cases, with 52.6% occurring in men and 47.4% in women. The prevalence of stroke showed a similar pattern, with 51.0% of cases in men and 49.0% in women. Stroke-related deaths were slightly higher in men, accounting for 52.1%, compared to 47.9% in women. Additionally, men contributed 55.0% of stroke-related disability-adjusted life years (DALYs), while women accounted for 45.0% (Feigin et al. 2024). Stroke leads to long-term disability with severe physical, cognitive, and emotional impairments. The impact of stroke extends beyond the individual but affects whole families, communities, and healthcare systems. The economic burden includes direct costs for medications and hospitalizations but also indirect costs such as lost productivity and sourcing of long-term care (Feigin et al. 2017; Vos et al. 2020). In high-income countries, for example, in the European Union, the economic burden of stroke is estimated to be €60 billion annually (Luengo-Fernandez et al. 2024).

Ischemia accounts for 62% of all incidence strokes, intracerebral haemorrhage for 28% of cases, and subarachnoid haemorrhage for 10% of cases worldwide (Krishnamurthi et al. 2013).

2.1 Short History of Stroke

Historically, "apoplexy" and "brain softening" were used to describe many conditions now recognized as strokes. Johann Jakob Wepfer (1650-1695) was the first to draw an association between apoplexy and cerebral haemorrhage. (Wepfer, J.J. Observationes Anatomicae, ex Cadaveribus Eorum, quos Sustulit Apoplexia, cum Exercitatione de eius Loco Affecto; Joh Caspari Suteri: Schaffhausen, Switzerland, 1658.) In 1847, Rudolf Virchow (1821–1902) made decisive arguments confirming the vascular theory of softening by introducing the concepts of thrombosis and embolism (Virchow, R. Über die akute Entzündung der Artérien. Arch. Für Pathol. Anat. Und Physiol. Und Für Klin. Med. (Virchow Arch.) 1847, 1, 272–378.):

> "These clots never originate in the local circulation but are torn off at a distance and carried along in the blood stream as far as they can go" *(Rudolf Virchow)*

Early Knowledge and Anatomical Findings

Understanding brain anatomy, particularly the arteries, has improved immensely over the centuries. Initially, anatomical diagrams of the brain lacked detail regarding blood vessels, leaving a gap for a long time. The discovery and study of brain arteries may be divided into two eras: the first focused on observing the major arteries along the brain's base, while the second concentrated on studying the branching patterns in detail through techniques like intra-arterial injection. Charles Foix (1882–1927) - the first modern vascular neurologist - made significant contributions by translating anatomical knowledge into practical clinical applications (Caplan 1990).

Stroke Concept, Pathophysiology, Stroke Imaging

The 19th century introduced concepts like cerebral ischemia and infarction, now understood as the most common forms of stroke. During this period, systematic research into the pathophysiology of cerebrovascular diseases (CVD) laid the foundation for modern neurology.

Imaging has been pivotal in the evolution of stroke treatment - a significant breakthroughs occurred only in the 20th century when computed tomography (CT) and magnetic resonance imaging (MRI) were established. These advancements have revolutionized the diagnosis and treatment of strokes effectively by quickly identifying large vessel occlusions salvaging the ischemic penumbra—a critical area

around the core of an ischemic stroke (Astrup et al. 1981).

Stroke Units and Trials

Before 1950, a clinical management was barely existing. It was Charles Miller Fisher (1913–2012) who challenged old beliefs and newly described transient ischaemic attacks (Fisher 2001). Implementing specialized stroke units (Drouin et al. 2023) in hospitals that are dedicated solely to stroke patients further evolved the clinical management of stroke. The first stroke unit was described in the 1950s, and subsequent studies throughout the 20th century demonstrated that organized stroke care significantly reduces mortality and improves outcomes. In 1957, the first clinical trial started investigating anticoagulant therapy in strokes. The development of stroke registries has also contributed to improving care quality by providing feedback on clinical practices through the collected data.

2.2 Definitions

In the present study, the term "sex" as it pertains to ischemic stroke shall be construed as a truncated form of biological sex. The present study recognizes the existence of a spectrum of biological sex. The concept of gender encompasses various social constructs such as gender identity, expression, roles, and stereotypes, which are attributed to individuals who identify as female, male, or gender diverse. Although sex and gender are not binary, the majority of data collection in trials and cohorts has been binary in nature, using the two terms interchangeably. Therefore, due to the retrospective nature of data collection, the simplified categories of "women/men" or "female/male" are employed.

2.3 Definition of ischemic stroke

The word *apoplexy* was already in use by Hippocrates about 400 BC and ascribed mainly to a nontraumatic brain injury. (Hippocrates. The Genuine Works of Hippocrates: Translated From the Greek With a Preliminary Discourse and Annotations by Francis Adams. Adams, trans-ed.Baltimore, MD: Williams & Wilkins; 1939.) In "Physico-Medical Essay Concerning the Late Frequencies of Apoplexies," Willian Cole very likely described the word stroke the first time. (Cole W. A Physico-Medical Essay Concerning the Late Frequency of Apoplexies Together With a General Method of Their Prevention and Cure: In a Letter to a Physician. Oxford, United Kingdom; The

Theater; 1869. Reprinted by: New York, NY: Classics of Neurology & Neurosurgery Library; 1995.) (Cole 1693)

Today a modern, updated definition is followed: Sacco and coworkers defined infarction of the "central nervous system (CNS) or spinal cord, or retinal cell death attributable to ischemia, based on 1. pathological, imaging, or other objective evidence of cerebral, spinal cord, or retinal focal ischemic injury in a defined vascular distribution; or 2. clinical evidence of cerebral, spinal cord, or retinal focal ischemic injury based on symptoms persisting 24 hours or until death, and other etiologies excluded." (Sacco et al. 2013)

Ischemic stroke is further defined as "episode of neurological dysfunction caused by focal cerebral, spinal, or retinal infarction." and silent infarction of the CNS as "imaging or neuropathological evidence of CNS infarction, without a history of acute neurological dysfunction attributable to the lesion."

2.4 Importance of studying sex differences in ischemic stroke

Investigating ischemic stroke with an emphasis on the differential attainment of biological sex is essential for enhancing our understanding of the disease. It ultimately leads to more effective, individualized therapies for both sexes. Sexual dimorphism in brain structure and function, hormonal states, and underlying genetics might influence the risk for stroke, the course of the disease, and its recuperation (Szadvári et al. 2023). By looking at these differences, researchers may be able to find risk factors and protective mechanisms that are unique to each sex. This could lead to new ideas for targeted therapies that are made to meet the needs of each sex.

When analyzing sex as a biological variable, it is imperative to examine differences using adequate scientific methodologies. Their absence may result in misunderstanding of findings, exaggeration of sex differecunces, or concealment of sex-specific effects when data from males and females are simply aggregated. Out of 147 papers from many scientific fields, Garcia-Sifuentes and Maney discovered that researchers often failed to statistically assess whether the treatment response varied across sexes. To circumvent these difficulties, it is essential that researchers examine interactions between sex and other factors, instead of only comparing outcomes within each sex (Garcia-Sifuentes and Maney 2021).

2.5 Translational links between age and the (patho)physiological basis of sex differences within the neurovascular unit

2.6 Age, Neurovascular Unit and Sex

The neurovascular unit - introduced by del Zoppo in 2006 - describes the concept focuses not only on the neuron itself, but rather holistically on the complex of neurons and the supplying (micro)vessels aside from astrocytes, other glial cells, and resident inflammatory cells (Del Zoppo 2006). Translational research on the neurovascular unit (NVU) has shown significant sex variations in the response to ischemic stroke (Tang et al. 2022).

In *premenopausal* women, estrogen and progesterone exert neuroprotective effects by regulating the elements of the NVU. Estrogen increases neuronal survival, facilitates vasodilation, diminishes excitotoxicity, and preserves blood-brain barrier integrity. Death of neurons is minimized, astrocyte activation is limited, and cerebral perfusion is enhanced, hypothesizing better stroke outcomes for women compared to men of equivalent age.

On the other hand, *postmenopausal* women have reduced (protective) hormones, which may increase vulnerability to stroke and worse results compared to age-matched males (Lang and McCullough 2008). The aging process modifies hormonal equilibrium and immunological reactions, weakening neuroprotective systems and perhaps making hormone replacement therapy less effective or even harmful. Moreover, genetic and epigenetic factors—such as variations in X chromosome gene expression and histone modifications—contribute to sex-specific responses to stroke. These elements affect neuronal apoptotic mechanisms, immune cell activation, and vascular functionality within the neurovascular unit (Tang et al. 2022).

2.7 Epidemiology of ischemic stroke

Descriptive epidemiology in women and men

The incidence and prevalence of ischemic stroke differ between men and women [Petrea et al. (2009)](Fukuda et al. 2009).

Historically, men have been found to have a higher overall incidence of stroke (Petrea et al. 2009), but women tend to have higher stroke

incidence above 85 years of age, lower at all other ages, and a higher lifetime risk of stroke at all ages.

young women have poorer outcomes than men after stroke [Reeves et al. (2008)](Persky et al. 2010)

In the female population, stroke is more frequently observed as the initial presentation of cardiovascular disease, while in males, coronary heart disease is a more prevalent occurrence (Leening et al. 2014).

2.8 Geographic and ethnic variations

The increase in cardiovascular risk factors observed from 1990 to 2010 suggests a worldwide epidemiological shift, although it conceals significant regional variations (Bennett et al. 2014). Hypertension, tobacco consumption, alcohol consumption, and a high body mass index were essential risk factors across North and South America, Europe, and Asia-Pacific. Conversely, being underweight during childhood, exposure to household air pollution from solid fuels, suboptimal breastfeeding practices, and iron deficiency were found to be primary contributors to disease burden in most African regions (Yusuf et al. 2020).

Ethnic variations contribute as well to the observed sex differences in stroke. For example, African American individuals in the United States are more susceptible to stroke than their non-Hispanic white counterparts. A further disparity in stroke risk exists between African American men and women, with the former having a 1.5-fold higher risk. Similarly, non-Hispanic white men have a 1.3-fold higher risk of stroke compared to non-Hispanic white women. [Howard et al. (2019)](Graham 2015)

2.9 Temporal trends

Two studies are presented, one concerning stroke incidences and one concerning stroke management differences in temporal trends.

Research from the The Greater Cincinnati/Northern Kentucky Stroke Study (GCNKSS) indicated that both sexes experienced notable reductions in the overall incidence of stroke and ischemic stroke from 1993/1994 to 2015. In women, the incidence of IS declined from 202 per 100,000 in 1993/1994 to 151 per 100,000 in 2015 ($P<0.05$). In men, it decreased from 254 to 182 per 100,000 ($P<0.05$). In age-specific analyses, the incidence among individuals aged 65–84

showed a significant decrease in both sexes. In the 20–44 age group, stroke incidence remained stable among women, while it significantly increased among men, rising from 15 to 31 per 100,000 ($P<0.05$). In the age group of 85 and older, there was a significant decrease in incidence among men, whereas no such decrease was observed in women. In 2015, the 30-day case fatality rates indicated that women's rate rose to 12.8%, exceeding men's rate of 9.2% ($P<0.05$). This represented the first instance of women's rates surpassing those of men, even after controlling for age and race. The findings indicate that, although the overall incidence of IS has declined, disparities based on sex remain evident in certain age cohorts. (Madsen et al. 2020)

From the Stroke Registry of Northwestern Germany covering 2000 to 2018 stroke treatment underwent relevant changes concerning women and men. In the early 2000s, women were less likely than men to receive intravenous thrombolysis (IVT) for acute ischemic stroke (AIS) when only age and admission year were considered. However, this disparity shifted in the period from 2010 to 2018, with unadjusted analyses showing women were slightly more likely to receive IVT. Importantly, these differences between men and women in IVT administration went away when other clinical factors were taken into account, such as the severity of the stroke at admission, the time from the start of symptoms to admission, comorbidities, and the cause of the stroke. This suggests that earlier observed disparities were not due to inherent sex differences but were influenced by other variables. Overall, the utilization of IVT increased substantially for both sexes, from 2.4% in 2000 to 20.5% in 2018, reflecting advancements in stroke treatment protocols. (Bonkhoff et al. 2021)

In contrast, women consistently had a higher likelihood of receiving intra-arterial therapy (IAT) during the 2010–2018 period, even after adjusting for multiple covariates (odds ratio for women receiving intra-arterial treatment: 1.12 (95% CI, 1.08–1.15)). Interestingly, clinical factors like age, premorbid disability, stroke severity, or cause could not fully account for this difference. The overall use of IAT also rose markedly during this time, from 1.7% in 2010 to 9.7% in 2018, signifying its growing role in AIS management. The reasons behind the higher IAT rates in women remain unclear Moreover, despite having more severe strokes upon admission (odds ratios of 1.10 and 1.09 for the periods 2000–2009 and 2010–2018, respectively), women experienced better early outcomes compared to men. They also had lower in-hospital mortality rates (odds ratios of 0.92 and 0.91 for the respective periods) and were more likely to be discharged with

favorable functional outcomes. The findings remained consistent even after adjusting for covariates, suggesting that women may have a more favorable in-hospital recovery. (Bonkhoff et al. 2021)

These temporal trends illustrate that while some sex disparities in stroke treatment, such as in IVT administration, have diminished over time, others persist. Overall, the evolution of stroke treatment reflects a growing awareness and adjustment to sex differences.

2.10 Sex Differences in Risk Factors of Stroke

Understanding the sex differences in the risk factors is crucial for developing targeted prevention strategies. This chapter explores the nonmodifiable and modifiable risk factors of stroke, emphasizing how they differ between women and men.

Nonmodifiable Risk Factors

Age and Sex Relationship in Stroke Risk

Age is one of the most significant risk factors for stroke, but it plays out differently between the sexes. The relationship between age and stroke incidence is nonlinear, with the risk of stroke increasing more rapidly after age 65 for both women and men (Reeves et al. 2008). Women are typically five years older than men when experiencing a stroke. This difference is usually attributed to an estrogen-protective effect and a generally more extended life expectancy of women (Appelros 2009). A decline in estrogen levels—as after menopause—levels out their risk of stroke compared to men.

Age significantly impacts patient outcomes following a stroke, which occurs primarily in older adults. As women are, on average, older when a stroke occurs, their comorbidities and pre-existing conditions may ultimately complicate long-term outcomes. Aged stroke patients have higher mortality and morbidity and poorer functional recovery than younger patients. Ischemic stroke patients are biologically older than their chronological age, and the difference between biological age and actual chronological age would indicate an individual's ageing level. In younger generations, males have a higher incidence of ischemic stroke and poorer functional outcomes than females (Rexrode et al. 2022).

The higher stroke risk among women at younger ages likely reflects risks related to pregnancy and the postpartum state, as well as other hormonal factors, such as the use of hormonal contraceptives (Demel

et al. 2018). In middle age, the rates of ischemic stroke begin to increase for women, concurrent with the onset of menopause and loss of female sex hormones. After middle age, stroke rates continue to grow in women, with some reports of higher stroke incidence in older women (age >85 years) compared with older men (Bushnell et al. 2018).

Mortality risk in ischemic stroke is high, with estimated 30-day case fatalities ranging from 16% to 32%. This complex relationship between age and sex complicates the assessment of sex differences in stroke-related mortality, as no independent effect of sex on stroke mortality risk was observed. Earlier reports suggested higher mortality in women because of a nonlinear relationship between age and mortality rate. More recently, it was suggested that higher mortality—especially in older women—could most likely be explained by advanced age, stroke severity, stroke morbidity, and atrial fibrillation as a risk factor (Reeves et al. 2008).

Pre-Stroke Disability

In addition to age, another nonmodifiable factor is pre-stroke disability. Women are more likely to have pre-stroke disabilities than men (Hoyer et al. 2022). For instance, conditions like arthritis, osteoporosis, and age-related mobility issues are more prevalent in women, leading to greater dependency on daily activities even before a stroke occurs (Ospel et al. 2023). Additionally, women often live alone more frequently than men. Living alone may have an impact on stroke recognition and immediate access to acute care. Furthermore, it may also act as a confounder of sex differences when determining functional outcome (Renoux et al. 2017).

Modifiable Risk Factors and Sex Differences

Modifiable risk factors are crucial because intervention strategies to reduce them may lower stroke risk. Several well-established risk factors contribute to the risk of stroke—for example, hypertension, diabetes mellitus, hyperlipidemia, and smoking. In addition, new or emerging risk factors are continuously being studied (Peters et al. 2020). Most reliable information on conventional risk factors and their differences between the sexes comes from the INTERSTROKE research, which was a case-control study including 26,919 first-ever stroke cases from 32 nations (O'Donnell et al. 2016).

One of the key messages was that almost 90% of the population-

attributable risk (PAR) for stroke may be attributed to many modifiable risk factors in both women and men. These factors encompass arterial hypertension, active smoking, diabetes mellitus, dietary habits and abdominal obesity (assessed via waist-to-hip ratio), physical inactivity, amount of alcohol intake, cardiac conditions (such as atrial fibrillation, previous myocardial infarction, rheumatic valve disease, or prosthetic heart valves), and pathological lipid profiles. Among these risk factors, hypertension stands out due to its significant impact on stroke risk across both sexes, yet it manifests differently in women and men.

Hypertension

Arterial Hypertension

Hypertension is one of the leading risk factors for stroke in both sexes, but the aforementioned age-specific sex differences also apply to hypertension. High blood pressure is a major risk factor that can be modified to reduce the risk of cardiovascular disease (Peters et al. 2020). Irrespective of whether a patient is classified as having arterial hypertension, older age comes with higher blood pressure. About two-thirds of people aged 65 or older have hypertensive blood pressure. After menopause, women are more susceptible to hypertension due to hormonal changes that affect blood vessel elasticity and salt sensitivity. Studies indicate that even after adjusting for antihypertensive medication use, women with hypertension have a higher stroke risk than men (Madsen et al. 2019).

In the INTERSTROKE study, hypertension contributed to a higher PAR in women (52.3%) compared to men (45.2%). The odds ratios for hypertension were comparable across women (OR 3.21; 99% CI, 2.74–3.76) and men (OR 2.87; 99% CI, 2.55–3.23), highlighting the significance of hypertension as a stroke risk factor in both sexes (O'Donnell et al. 2016). Not only does mean blood pressure seem to predict stroke, but variability in blood pressure is also a risk factor independent of mean blood pressure. Recent research analyzing four randomized trials of patients with hypertension, previous stroke, or previous transient ischemic attack found that variability in 2 to 10 blood pressure measures over two years is a risk factor for stroke independent of mean blood pressure (Rothwell et al. 2010).

Atrial Fibrillation

Women have a higher incidence of atrial fibrillation (AF) but tend to be underdiagnosed and undertreated. AF is the predominant form of sustained cardiac arrhythmia and has a five-fold risk of stroke and thromboembolic events (Lip et al. 2017). Although men have a higher prevalence of AF, women (especially those 75 years old) appear to be at an increased risk for cerebrovascular events—stroke in particular (Feinberg 1995).

On the other hand, female patients with AF aged less than 65 have no excess risk of stroke compared to males. Cardiac risk factors, including atrial fibrillation, were associated with a greater odds ratio (OR) for stroke in women (OR 4.06; 99% CI, 3.06–5.40) than in men (OR 2.73; 99% CI, 2.21–3.37). Factors contributing to this gap may include less determined treatment initiation for women or concerns about bleeding risks. Differences in the vasculature and myocardial structure based on sex may lead to changes in blood flow, shear stress, and endothelial function. Additionally, research indicates a possible increase in systemic inflammatory and procoagulant markers, thrombogenic particles, and platelet aggregation in females, particularly after menopause, which can contribute to a prothrombotic environment (Taqueti 2018).

Gage and colleagues developed the $CHADS_2$ stroke risk stratification schema (C = congestive heart failure [1 point], H = high blood pressure [1 point], A = age 75 or older [1 point], D = diabetes mellitus [1 point], and S2 = previous stroke or TIA [2 points]) combining two other classification schemes (Gage et al. 2001). Biological sex has not consistently been included in risk stratification models, but was noted to independently confer elevated risk—for example, by the SPAF Investigators (female relative risk [RR] 1.6, p=0.01, (Hart et al. 1999)). Consequently, the $CHA_2DS_2 - VASc$ index arose, refining the risk calculation by adding three more variables (V = Vascular Disease [1 point], A = Age $>$ 65 [1 point], and Sc = Sex Category [female = 1], [Lip et al. (2010b)](Lip et al. 2010a)).

Diabetes Mellitus

Diabetes mellitus Type 2 (T2DM) is an established risk factor for cardiovascular disease (CVD), including sex differences in risk, pathophysiology, and complications (Kautzky-Willer et al. 2016). Especially the latter translates into a higher risk of coronary heart disease and stroke for females. The reasons are not entirely understood, but

in women with T2DM, traditional risk factors, such as hypertension, dyslipidemia, and obesity, may contribute more to the increased risk than in men (Al-Salameh et al. 2019).

Diabetic women have a 3.5-fold risk of cardiovascular complications compared to non-diabetic women (Franconi et al. 2012); for men, the risk is slightly lower (2.1-fold). Premenopausal women usually have a lower risk of cardiovascular diseases than age-matched men and postmenopausal women, but this advantage disappears once women are afflicted with diabetes mellitus (Ren and Ceylan-Isik 2004). Studies have shown that patients who previously had no incident cerebrovascular events, the presence of characteristics of the metabolic syndrome—including diabetes—was associated with a higher risk of incident stroke. Women's stroke risk was even more pronounced (hazard ratio: 2.0) than men's (hazard ratio: 1.1) when metabolic syndrome was present.

T2DM is one crucial piece contributing to sex differences in cerebrovascular disease. Related to diabetes is the issue of obesity and metabolic syndrome, which also show distinct patterns between women and men in relation to stroke risk.

Obesity and Metabolic Syndrome

Obesity is a well-known risk factor in stroke, but it seems that the association between obesity and stroke risk is stronger for women. Reasons may potentially be due to sex-specific fat distribution and hormonal influences. Obesity in women is also more closely linked with type 2 diabetes, which further elevates their stroke risk. The concept of metabolic syndrome was initially introduced approximately two decades ago in 1988 by Reaven, and since then, different national and international organizations have proposed various definitions.

The National Cholesterol Education Program (NCEP) Adult Treatment Panel III gained popularity for its simplicity, relying on waist circumference, blood pressure, and plasma levels of fasting glucose, triglycerides, and high-density lipoprotein cholesterol. In a substudy of the Northern Manhattan Study, having the characteristics of the metabolic syndrome was associated with a heightened risk of stroke (hazard ratio: 1.5; 95% confidence interval: 1.1–2.2) even after adjusting for sociodemographic and risk factors. Moreover, women's stroke risk was even more pronounced (hazard ratio: 2.0; 95% confidence interval: 1.3–3.1) than men's (hazard ratio: 1.1; 95% confidence interval: 0.6–1.9).

In the INTERSTROKE study, abdominal obesity contributed to a higher PAR in women (25.8%) compared to men (12.7%). Interestingly, abdominal obesity and cardiac factors had comparable prevalence rates across the sexes, although they are linked to an elevated stroke risk in women. In addition to obesity, dyslipidemia plays a pivotal role in stroke risk, with lipid profiles affecting women and men differently.

Dyslipidemia

Blood lipids play a causal role in the probability of having a stroke. The relationship between dyslipidemia and stroke risk is complex, with an increased risk for ischemic stroke with increased total cholesterol and a decreased risk for ischemic stroke with elevated high-density lipoprotein cholesterol.

High levels of HDL cholesterol are associated with a lower risk of ischemic stroke, especially small vessel stroke, as opposed to high levels of low-density lipoprotein (LDL) cholesterol, which has been demonstrated to increase the risk of ischemic stroke. Furthermore, despite a possible small increase in hemorrhagic stroke, large-scale randomized clinical studies have shown that using statins lowers the incidence of ischemic and total stroke. Some hypothesized that each lipid-related component might be a unique causal player or that one characteristic, such as apoB, predominates and explains the relationships of related lipoprotein particle entities.

The imprecise quantification of atherogenic lipoproteins arises from the significant variation in cholesterol and triglyceride levels among lipoprotein particles. While the levels of LDL cholesterol and triglycerides provide a measure of the circulating lipoprotein-carried lipid substances, they do not accurately reflect the number of atherogenic lipoproteins. However, every circulating atherogenic lipoprotein particle comprises a single apoB molecule. The concentration of apoB molecules in the bloodstream is directly proportional to the number of atherogenic particles present. Cholesterol-rich and triglyceride-rich apolipoprotein-B-containing remnant lipoproteins have emerged as a major driver of human atherosclerosis.

As for sex differences, Kurth and colleagues investigated women participating in the Women's Health Study (n = 27,937, aged 45 years). Interestingly, after age adjustment, total cholesterol, low-density lipoprotein cholesterol, the total cholesterol to high-density lipoprotein cholesterol ratio, and non-high-density lipoprotein cholesterol were associated with increased risk of ischemic stroke. In the INTER-

STROKE study, unfavorable lipid profiles contributed to a higher PAR in women (29.2%) against 25.1% in men. Overall, biological factors like lipid levels are important to consider - furthermore the choice of lifestyle (e.g. smoking) also needs to be considered in the risk of stroke and potential sex-specific effects.

Smoking

Smoking is a highly linked risk factor for cardiovascular morbidity and mortality. The risk for smoking-related disease rises proportionally to the number of cigarettes smoked. Published studies on the associative link of smoking and stroke are highly convincing. While smoking rates have traditionally been higher in men, the adverse effects of smoking on stroke risk are *disproportionately greater in women.* This increased vulnerability may stem from hormonal interactions, as smoking decreases estrogen levels, worsening vascular damage. Moreover, women metabolize nicotine differently, potentially causing more harm.

A meta-analysis including 3,980,359 individuals from 81 cohorts and 42,401 strokes indicated that women in Western populations may be more harmed by smoking than men (relative risk ratio 1.10 [95% confidence interval 1.02–1.18]) as compared to the Asian population (relative risk ratio 0.97 [95% confidence interval 0.87–1.09]). Differences may be due to influences of sex-specific smoking prevalences in certain regions, the generally higher percentage of heavy smokers in men, and the underreporting of smoking habits in women.

In the INTERSTROKE study, smoking contributed to a higher PAR in men (16.6%) compared to women (5.3%), which may be because of a greater prevalence of smoking in men (32.4%) than in women (7.7%). Alongside smoking, physical inactivity is another modifiable risk factor that should be considered.

Physical Inactivity

Physical inactivity has been linked to a multitude of adverse health outcomes, including stroke. Individuals who engage in regular physical activity exhibit a decreased susceptibility to stroke and stroke-related mortality when compared to their sedentary counterparts. The correlation between physical activity and stroke may be attributed to the concomitant reduction in blood pressure, diabetes mellitus, and excess body weight.

The Women's Health Study reported results from 473 ischemic strokes

(in 39,315 women) regarding their ascending kcal per week of leisure-time physical activity. After adjustment for several factors, including age, body mass index, diabetes, and other risk factors, women's stroke risk tended to be lower with increased leisure-time physical activity, particularly walking. A recent systematic review looked at 17 studies that reported levels of physical activity in both women and men. Although no meta-analysis was conducted, the authors concluded a relative risk reduction between 20%–40% for women based on the majority of included studies.

Alcohol Consumption

Alcohol consumption and the risk of stroke is associated in a J-shaped fashion. Moderate consumption (2 drinks per day in men and 1 drink per day in women) seems to confer a reduced stroke risk, while excessive drinking may elevate this risk Hillbom et al. (1999). Alcohol overuse is more prevalent among men, but women are more susceptible to its harmful effects even at lower consumption levels. Due to physiological differences, women have a lower tolerance for alcohol, leading to higher blood alcohol concentrations.

Chronic alcohol abuse in women can result in hypertension, atrial fibrillation, and other cardiovascular issues that elevate stroke risk. Moreover, societal stigma may prevent women from seeking help for alcohol dependence, highlighting the need for sex-sensitive interventions. In the INTERSTROKE study, excessive alcohol intake contributed to a higher PAR in men compared to women, which may be because of a greater prevalence of these activities in men (excessive alcohol intake: 7.1% in men versus 2.4% in women,). One possible mechanism of vascular damage is via hypertension and suboptimal blood pressure management in hypertensive individuals who engage in alcohol consumption (Rantakömi et al. (2012) Hillbom et al. (2011)). Beyond these well-established factors, other risk factors may also contribute to stroke risk and may be sex-dependent.

2.11 Other Risk Factors

Migraine

Migraine, particularly migraine with aura, is more prevalent in women and has been associated with an increased risk of ischemic stroke. Women with migraine with aura have a two- to three-fold higher risk of stroke compared to those without migraine. The risk is further

increased in women who smoke or use oral contraceptives. The underlying mechanisms may involve cortical spreading depression, endothelial dysfunction, and a prothrombotic state (Schurks et al. 2009).

2.12 Sex-Specific Risk Factors

Age at Menarche and Menopause

Reproductive factors unique to women can influence stroke risk. Early menarche (before age 10) and late menarche (after age 17) have been associated with increased cardiovascular disease risk (Canoy et al. 2015). Similarly, early menopause (before age 45) is linked to a higher risk of stroke. The duration of exposure to endogenous estrogen during a woman's reproductive lifespan may impact cardiovascular health. Shorter exposure due to early menopause or surgical removal of ovaries may increase stroke risk. Conversely, longer exposure may be protective (Muka et al. 2016).

Pregnancy and Pregnancy Complications

Pregnancy introduces unique physiological changes that can increase stroke risk (Sharshar et al. 1995). The risk is highest during the third trimester and postpartum period. Pregnancy-related complications such as preeclampsia, eclampsia, gestational hypertension, and gestational diabetes are associated with increased stroke risk during pregnancy and later in life. Preeclampsia and eclampsia account for a significant proportion of pregnancy-related strokes. Women who experience these conditions have a two-fold increase in stroke risk later in life. The underlying mechanisms may involve long-term vascular changes and heightened inflammatory states (Wu et al. 2017).

Exogenous Hormone Use

Hormonal Birth Control

Use of hormonal contraceptives, especially those containing estrogen, has been associated with an increased risk of stroke, particularly ischemic stroke. The risk is dose-dependent, with higher estrogen doses leading to greater risk of stroke. Women who smoke, have migraines with aura, or have hypercoagulable disorders are at higher risk when using hormonal contraceptives (Gillum et al. 2000). Progestin-only

contraceptives have not been associated with increased stroke risk (Lidegaard et al. 2012).

Hormone Replacement Therapy

Hormone replacement therapy (HRT) used to alleviate menopausal symptoms has been linked to an elevated stroke risk. Large studies such as the Women's Health Initiative (WHI) and the Women's Estrogen for Stroke Trial (WEST) found increased stroke risk in women using HRT Viscoli et al. (2001). However, the "timing hypothesis" suggests that initiating HRT early after menopause may have cardiovascular protective effects, while initiating it later may not confer benefits and may increase risks. Reanalysis of studies indicates that HRT may be safe and possibly beneficial when started in early menopause (Hodis et al. 2016). However, current guidelines do not recommend HRT for primary prevention of stroke or other chronic diseases.

Low Testosterone Levels in Men

In men, low testosterone levels have been associated with increased risk of stroke. Testosterone deficiency can lead to unfavorable lipid profiles, inflammation, and endothelial dysfunction, contributing to atherosclerosis (Traish et al. 2009). Men receiving androgen deprivation therapy for prostate cancer have an elevated risk of ischemic stroke (Punnen et al. 2011). Recognizing low testosterone as a sex-specific risk factor for men emphasizes the importance of hormonal evaluation and management in male patients at risk.

Understanding these sex-specific risk factors sets the stage for exploring how stroke symptoms themselves may differ between women and men, influencing diagnosis and treatment.

2.13 Differences in stroke symptoms between men and women

2.14 Sex-specific differences in stroke severity and location

2.15 Delirium in stroke patients

Incidence and Prevalence of Post-Stroke Delirium by Sex

Delirium in patients suffering from acute ischemic stroke is a common yet often underdiagnosed syndrome.
Delirium complicates the acute phase of ischemic stroke, with data suggesting incidence rates from 13% to 48% Zhang et al. (2024). Notably, these may be higher than the incidence rates of patients admitted to the general wards, where 10% to 25% develop delirium (Siddiqi et al. 2006). The high variance may be particularly explained by lower screening rates throughout the year within reports before 1999 (heterogeneity I_2 94.6).

Other factors contributing here are differences in described settings (acute hospital versus rehabilitation unit), which screening tools have been used, and whether or not specific symptoms like aphasia or psychiatric have been excluded upfront.

Definition of delirium

No universal definition of delirium is agreed upon, but most scientific work defines it as an acute, transient, and fluctuating disorder of consciousness, attention, and cognition.

A definition of delirium by the Diagnostic and Statistical Manual of Mental Disorders is defined if the following criteria are fulfilled: „A. Disturbance in attention (i.e., reduced ability to direct, focus, sustain, and shift attention) and awareness (reduced orientation to the environment). B. The disturbance develops over a short period (usually hours to a few days), represents a change from baseline attention and awareness, and tends to fluctuate in severity during the day. C. An additional disturbance in cognition (e.g., memory deficit, disorientation, language, visuospatial ability, or perception). D. The disturbances in criteria A and C are not explained by another preexisting, established, or evolving neurocognitive disorder and do not occur in the context of a severely reduced level of arousal, such as coma. E. There is evidence from the history, physical examination,

or laboratory findings that the disturbance is a direct physiologic consequence of another medical condition, substance intoxication or withdrawal (i.e. because of a drug of abuse medication), or exposure to a toxin, or is because of multiple etiologies.“ (Slooter et al. 2020)

The critical diagnostic symptoms of delirium are acute onset, inattention, disorganized thinking, and altered level of consciousness. Usually, an underlying medical condition triggers delirium, which is then not better explained by another preexisting, evolving, or established neurocognitive disorder. In recent years, delirium subtypes have been focused on differentiating. For example, in one study, the prevalence of hyperactive delirium was lower (4% [95% CI, 3–6]), being surpassed by hypoactive (17% [95% CI, 13–22]) and mixed form(10% [95% CI, 6–16]) (Krewulak et al. 2018). Having established what constitutes delirium, it is important to identify the factors that predispose patients to this condition, particularly in the context of stroke.

Predisposing and precipitating risk factors

Risk factors for delirium in acute ischemic stroke are age and frailty (Inouye et al. 2014), stroke severity/atrial fibrillation (Lim et al. 2017) premorbid diseases (Inouye 1996), type of medications (Ormseth et al. 2023), acute stress, acute infections, sleep disorders or disturbed day/night rhythm (Sandberg et al. 2001), dehydration and imbalances of electrolytes, sensory deprivation, premorbid cognitive disabilities, cigarette smoking (Lim et al. 2017) and damage to brain regions (Ormseth et al. 2023) and coma (Gravante et al. 2021).

The most common analyzed risk factor for delirium is age (odds ratio 1.04, 95% CI (1.02–1.07) Inouye et al. (2014). However, biological sex was also identified in some studies (odds ratio 1.24, 95% CI 0.63–2.43). Interestingly, thrombectomy using general anesthesia was not associated with increased delirium risk while overall number of procedures was (Sachdev et al. 2024). The natural course of delirium associated with stroke remains largely unknown. Some available data report occurrence in the first few days after stroke A. W. Oldenbeuving et al. (2011) with two thirds within 24h (Mitasova et al. 2012).

Pathophysiology of delirium

Neuroinflammation and neurodegenerative processes are likely the main causes of delirium. Acute medical conditions such as structural

trauma, surgery, or sepsis can trigger these mechanisms. Activated microglia and astrocytes produce pro-inflammatory cytokines such as IL-1 and TNF and release reactive oxygen species, which can disrupt normal neuronal activity and connectivity Wilson et al. (2020).

Delirium is also strongly linked to imbalanced *brain energy metabolism*. The brain's high energy demand makes it sensitive to oxygen or glucose deprivation. Conditions like a reduced cerebral blood flow with local or global hypoxia or hypoglycemia can result in cerebral metabolic insufficiency, impairing the brain's ability to maintain normal neuronal function. Inflammatory states may exacerbate these metabolic disturbances by reducing neurovascular coupling and increasing the permeability of the blood-brain barrier.

Additional factors in the development of delirium are an *imbalance of neurotransmitters*, particularly acetylcholine, dopamine, and GABA. Delirium is associated with cholinergic deficits, and drugs that antagonize acetylcholine receptors can induce delirium-like symptoms . Conversely, hyperdopaminergic states, such as those caused by certain medications or withdrawal states, can contribute to the psychomotor disturbances seen in delirium. Additionally, GABAergic dysfunction, often due to sedatives or anaesthetics, is frequently implicated in delirium, particularly in critically ill patients.

In this context, delirium may lead to *disruptions in neuroanatomical and functional connectivity* within and between core brain networks. Several fMRI studies have shown that delirium is characterized by weakened connectivity in the default mode network and other large-scale brain networks responsible for higher cognitive functions. This loss in network connectivity is thought to underlie the cognitive and attentional deficits that are hallmark features of delirium (Shaw et al. 2019). Important to note, right-sided stroke may have a higher incidence of delirium after stroke Ott et al. (2023). In this context a preexisting or acute strucutral brain damage or a clinical syndrome of dementia (accompanied by brain atrophy) may also be important factors for the occurrence of delirium (Fick et al. 2002). Understanding of the underlying hypothesized mechanisms of delirium may inform the development of bedside assessment tools.

Bedside Delirium Instruments

Manifold screening tools exist for patients admitted to the general ward or intensive care unit (Wong et al. 2010). The most commonly used and most validated tool is the Confusion Assessment Method (CAM, Inouye (1990)) or CAM-based tools, which were further re-

fined. Regarding a stroke-specific delirium screening tool, Mansutti and coworkers (Mansutti et al. 2019) aimed to identify available instruments systematically. Amongst others, the 4-Assessment Test for delirium (4AT) had a sensitivity from 90.2 to 100% and a specificity from 64.5 to 86%. The 4AT finds more use in general ward settings.

In contrast, the Confusion Assessment Method-Intensive Care Unit (CAM-ICU) had a lower sensitivity of 76% (95% Confidence Interval [CI] 55–91) but with a higher specificity of 98% (95%CI 93–100) and is more prevalent in intensive and intermediate care settings. Because a universal definition of delirium is not established and there is a difficulty in diagnosing Bergeron and coworker aimed to develop the Intensive Care Delirium Screening Checklist (ICDSC, Bergeron et al. (2001)). It is nowadays used as possible alternative to CAM-ICU in the intensive or intermediate care setting (Wilson et al. 2020). ISDSC mainly covers eight domains including altered level of consciousness, inattention, disorientation, hallucination, delusions, agitation , inappropriate speech, sleep-wake disturbances, and fluctuation of symptoms. Even when communication to the patient is compromised - for example when the patient is intubated - ISDSC achieved a sensitivity is 99% and specificity is 64% emphasizing an early diagnosis with a high true positive rate. More detailed information may be found in **?@tbl-delirium-tools** (adapted from Mansutti et al. (2019), Ringleb et al. (2021))

Relevance of delirium detection in stroke patients

Delirium has a negativ impact on the prognosis of stroke patients in the short and long term (Gjestad et al. 2024). In a meta-analysis in 2012 by Saposnik and colleagues (Shi et al. 2012), the authors recognized that delirium after stroke directly impacts essential outcomes. For example, stroke patients with delirium had longer hospital stays than those without delirium (mean difference, 9.39 days; 95% CI, 6.67–12.11). Additionally, patients with delirium were more likely to be discharged to a nursing home or any other institution than in the absence of delirium (OR, 3.39; 95% CI, 2.21–5.21). Stroke patients with delirium had higher hospital mortality (OR, 4.71; 95% CI, 1.85–11.96) but also higher mortality that persisted up to 12 months (OR, 4.91; 95% CI, 3.18–7.6) after stroke.

A more recent meta-analysis from 2024 by Gong and colleagues could confirm this high mortality rate (Gong et al. 2024) and functional outcomes are also affected. Delirium patients also experienced risk

for poor functional outcome at three months after stroke (RR 2.93, 95% CI: 1.86, 4.61; I2 = 73.9%, N = 4) as compared to non-delir patients. Delirium is known to influence the length of hospital stay (Ely 2004) in-hospital mortality Seiler et al. (2021) and functional assessments (Rudolph et al. 2010). For stroke patients, existing studies have limited and inconsistent results Mc Manus et al. (2011). While the topic of delirium itself has long been underrecognized, sex differences within this topic have rarely been addressed.

In a review of the literature about sex differences on delirium of stroke we could not find any report directly addressing this issue. However, a recent review and meta analysis investigating vascular risk factors also looked at sex as main effect variable, reporting data from 36 studies. Overall, 2589 patients had a delirium and 8083 patients had no delirium with an odds ratio for sex of 0.98 (95% CI 0.87–1.11). (Siokas et al. 2022)

Delirium prediction models in stroke patients

Nakamizo and coworkers developed a scoring system to predict the occurrence of delirium at stroke units. (Nakamizo et al. 2020). In their Japanese cohort, 42 of 387 developed delirium as measured by ICDSC. The scoring system included prior delirium, daily consumption of more than 40 grams of alcohol, NIHSS 5, dementia diagnosis prior to admission, and auditory/visual impairment (PANDA). The cohort consisted of patients with a low to mild stroke severity (NIHSS was median 4 points, interquartile range 2–9).

Wischmann and colleagues investigated 525 patients who were admitted to the stroke unit and intensive care unit. In their German cohort, stroke severity was also mild (patients that had delirium had a median NIHSS of 7 points (interquartile range 3–12), and patients with no delirium had a median NIHSS of 2 points (interquartile range 0-6). The analysis results in the Risk Assessment and PredIction of Delirium in acute stroke patients (RAPID) score, which consisted of Glasgow Coma Scale <15 points at admission, Fazekas Score 1 point in non-contrast computed tomography, global brain atrophy in non-contrast computed tomography, age 68 years, National Institutes of Health Stroke Scale 1 point, premodified Rankin Scale 0 points. Overall, 29.7% of patients developed a delirium. The model's accuracy was 0.85, and the area under the curve was 0.89 (Wischmann et al. 2023)

2.16 Aim of this work

This introduction may give the reader an understanding of the current knowledge of differences in biological sex, establishing the need for more research on this topic. In addition, delirium - as discussed - is an underrecognized entity despite its impact on the prognosis of stroke patients. Available literature on sex-based differences and its influence on delirium is very limited. The aim of this work is to address this gap by (Figure 2.1):

- investigating the *difference between the sexes* in acute ischemic stroke patients during the hospital stay with a *special emphasis on delirium*
- identify influential *factors of delirium occurrence* and their *relationship between females and males*
- evaluate the *impact of delirium* and its possible relationship to biological sex on the short and long-term *prognosis of stroke* patients

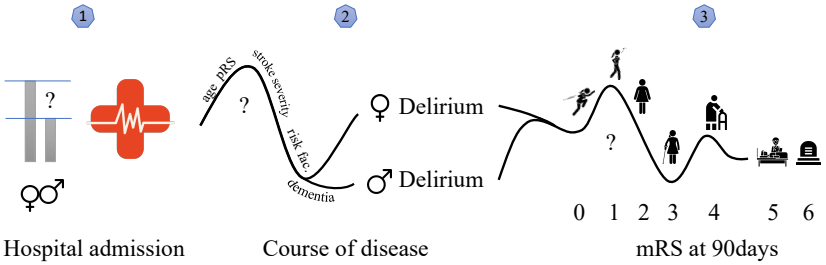

Figure 2.1: Pictogramm of research hypothesis. (1) Evaluation of sex differences at admission (2) Identification of influencal factors contributing to delirium during course of disease (3) Impact of delirium on outcome. mRS indicates modified Rankin Scale, pRS indications premorbid Rankin scale.

Chapter 3

Methods

3.1 Methodological Excursus: A short introduction to Bayesian statistics

Definition of Bayesian statistics

In 1763, Thomas Bayes wrote a paper called "An Essay towards solving a Problem in the Doctrine of Chances". At its core, it describes how *Bayesian theory* allows us to update prior knowledge as one gathers new data. Prior information is used in the form of distributions, so-called prior distributions, which may take different levels of information. (Van De Schoot et al. 2021)

- A probability distribution is defined as a mathematical function describing the likelihood of different outcomes or values. A prior distribution, or simply *Prior*, represents the potential knowledge before observing the data and is included in the Bayesian models as a probability distribution (@fig-priordemo).

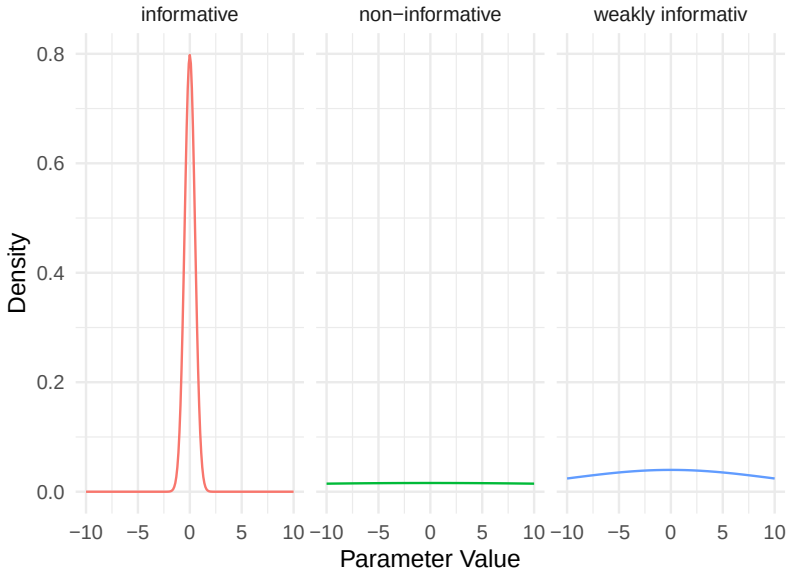

Figure 3.1: Demonstration of different forms of priors

- The likelihood function is the probability of the observed data given a particular parameter value. It reflects which parameter values are the most consistent with the observed data.
- The *posterior distribution* – or short posterior combines the prior distribution and the likelihood of the observed data. Using computational methods applying Bayes' Theorm (see below), a new probability distribution results. One can think of it as the updated knowledge after observing the data.
- *Bayes' Theorem* is the mathematical formula that describes the relationship between the prior, likelihood, and posterior: The bayesian theorem can be expressed as follows:

$$P(A|B) = \frac{P(B|A) \cdot P(A)}{P(B)}$$

Where: $P(A\|B)$ is the conditional probability of A given B,
$P(B\|A)$ is the conditional probability of B given A,
$P(A)$ is the probability of A ("the prior"), and
$P(B)$ is the probability of B ("the posterior").

$$P(\theta|\text{Data}) = \frac{P(\text{Data}|\theta)P(\theta)}{P(\text{Data})}$$

where P(| Data) is the posterior, P(Data |) is the likelihood, P( ) is the prior, and P(Data) is the marginal likelihood (normalizing constant).

The Markov Chain Monte Carlo (MCMC) methods are computational algorithms that simplify the calculations needed to draw samples from posterior distributions. In recent years, the most commonly used advanced MCMC algorithms were Hamiltonian Monte Carlo (HMC). HMC improves sampling efficiency by using information about the gradient of the probability distribution.

A *simple example* shall add to the understanding of the given terms. Please consider a card game with a deck of 52 cards. Your game partner pulls one card and its your turn to guess which card. Each card (C) has equal probability $P(C_i) = \frac{1}{52} \approx 0.0192$ (prior distribution). Then you get a new information that the card is a heart. Non-hearts (Cnh) would have a likelihood of P(Hint|Cnh) = 0, and all hearts would be P(Hint|Ch) = 1. Using Bayes' Theorem, the updated probability for each card: $P(C_i|\text{Clue}) = \frac{P(\text{Clue}|C_i) \cdot P(C_i)}{P(\text{Clue})}$For each card of hearts (Ch) the updated posterior probability would be: $P(C_h|\text{Clue}) = \frac{1 \times \frac{1}{52}}{\frac{13}{52}} = \frac{1}{13} \approx 0.0769$.

Summarized shorty, the Bayes Theorem facilitates an integrative approach, combining a *prior distribution* with a *likelihood* that is derived from the new data; together they form the probability distribution (so-called *posterior distribution*). McElreath (2020)

Table 3.1

Viewpoints	**Frequentist**	**Bayesian**
Probabilities computed	Probabilities about data	Probabilities about the effects that generated the data
Formal aim	Draw conclusions	Make decisions
Method of inference	Indirect: assuming no effect, attempting proof by contradiction	Direct: using prior data, computing probability of effect given the data
Viewpoint of evidence	Evidence against an assertion	Evidence in favor of an assertion
Analogy of disease diagnosis	1 - specificity = P(test positive | disease absent)	P(disease present | test result)
Calculations	Simplified by assuming H_0 when design is simple	Computationally demanding/complex
Adaptive flexibility	Low; design adaptations affect	High

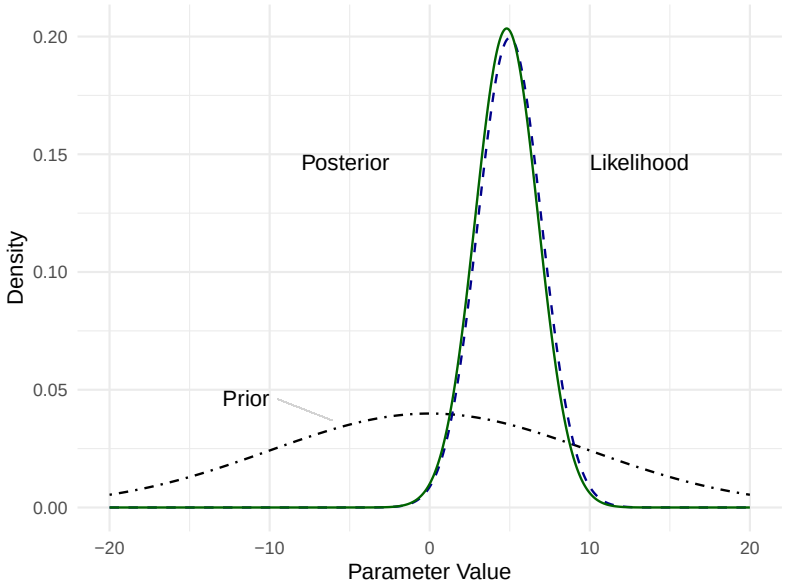

Figure 3.2: Prior, Likelihood, and Posterior

This contrasts with more traditional forms of statistical inference, notably frequentist statistics, which do not directly incorporate prior beliefs. Another major advantage of bayesian statistics is the ability of directly interpreting the probability of an effect given the data. A quick overview of advantages and disadvantages of frequentist and bayesian statistics is presented (#tbl-freq-bayes, adapted from [DO CITATION]).

Definition of Bayesian Model Indices

N represents the full amount of data available for analysis. In Bayesian models not all data points contribute equally to the inference process as the quality of the sample varies depending on factors like correlation among data points. N_{eff} measures the number of independent and informative data points that contribute for making accurate estimates. For example, a high N_{eff} relative to N indicates that the data is used efficiently, with minimal redundancy or bias, resulting in more reliable and precise estimates.

Indices in Bayesian statistics may be classified into three interrelated categories: i) Bayes factors, ii) *posterior* indices, and iii) *Region of Practical Equivalence (ROPE)*-based indices. Bayes factors have their strength in the comparison of models. Indices that analyse posterior distributions include the proportion of strictly positive values (*probability (P)* of direction or $P(\beta > O)$. They also enable the derivation of valid statements that express the likelihood of an effect falling within a specified range, in analogy to the inferences associated with frequentist confidence intervals. More recently, ROPE-based indices emerged as a means to redefine what would be the null hypothesis in frequentist analysis. Rather than adhering to the traditional point-null hypothesis, researchers now consider a range of values that are deemed inconsequential or lacking practical significance. Typically, the ROPE is symmetrically distributed around 0, with values such as [-0.1; 0.1] commonly employed. The underlying premise of this index postulates that an effect rarely attains an absolute zero. (Makowski et al. 2019) However, since ROPE-based indices are rather new and not standardly implemented in bayesian statistical software, and, the intervals determining the region of practical equivalence are not yet universally agreed upon, this work will primarily consider the probability of direction and the Bayes factor.

3.2 Practical considerations of Bayesian Results Interpretation

This paragraph is to inform the interested reader in pitfalls of interpretation of Bayesian results, especially having previously worked with frequentist statistics. Comparing most distributions or analysing association in regression models a probability value is calculated. Of note, the $P(\beta > 0)$ is not the same as the probability of the null hypothesis being true. The former is the probability of the effect being positive, given the data and the prior, resulting in e.g. a

probability of 0.985, which means that the effect is positive in 98.5% of the cases. If the probability was 0.015 it would mean that also a meaningful association is present and that the effect is positive in 1.5% of the cases, that is the effect is negative in 98.5% of the cases. For a more detailed information including examples the reader is advised to McElreath (2020).

3.3 Patients and patient selection

The study cohort was based on the consecutive *Heidelberg Rekanalisation (HeiReKa)* registry and — for this work — consits of n=5799 cases. It covers a time span of 24 years, where the overall distribution between females (n=2862, 49.4%) and males (n=2937, 50.6%) is nearly fully balanced. Within the registry various locations of stroke occurrence are collected (left, right, posterior, bilateral, spinal, retinal). It is important to note that the inclusion of the latter two locations in the following analysis would introduce potential bias. Therefore, they are discarded. The same applies for cases where intravenous thrombolysis was not administered in the standard regimen, but rather as individual rescue therapy for patients in whom free floating thrombus was detected during the hospital stay. For interest in those patients the reader is kindly advised to visit (Hametner et al. 2013). The dataset also includes patients (n=6), who were treated with a reduced dose of 0.6 mg per kilogram body weight. For the analysis, those patients and patients who received 0.9 mg per kilogram body weight were condensed into one category. This work complies with the Strengthening the reporting of observational studies in epidemiology. (Elm et al. 2007)

3.4 Statistical software

This work uses principles of literate programming (Knuth 1984). It aims at reproduceability. All input data were being left unchanged. Instead they are imported and processed by R code to fit the need for desired modifications and analysis. The R software with a graphical user interface of RStudio (Posit Software, PBC, 2024) was used to write and execute code. Version details and attached packages are as follows:

```
cat(paste0(capture.output(sessionInfo()), collapse="\\n"))
```

```
R version 4.4.1 (2024-06-14)\nPlatform: aarch64-apple-darwin20\nRunning under: macOS Sonoma 14.2.1\n\n
arm64/Resources/lib/libRblas.0.dylib \nLAPACK: /Library/Frameworks/R.framework/Versions/4.4-
```

arm64/Resources/lib/libRlapack.dylib; LAPACK version 3.12.0\n\nlocale:\n[1] en_US.UTF-
8/en_US.UTF-8/en_US.UTF-8/C/en_US.UTF-8/en_US.UTF-8\n\ntime zone: Europe/Berlin\ntzcode source: inter
1 ggplot2_3.4.4 data.table_1.16.0 \n[17] ggtext_0.1.2 magrittr_2.0.3 modelsummary_2.2.0 flextable
1 rms_6.8-2 Hmisc_5.1-3 \n[29] targets_1.7.1 \n\nloaded via a namespace (and not attached):
2 \n [4] farver_2.1.2 rmarkdown_2.28 ragg_1.3.2 \n [7] vctrs_0.6.5 askpass_1.2
3 \n [10] tinytex_0.52 rstatix_0.7.2 htmltools_0.5.8.1 \n [13] polspline_1.1.25 curl_5.2.2
5 StanHeaders_2.32.10 htmlwidgets_1.6.4 \n [19] sandwich_3.1-
0 zoo_1.8-12 uuid_1.2-1 \n [22] igraph_2.0.3 lifecycle_1.0.4 pkgconfig_2.0.3
0 R6_2.5.1 fastmap_1.2.0 \n [28] digest_0.6.37 colorspace_2.1-
1 ps_1.7.7 \n [31] textshaping_0.4.0 base64url_1.4 labeling_0.4.3 \n [34] fansi_1.0.6
5 \n [37] httr_1.4.7 compiler_4.4.1 fontquiver_0.2.1 \n [40] withr_3.0.1 htmlTable_
5 viridis_0.6.5 \n [46] QuickJSR_1.3.1 pkgbuild_1.4.4 ggsignif_0.6.4 \n [49] MASS_7.3
60.2 quantreg_5.98 openssl_2.2.1 \n [52] loo_2.8.0 tools_4.4.1 foreign_0.8-
86 \n [55] zip_2.3.1 nnet_7.3-19 glue_1.7.0 \n [58] callr_3.7.6 nlme_3.1-
164 gridtext_0.1.5 \n [61] grid_4.4.1 checkmate_2.3.2 cluster_2.1.6 \n [64] generic
2 xml2_1.3.6 \n [70] utf8_1.2.4 tables_0.9.31 pillar_1.9.0 \n [73] splines_4.4.1
6 renv_1.0.3 \n [76] survival_3.6-4 SparseM_1.84-2 tidyselect_1.2.1 \n [79] fontLibera
20 officer_0.6.6 gdtools_0.4.0 \n [94] BiocManager_1.30.25 cli_3.6.3 RcppParallel_5.1
3 assertthat_0.2.1 \n[106] viridisLite_0.4.2 mvtnorm_1.3-1 scales_1.3.0 \n[109] insight_0.
26

Selected Custom Functions in R

As the whole code would be too overwhelming to present, selected R-code shall demonstrates the relevant methodology applied. A *GitHub repository* shows the full code. Although many variable are already present in the HEIREKA database in highest quality, some were re-evaluated by leveraging different data sources and others newly created. The following functions are examples how data were extracted and processed:

Function *'smoking'*

One example would be whether the patients has been smoking recently or not. The function getPrevSmoke executes a multi-stage process that involves extracting smoking-related data from diverse sources and subsequently integrating them:

During the initial phase, the 'extractFromDia' function is employed to retrieve data on smoking, with a particular focus on the variable "F17". During the second stage, data is extracted from case records from admission ('*df_neur_aufnb*') including variables of actively smoking ('*dx_rf_smoke_active*') and - if present - information on pack years ('*dx_rf_smoke_py*'). The third stage utilises a

set of predetermined regular expressions (py_str, prev_smoke_str, active_smoke_str) to extract targeted data across four distinct medical record data sources (*'df_neur_aufnb'*, *'df_neur_stwbr'*, *'df_neur_int'*, *'df_neur_stabr'*). For example prev_smoke_str:

```
(?:[E|e]hemal(iger)?|[V|v]ormals?.|[A|a]bstinen.?).{1,20}
([R|r]aucher|[N|n]ikotin)|(?:Z\.?n\.?)\s([R|r]aucher|[N|n]ikotin)
```

It facilitates *regular expression* extracting the desired information using several terms and combinations (including some degree of typing error). This way information on 'being an active smoker', 'pack years', and having 'previously smoked' are gathered. During the fourth stage, information extracted from 'df_hei' is carefully chosen, manipulated, and saved into df4, while preserving the '*case_id*' and 'dx_rf_smoke_active' variables. The four dataframes are merged using 'case_id' as the primary identifier and coalesce and maximum value extraction as data transformation techniques. This results in one validated variable 'dx_rf_smoke_active' and two new variables ('dx_rf_smoke_prev', 'dx_rf_smoke_py').

Function *'getHandedness'*

Using the 'getHandedness' function, new variables are derived, particularly for identifying left-handedness, right-handedness, and ambidextrousness. Handedness information is extracted from different sources of medical documents - "aufnb", "stwbr", "int", and "stabr" - using the function 'extractHandednessFromLetters'. A join operation and post-join transformation using 'case_id' as key brings together all extracted information. The final 'var_handed' variable is converted into a factor.

Function *'extractLab'*

The extractLab function is intended to extract particular pieces of information from laboratory results (labs) associated with specific cases (case_id) and takes multiple parameters. It uses data filtering and processing techniques for a desired variable selection (e.g. 'Natrium'), carefully considering the elimination of redundant entries and noting the exact date and time of laboratory examinations. Using the data frame of hospital admission information ('kenn'), labs are processed based on case_id selection noting the duration between the hospital admission and laboratory test ('timeDiff'). Data cleaning involves the removal of specific characters from laboratory results and parsing of numerical values. Observations with missing values in the variable ('Wert') are discarded. If desired - especially

in case several lab values are available during the hospital stay - the function determines the quantity of laboratory values per case ('n'), median, minimum, maximum, 25th percentile (q25), and 75th percentile (q75). Some analysis of lab values (e.g. glucose at hospital admission) may demand time range filtering, which is realised by implementing 'timeCutStart' and 'timeCutEnd'. Also, the entry with the shortest time difference between hospital admission and lab test can be obtained for each case ID ('slicing').

Function *'getMedsPrior'*

The getMedsPrior function extracts medication data from several sources with a specific priority order: STWBR > AUFNB > NOT. It processes multiple data frames containing medication information, consolidates them, cleans the data, de-identifies it, and then categorizes the medications using an automated system.

The latter uses the custom extractMedsWithGPT_v2 function, which utilizes the advanced programming interface from OpenAI for extracting the medication names. The model used most recently was GPT-4 - last accessed in February 2024. The prompt for the language model was "#CONTEXT# I want to extract information from medical records concerning medications taken by the patients. #OBJECTIVE# Extract all medications, classify each according to the ATC classification system in „SUBSTANCES (=ATC level 5)", „SUBGROUPS (=ATC level 4)", and „CLASSES (ATC level 2)". Ensure precision by omitting any irrelevant text or unnecessary line breaks. The extracted data should strictly pertain to medications. In case of a medications that contain two or more SUBSTANCES, please make two or more TARGETS, respectively. #FORMAT of RESPONSE# Respond with identified TARGET, ATC code, SUBSTANCES, SUBGROUPS, CLASSES, PRESCRIBED. Use information such as '(Pause)' or 'pausiert' or similar to indicate PRESCRIBED=0. Follow the following format: E.g. 'Marcumar' would be a found TARGET. The RESPONSE would be: ' ''Marcumar; B01AA04; Phenprocoumon; Vitamin K antagonists; Antithrombotic agents; 0' '. Please skip commenting, and only return desired information. If there are hints for no prior medication' such as 'keine' or 'Vormedikation: keine' or similar, please indicate so - ' ''no prior medication; no prior medication; no prior medication; no prior medication; no prior medication; 0' '. Separate each response using';;;' without introducing whitespace. In case of NA - leave 'NA'. Remember that each response contains six items. When a substance was found reliably, there can be no 'no prior medication'. When you cannot identify a substance for a TARGET, use a web search to identify the SUBSTANCE (e.g. 'Substance of [TARGET]' - e.g. 'Substance of Godamed' and go from there. When you cannot find a TARGET stick to 'NA'. When the text apears to be recommendation from discharge rather admission medication stick to 'NA'. #INPUT# (desired text was appended here).

Importantly, *only preprocessed anonymized text snippets were being processed*, text prompts were continuously improved and results manually checked in a forward loop fashion until the desired quality was reached. This ensured a highest accuracy for the language model available at the time by providing a particular task. The function ultimately returns a list of three data frames: CLASS, GROUP, and SUBSTANCE, each representing different levels of medication classification.

Function *getDelir*

The 'getDelir' function generates a new variable, "Delir," from various medical data sources, including diagnoses, medical notes, laboratory results, and other risk factors. This function processes data from these sources, merges them by case identifier (case_id), and creates a comprehensive data frame that summarizes delirium-related information for each case. The function categorizes delirium into specific subtypes based on the extracted information. These subtypes are as follows:

1. Multifactorial Delirium is identified using the keyword "gemischt" (German for "mixed") or when multiple specific subtypes of delirium are present, marked by the variable outcome_delir_multi.
2. Alcohol-related Delirium is detected through patterns related to alcohol, such as variations of "Alkohol" (alcohol), "C2", "Entzugs" (withdrawal), "Alkoholdelir" (alcohol delirium), "Entzugsdelir" (withdrawal delirium), and "Entzugssyndrom" (withdrawal syndrome). Cases identified with these patterns are marked by outcome_delir_alc.
3. Dementia-related Delirium is recognized by searching for terms indicating dementia in conjunction with delirium, using patterns like "Delir" (delirium) within 30 characters of "Demenz" (dementia) or where "Demenz" appears within 50 characters of "Delir". These cases are marked by outcome_delir_dem.
4. Postoperative Delirium is identified by terms related to postoperative conditions, such as variations of "postop" or "Postop", and is marked by outcome_delir_postop.
5. Seizure-related Delirium is detected through terms related to seizures or epilepsy, such as "Dämmer" (twilight state) and "epilept" (epileptic). Cases with these patterns are marked by outcome_delir_seiz.
6. Infection-related Delirium is recognized by terms related to infections or inflammatory conditions, using patterns like "Delir"

within 30 characters of terms like “Infekt” (infection), “Fieber” (fever), “Pneumonie” (pneumonia), and “Entzündung” (inflammation), or where these terms appear within 50 characters of “Delir”. These cases are marked by outcome_delir_inf.

7. Unspecified Delirium serves as a general classification when delirium is identified but does not fit into the other specific subtypes, marked by outcome_delir.
8. No Delirium is assigned when none of the indicators for delirium are present, marking the case as having no delirium.

3.5 Data Sources, Variables and Selection

Description of data sources

LysePat.accdb is a database, which was set up in 1998 by Prof. Dr. med. P.-A. Ringleb, who meticuously curates the data improving its data quality ever since. It served as one of the main sources of information for this work. Other databases that found integration included those for heart and carotid ultrasound. Labaratory values and hospital diagnosis and medical records were extracted from hospital information system. As a consequence variables were updated, some validated by synchronization with different sources, and newly created (Table 3.2).

Table 3.2: Selected variables and description of repsective data sources

Category	Variable	Description	N	Sources
Characteristics	*pRS*	Premorbid Rankin Scale scores	2	df_hei, qs
	var_handedness	Handedness information	4	df_neur_aufnb, df_neur_stwbr, df_neur_int, df_neur_stabr
	var_aphasia	Aphasia status	5	df_hei, qs, dia, df_neur_stwbr, df_neur_int, df_neur_stabr
	var_neglect	Neglect status	4	dia, df_neur_aufnb, df_neur_stwbr, df_neur_int, df_neur_stabr
	var_prev_stroke	Previous stroke history	5	qs, df_neur_aufnb, df_neur_stwbr, df_neur_int, df_neur_stabr, df_hei

(continued)

Category	Variable	Description	N	Sources
	var_prev_mi	Previous myocardial infarction history	4	dia, df_neur_aufnb, df_neur_stwbr, df_neur_int, df_neur_stabr
	var_prev_thyr	Previous thyroid disease history	5	dia, df_neur_aufnb, df_neur_stwbr, df_neur_int, df_neur_stabr, lab_thyr
	var_prev_alc	Previous alcohol abuse history	4	dia, df_neur_aufnb, df_neur_stwbr, df_neur_int, df_neur_stabr
	dx_prev_dementia	Previous dementia diagnosis	4	dia, df_neur_aufnb, df_neur_stwbr, df_neur_int, df_neur_stabr
	dx_prev_copd	Previous COPD diagnosis	4	dia, df_neur_aufnb, df_neur_stwbr, df_neur_int, df_neur_stabr
	var_stroke_care	Stroke care received	4	ops, fakar, df_neur_stwbr, df_neur_int, df_neur_stabr
	dx_rf_smoke	Smoking status	4	df_hei, dia, df_neur_aufnb, df_neur_stwbr, df_neur_int, df_neur_stabr
Etiology	*etio_pfo*	Patent Foramen Ovale presence	1	dia
	etio_endocarditis	Endocarditis presence	1	dia
	etio_cs	Carotid stenosis presence	1	dia
Outcome	*outcome_delir*	Delirium occurrence	5	dia, df_neur_stwbr, df_neur_int, df_neur_stabr
	outcome_mi	Myocardial infarction occurrence	1	dia
	outcome_nihss_discharge	NIHSS score at discharge	4	df_neur_stwbr, df_neur_int, df_neur_stabr, df_hei
	outcome_lengthHospStay	Length of hospital stay	1	

(continued)

Category	Variable	Description	N	Sources
	outcome_ventilationDays	Number of days ventilated	1	
	outcome_pneumonia	Pneumonia occurrence	4	qs, dia, df_neur_stwbr, df_neur_int, df_neur_stabr
	outcome_uti	Urinary tract infection occurrence	4	dia, df_neur_stwbr, df_neur_int, df_neur_stabr, lab_ustix
	outcome_sepsis	Sepsis occurrence	4	dia, df_neur_stwbr, df_neur_int, df_neur_stabr
	df_barthel_index	Barthel Index score at hospital discharge	1	qs
	outcome_palliativeCare	Palliative care received	1	qs
	outcome_tvt	Thromboembolic events occurrence	1	dia
	outcome_lae	Pulmonary lung embolism occurrence	1	dia

Clinimetric intstruments

National Institutes of Health Stroke Scale (NIHSS)

The NIHSS is a widely accepted tool for assessing stroke severity in acute ischemic stroke. Its aim is to provide a quantitative measure of the neurological impairment, which is easily comminicable. The scale consists of 11 items investigating aspects of Level of consciousness, gaze, visual fields, facial weakness, motor performance, sensory deficits, coordination, language, speech, and inattention (neglect). The score ranges from 0 to 42, with higher scores indicating more severe stroke symptoms. The individual items and their scoring criteria are presented in Table 3.3.

Origin

The NIHSS was developed by Brott and colleagues at the University of Cincinnati (Ohio) and first publicly described in 1989. (Brott et al. 1989) It was a composition of items of the Toronto Stroke Scale, the Oxbury Initial Severity Scale and the Cincinnati Stroke Scale, the Edinburgh-2 Coma scale. Interstingly, item like pupillary response and plantar response were intially included, but removed later.

Limitations

The scale has varying inter-rater reliability: depending on individual items. For exampel, assessments of limb ataxia and facial weakness show lower agreement compared to other items, with only moderate or fair consistency, though it performs comparably to other scales overall. The NIHSS favors left hemispheric strokes, as it includes seven points related to language function but only two points for neglect. This results in larger lesion volumes for right hemisphere strokes receiving the same NIHSS score as left hemisphere strokes. The scale does not include the whole spectrum assessment of cranial nerves. Therefore, this may lead to an underestimation of stroke severity in vertebrobasilar strokes. The NIHSS provides ordinal-level data rather than interval-level data, which means that adding up individual rankings to get a total score might be misleading. The scale is more useful for tracking changes in a patient's neurological status over time rather than relying solely on the total score for clinical decision-making. Makharia et al. (2024)

Table 3.3: National Institutes Of Health Stroke Scale Score (Brott et al. 1989)

Test	Scale
1a. Level of Consciousness (LOC)	0 = Alert; keenly responsive.\n1 = Not alert; arousable by minor stimulation. 2 = Not alert; requires strong or painful stimulation. 3 = Totally unresponsive.
1b. LOC Questions	0 = Answers both questions correctly. 1 = Answers one question correctly. 2 = Answers neither question correctly.
1c. LOC Commands	0 = Performs both tasks correctly. 1 = Performs one task correctly. 2 = Performs neither task correctly.
2. Best Gaze	0 = Normal. 1 = Partial gaze palsy. 2 = Forced deviation or total gaze paresis.
3. Visual	0 = No visual loss. 1 = Partial hemianopia. 2 = Complete hemianopia. 3 = Bilateral hemianopia (cortical blindness).
4. Facial Palsy	0 = Normal symmetrical movements. 1 = Minor paralysis. 2 = Partial paralysis. 3 = Complete paralysis.
5a. Left Arm Motor	0 = No drift. 1 = Drift, limb holds position but drifts down. 2 = Some effort against gravity. 3 = No effort against gravity. 4 = No movement.
5b. Right Arm Motor	0 = No drift. 1 = Drift, limb holds position but drifts down. 2 = Some effort against gravity. 3 = No effort against gravity. 4 = No movement.
6a. Left Leg Motor	0 = No drift. 1 = Drift, leg falls by end of period. 2 = Some effort against gravity. 3 = No effort against gravity. 4 = No movement.
6b. Right Leg Motor	0 = No drift. 1 = Drift, leg falls by end of period. 2 = Some effort against gravity. 3 = No effort against gravity. 4 = No movement.
7. Limb Ataxia	0 = Absent. 1 = Present in one limb. 2 = Present in two limbs.
8. Sensory	0 = Normal. 1 = Mild to moderate sensory loss. 2 = Severe to total sensory loss.
9. Best Language	0 = No aphasia. 1 = Mild to moderate aphasia. 2 = Severe aphasia. 3 = Mute/global aphasia.
10. Dysarthria	0 = Normal. 1 = Mild to moderate dysarthria. 2 = Severe dysarthria.
11. Extinction and Inattention	0 = No abnormality. 1 = Inattention or extinction in one modality. 2 = Profound inattention or extinction in multiple modalities.

Barthel Index

The Barthel Index is a means for measuring a patient's ability to perform activities of daily living (ADL). Developed in 1965, it assesses ten items related to mobility and self-care, measuring the overall objective being independent. The score ranges from 0 to 100, with higher scores indicating more independence. Scoring of each task considers the amount of assistance required. (Mahoney and Barthel 1965)

Table 3.4: The Barthel Index (Mahoney and Barthel 1965)

Item	Description	Scores
Feeding	Ability to eat independently	0 = Unable; 5 = Needs help; 10 = Independent
Bathing	Ability to bathe or shower independently	0 = Dependent; 5 = Independent
Grooming	Ability to perform personal grooming	0 = Dependent; 5 = Independent
Dressing	Ability to dress and undress	0 = Unable; 5 = Needs help; 10 = Independent
Bowel Control	Ability to control bowels	0 = Incontinent; 5 = Occasional accidents; 10 = Continent
Bladder Control	Ability to control bladder function	0 = Incontinent; 5 = Occasional accidents; 10 = Continent
Toileting	Ability to use the toilet independently	0 = Dependent; 5 = Needs help; 10 = Independent
Transfers (bed to chair)	Ability to transfer from bed to chair	0 = Unable, no sitting balance; 5 = Major help; 10 = Minor help; 15 = Independent
Mobility (on level surfaces)	Ability to walk or propel wheelchair on flat surfaces	0 = Immobile; 5 = Wheelchair independent; 10 = Walks with help; 15 = Independent
Stairs	Ability to ascend and descend a flight of stairs	0 = Unable; 5 = Needs help; 10 = Independent

Modified Rankin Scale (mRS)

The Modified Rankin Scale (mRS) is a pivotal tool in neurology and stroke research, offering a standardized measure of the degree of disability or dependence on activities of daily living in stroke patients. Developed initially by Dr John Rankin in 1957 (Rankin 1957) and later modified (Sulter et al. 1999) for enhanced reliability and applicability, the mRS is widely recognized for its simplicity and effectiveness in clinical settings and research. It is a 7-point score (ranging from 0 to 6), with each level corresponding to specific criteria outlined in Table 3.5.

Table 3.5: Modified Rankin Scale (mRS)

Score	Description	Explanation
0	No symptoms	The individual has no symptoms and is fully functional.
1	No significant disability	The individual is able to carry out all usual activities, despite some symptoms.
2	Slight disability	The individual is able to look after their own affairs without assistance but is unable to carry out all previous activities.
3	Moderate disability	The individual requires some help but is able to walk unassisted.
4	Moderately severe disability	The individual is unable to attend to their own bodily needs without assistance and is unable to walk unassisted.
5	Severe disability	The individual is bedridden, incontinent, and requires constant nursing care and attention.
6	Death	The individual has died.

Inter-rater reliability and validity of mRS are robust, underscoring its critical role as outcome parameters in clinical trials and routine patient assessments. Further advantages include its simplicity and ease of use, which are widely accepted and do not require extensive training. Disadvantages comprise some degree of subjectivity in interpreting different levels, decreased sensitivity in rehabilitation trials (McGill et al. 2022), and it focuses on physical disability. The latter aspect is essential as neurophysiological and cognitive impairments might impact an individual's daily life even more.

Stroke Etiology

Stroke Etiology within this database is following the principles of the Trial of ORG 10172 in Acute Stroke Treatment, short: TOAST), which classifies five subtypes namely large artery atherosclerosis, cardioembolism, small artery occlusion, stroke of other determined cause, and stroke of undetermined cause. (Adams et al. 1993)

Chapter 4

Discussion

The present study offers a comprehensive analysis of new-onset delirium in a large cohort of stroke patients, emphasizing the significant role of biological sex and various clinical factors in its occurrence. By integrating a wide range of variables—including demographics, clinical presentations, therapeutic interventions, and medications—the study provides valuable insights that contribute to the existing literature on post-stroke delirium and have important implications for clinical practice and future research.

Occurrence of Delirium and Sex Differences

Delirium occurred in 6.3% of patients in this study, with a notably higher incidence in males (7.3%) compared to females (4.8%). This significant sex difference persisted even after adjusting for confounding factors such as age and stroke severity, with male sex remaining an independent predictor of delirium (odds ratio 2.1, 95% credible interval 1.68–2.66). These findings align with several previous studies that have reported a higher risk of delirium in males following stroke or other acute medical conditions. For instance, Oldenbeuving et al. (2011) identified male sex as a risk factor for delirium in acute stroke patients, and similar associations have been observed in other settings, such as intensive care units (Zhang et al., 2013).

In a meta-analysis of vascular risk factors Siokas and colleagues investigated also the influence of biological sex on delirium. They included

The biological underpinnings of this sex difference are not fully understood but may involve hormonal influences, differences in brain structure and function, or varying responses to stress and inflammation. Estrogen, for example, has been suggested to have neuroprotective

effects that could mitigate the risk of delirium in females (Barron et al., 2017). The implications of this finding are significant for clinical practice. Recognizing male sex as a risk factor for delirium can prompt healthcare providers to implement targeted monitoring and preventive strategies for male patients, potentially reducing the incidence and severity of delirium in this population.

Age and Its Interaction with Sex

The study demonstrated a meaningful association between age and the occurrence of delirium, with older patients exhibiting a higher probability of developing delirium. This is consistent with the well-established understanding that advanced age is a major risk factor for delirium due to age-related physiological changes, increased comorbidities, and decreased cognitive reserve (Inouye et al., 2014). Notably, the interaction between age and sex revealed that females between the ages of 70 and 90 were less likely to develop delirium compared to their male counterparts. This suggests that the protective factors associated with female sex may become more pronounced with advancing age. While some studies have reported similar findings (Fong et al., 2009), others have not observed significant sex differences in age-related delirium risk (Oh et al., 2015). The present study adds to this body of knowledge by highlighting the need for age- and sex-specific approaches to delirium prevention.

Premorbid Function and Delirium

The premorbid Rankin Scale (pRS) was used to assess the relationship between pre-stroke functional status and delirium occurrence. Contrary to expectations, none of the pRS levels showed a convincing association with delirium. This finding differs from previous research that has identified poor premorbid functional status as an independent risk factor for delirium (Pasinska et al. 2018). One possible explanation is the relatively low number of patients in the higher pRS categories in this study, which may have limited the statistical power for detection.

Stroke Severity, Location, and Delirium As anticipated, higher National Institutes of Health Stroke Scale (NIHSS) scores, indicating more severe strokes, were strongly associated with an increased probability of delirium (odds ratio 1.456). This aligns with existing literature, as severe strokes are more likely to result in extensive brain damage, increased intracranial pressure, and a greater burden of neurological deficits, all of which can contribute to delirium (Shi et al., 2019). Furthermore, strokes in the right hemisphere and

posterior circulation were linked to a higher likelihood of delirium compared to left hemispheric strokes. Right hemispheric strokes can affect attentional networks and spatial awareness, potentially leading to neglect and confusion, which are risk factors for delirium (Voyer et al., 2012). Posterior circulation strokes may involve the brainstem and cerebellum, areas critical for arousal and consciousness, thereby increasing the risk of delirium (Kase et al., 1995). These findings emphasize the importance of considering stroke location and severity in delirium risk assessments. Clinicians should be particularly vigilant in monitoring patients with severe strokes and those involving the right hemisphere or posterior circulation. Influence of Therapy Modes on Delirium The mode of therapy was also associated with the occurrence of delirium. Patients receiving endovascular therapy had higher odds of developing delirium than those receiving intravenous thrombolysis (odds ratio 0.749). After adjusting for age and NIHSS scores, this association was partially explained, suggesting that the increased delirium risk may be related to the severity of the stroke necessitating endovascular intervention. Previous studies have yielded mixed results regarding the impact of therapeutic interventions on delirium risk. Some research indicates that more invasive procedures may elevate delirium risk due to factors like anesthesia, procedural complications, and increased physiological stress (Brummel et al., 2014). However, other studies have not found significant differences between treatment modalities (Abelha et al., 2013). The present findings highlight the need for further investigation into how specific therapies influence delirium risk and underscore the importance of careful patient selection and perioperative care. Aphasia, Sex Differences, and Delirium The presence and severity of aphasia were analyzed in relation to delirium occurrence. While aphasia severity alone showed variable and uncertain effects, a significant interaction between aphasia severity and sex was evident. Males with moderate to severe aphasia were significantly more likely to develop delirium compared to females with the same level of aphasia. Aphasia can impair communication, leading to frustration, isolation, and difficulty in expressing needs, which may contribute to delirium (Smith et al., 2017). The observed sex difference may be related to differences in coping mechanisms, social support networks, or neurological factors such as brain plasticity and language processing. Some studies suggest that females may have a greater capacity for language recovery due to bilateral language representation in the brain (Friedrich et al., 2015). These findings suggest that male patients with aphasia are a high-risk group for delirium and may benefit from enhanced communication support and interventions aimed at reducing delirium

risk. Neglect Syndromes and Delirium Neglect syndromes, characterized by a lack of awareness of one side of space or the body, were associated with higher odds of delirium across all levels of severity. This association is consistent with the understanding that neglect can lead to disorientation, impaired mobility, and decreased ability to interact with the environment, all of which can contribute to delirium (Cherney & Halper, 2001). An interesting finding was the significant interaction between visual neglect and sex, with females being more at risk of developing delirium in this context. While some studies have reported that neglect is more common or severe in males (Buxbaum et al., 2004), the present study suggests that when females do experience neglect, it may have a greater impact on delirium risk. This could be due to differences in how males and females perceive and compensate for neglect or varying lesion patterns. Further research is needed to explore these sex-specific effects. Level of Consciousness and Delirium Reduced levels of consciousness at admission, such as somnolence, sopor, and coma, were associated with a higher likelihood of developing delirium. This is consistent with previous findings that decreased arousal and altered mental status are risk factors for delirium (Gusmao-Flores et al., 2012). Interestingly, males were less likely to present with worse levels of consciousness but had a higher likelihood of delirium when awake or somnolent. This suggests that even when presenting with similar levels of consciousness, males may be more susceptible to delirium, potentially due to differences in vulnerability to stressors, inflammatory responses, or other physiological factors. Microangiopathy and Delirium The presence of moderate to severe cerebral microangiopathy was associated with increased odds of delirium. Cerebral microangiopathy reflects small vessel disease, which can lead to white matter lesions, reduced cerebral blood flow, and impaired cognitive function (Patel & Markus, 2011). These changes can decrease the brain's resilience to acute insults like stroke, increasing the risk of delirium. Females exhibited a higher frequency of severe microangiopathy, which may be related to factors such as longer lifespan, hormonal influences, or comorbid conditions like hypertension and diabetes. The sex difference in microangiopathy prevalence and its impact on delirium risk warrants further investigation. Alcohol Consumption, Dementia, and Delirium Males were more likely to report moderate to severe alcohol consumption prior to stroke, but this did not show a significant association with delirium in the study. This contrasts with some literature suggesting that alcohol abuse is a risk factor for delirium due to withdrawal effects and neurotoxicity (Siddiqi et al., 2006). The lack of association may be due to un-

derreporting, the classification of alcohol consumption levels, or the influence of other variables. Known dementia was more prevalent in females (5.5%) than males (2.8%), and having a previous diagnosis of dementia increased the likelihood of developing delirium (odds ratio 1.92). This is consistent with extensive research indicating that pre-existing cognitive impairment is one of the strongest predictors of delirium (Inouye et al., 2014). The sex-specific interaction, with females having an increased risk of delirium when dementia is present, may reflect the higher prevalence of dementia in females and possibly differences in disease progression or brain reserve. Medications and Delirium The study examined the association between various medications and the risk of delirium, revealing several notable findings. Medications Associated with Increased Delirium Risk: Angiotensin II Receptor Blockers (ARBs): Patients using ARBs prior to stroke had higher odds of developing delirium (odds ratio 1.506). While ARBs are commonly prescribed for hypertension and have neuroprotective properties, some evidence suggests they may influence cognitive function and cerebral perfusion (Wright et al., 2013). Pyrazolones: This class, including metamizole, showed a positive association with delirium (odds ratio 1.354). Pyrazolones have analgesic properties but may cause central nervous system side effects. Other Antiepileptics (ATC code N03AX): Medications like lamotrigine and levetiracetam were associated with increased delirium risk (odds ratio 1.832), potentially due to their effects on neurotransmitter systems and sedation. Medications with Potential Protective Effects Against Delirium: Glucocorticoids: Associated with a decreased risk of delirium (odds ratio -0.90). Glucocorticoids have anti-inflammatory effects that may reduce cerebral edema and oxidative stress, potentially mitigating delirium risk (Schwab et al., 2011). However, they can also cause neuropsychiatric side effects, so this finding should be interpreted with caution. Potassium Supplementation: Showed a protective effect (odds ratio -0.73). Adequate potassium levels are essential for neuronal function, and hypokalemia may contribute to delirium (Vasudev & Shah, 2009). The interaction model revealed that certain medications had different effects on delirium risk depending on sex. For example, thiazides, digitalis glycosides, and aldosterone antagonists were associated with higher delirium risk in males. These medications can affect electrolyte balance and cardiovascular function, which may differentially impact males due to physiological differences. These findings highlight the importance of medication review in stroke patients and suggest that clinicians should be attentive to the potential neuropsychiatric effects of certain medications, especially in male patients. Outcomes and

Influence of Delirium and Sex Delirium was associated with worse outcomes, including longer hospital stays, lower Barthel Index scores at discharge, and higher mortality rates. Patients who developed delirium had greater dependency and poorer functional recovery, which is consistent with previous studies demonstrating the adverse impact of delirium on rehabilitation and long-term outcomes (McManus et al., 2009). Regarding sex differences, males had slightly better NIHSS scores at discharge and higher percentages of favorable outcomes on the modified Rankin Scale (mRS) after three months. However, females had a higher mortality rate at three months. These differences may reflect variations in stroke severity, access to rehabilitation services, comorbidities, or social support systems. Understanding the influence of sex on stroke outcomes is complex. Some research suggests that females may experience worse outcomes due to factors like older age at stroke onset, higher prevalence of atrial fibrillation, and differences in healthcare utilization (Bushnell et al., 2014). The present study underscores the need for sex-specific analyses in stroke research to identify and address disparities. Strengths of the Study Large Sample Size: The inclusion of 5,772 patients enhances the statistical power and generalizability of the findings. Comprehensive Variable Analysis: The study examined a wide array of variables, including clinical features, therapies, medications, and outcomes, providing a holistic view of factors influencing delirium. Use of Advanced Statistical Methods: The application of Bayesian logistic regression allowed for probabilistic interpretations and the incorporation of prior knowledge, improving the robustness of the results. Focus on Sex Differences: By specifically analyzing the role of biological sex, the study adds valuable insights into sex-specific risk factors and outcomes. Detailed Outcome Measures: The assessment of both short-term and long-term outcomes, including functional scores and mortality, provides a comprehensive understanding of the impact of delirium. Limitations of the Study Retrospective Design: The study's retrospective nature may introduce biases related to data collection, missing data, and unmeasured confounders. Incomplete Data: Missing information on certain variables, such as premorbid Rankin Scale and alcohol consumption, could affect the validity of the analyses. Diagnosis of Delirium: The methods for diagnosing delirium were not detailed, and variability in assessment tools or clinician expertise could influence the findings. Potential Confounding Factors: While adjustments were made for several variables, unmeasured factors like socioeconomic status, cognitive reserve, or genetic predispositions might impact the results. Medication Data: Reliance on self-reported medication use prior to admission may

be subject to recall bias, and over-the-counter or non-prescribed medications were not accounted for. Single-Center Data: If the data were collected from a single center or region, the findings may not be generalizable to different healthcare settings or populations. Implications for Future Research and Clinical Practice The findings of this study have significant implications for both clinical practice and future research. Risk Assessment and Monitoring: Identifying male sex, advanced age, severe stroke, aphasia, and neglect as risk factors for delirium can inform risk stratification and prompt early monitoring and intervention. Sex-Specific Interventions: The observed sex differences suggest the need for tailored approaches in delirium prevention and management, considering biological, social, and behavioral factors unique to each sex. Communication and Support Strategies: Enhancing communication support for patients with aphasia, particularly males, may reduce the risk of delirium and improve outcomes. Medication Management: Clinicians should carefully evaluate the risks and benefits of medications that may influence delirium risk, especially in male patients, and consider alternatives or additional monitoring. Delirium Prevention Programs: Implementing evidence-based delirium prevention protocols, including environmental modifications, cognitive stimulation, and early mobilization, may benefit high-risk patients. Further Research: Prospective, multicenter studies are needed to confirm these findings and explore underlying mechanisms. Research into the biological basis of sex differences, the role of hormones, and genetic factors could provide deeper insights. Conclusion This study underscores the complex interplay of biological sex, clinical factors, and therapeutic interventions in the occurrence of delirium after stroke. Males are at higher risk of developing delirium, and this risk is influenced by factors such as age, stroke severity, aphasia, neglect, and certain medications. Delirium, in turn, is associated with worse functional outcomes and increased mortality. Recognizing these risk factors allows healthcare providers to implement targeted strategies to prevent and manage delirium, ultimately improving patient outcomes. Future research should focus on elucidating the mechanisms behind sex differences in delirium risk and developing interventions that address these disparities.

Strength and limitation The study is retrospective and although it employed a meticulous methodological approach, limitations inherent to this design remain.

Concerning the detection of delirium it is essential to acknowledge that different types of delirium, including hypoactive delirium, may

have been underdiagnosed in our cohort. For instance, the overall rate of delirium in our cohort was 6xxx%. In a meta-analysis, Zhang and colleagues found significant variability in the occurrence of delirium, ranging from 4.9% to 66.2%. It's worth noting that our cohort, which was selected based on treatment indication, had a delirium frequency on the lower end of this spectrum. However, results from a very recent report in a severely affected stroke population that is comparable to this population, Sachdev and colleagues retrospectively found a delirium diagnosis in 24 out of 467 (5.1%) patients.

Cases of delirium might be misclassified because of inconsistent documentation practices or varying diagnostic criteria used by treating physicians. For instance, different clinicians might have interpreted symptoms of delirium differently, which leads to inconsistencies in case identification. Especially the diagnostic criteria of delirium, although following a standard operating procedure and applying well-known delirium detection scores, may have been variable over the years, may have been team-specific and individual-specific. Additionally, factors like nurse-to-patient ratios, hospital environment, and staff awareness and training on delirium recognition can affect the incidence and detection of delirium. Moreover, the study did not assess information on the severity or exact duration of delirium episodes. This may be most important for a better understanding of how delirium impacts outcome.

New variables were sourced through a semi-automatic process, which included diagnosis retrieval from the hospital information system and chart retrieval using search terms via regular expressions. Feedback loops were implemented to ensure accuracy, constantly improving the search terms and achieving a high true positive rate and a low false positive rate. Despite these measures, underdetection and misclassification cannot be entirely ruled out because of potential data entry errors and incorrect coding during chart reviews.

Moreover, the study period spans over 20 years. Over such a long time, changes in clinical practices, diagnostic criteria, and hospital standards and policies could introduce a temporal bias. However, analyses directly show differences in admission years, and admission years are accounted for in Bayesian regression analyses, which ultimately improves interpretability.

The cohort was selected based on specific treatment indications. Selection bias may be present, and the sample may not represent the general population. Additionally, it might exclude certain patient groups, limiting the generalizability of the findings to other settings

or populations. Although the Heidelberg stroke center is one of the first established in Germany and known for its high-quality standards, the study is monocentric, and results need external evaluation for generability.

The study tried to include many factors associated with delirium; however, unmeasured confounders may exist, which have not been accounted for. Factors such as socioeconomic status, ethnicity, educational background, or unrecorded comorbidities may influence the occurrence of delirium and, ultimately, functional outcomes. This may lead to residual confounding. Unmeasured psychological factors like stress and anxiety can contribute to delirium but are often not recorded in medical records, leading to incomplete risk factor assessment.

Additionally, a decline in precognition that previously did not result in a dementia diagnosis would have gone unnoticed, as only established dementia diagnoses at hospital admission were assessed. Therefore, although preexisting dementia was an independent predictor for many models already, it is important to note that the frequency of dementia in this cohort may be underestimated, which could potentially bias the study's results.

The variable selection process for individual models was based on available evidence from literature reviews and information on associations from univariable or bivariable models. Although the final multivariable models included many factors associated with delirium, the Bayesian models developed for prediction were not validated in external cohorts. The study actively and openly reports missing data for variables of interest. But missing data can reduce the statistical power of the study and introduce bias if the missingness is not random, as primarily assumed. To address this potential bias, final models were additionally calculated using multiple imputation datasets.

In this study, the time at which delirium was diagnosed during the hospital stay was unavailable. Therefore, a differentiation between early-onset and late-onset delirium could not be made. Additionally, as for other outcomes that occurred during hospital stay (e.g., pneumonia), associations to delirium can only be made without a clear direction of effect. For this reason, the focus for a delirium model was set on the very early stage at hospital admission. This study collected a great number of medications that were available at hospital admission, focusing on the drug substance itself rather than detailed dosing information. During the hospital stay and

thereafter, medications other than recombinant tissue plasminogen activator were not researched - this may limit the interpretability of associations of admission medications with outcomes.

This work did not focus on the exact diagnostic workup of stroke patients. Although unlikely, this may be a potential source of bias.

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Date / Year generell A increase over the years of delirium could be observed. This may have several reasons. First and foremost, screening conditions for delirium and the awareness of the diagnosis and its impact may contribute to this increase. Second, the increasing number of endovascular therapies and increasing number of procedures. This does not necessarliy mean that endocvascular therapy causally increases delirium, rather being a procedure / surgery, which is generally known to increase delirium. Additionally, the circumstances may play an important role, such as mode of sedation.

Chapter 5

Declaration of Generative AI and AI-Assisted Technologies in the Writing Process

In the creation of this work, the author utilized services provided by OpenAI, Inc. to support both writing and code development. All contributions these services were supplementary. Importantly, the author genuinely created the core intellectual content and made all final decisions.

For written text, the author employed services to review grammar, semantics, and overall language quality, using recent large language models (e.g. GPT-3, GPT-4, and GPT-4-turbo). Each response was carefully evaluated by the author for accuracy, quality of improvement, and to ensure that the original intent and meaning of the text remained intact. The author maintained full control over the content, ensuring that all substantive contributions and creative decisions were their own.

For code, prompts were used to review and address errors when needed. In specific instances, such as with the function 'getDelir,' the OpenAI advanced programming interface was employed to extract information from anonymized text. Similar to other methods used, such as regular expressions, prompts were iteratively refined until the desired quality was achieved. The author designed, refined and validated these solutions. Additional details are available in the methods section.

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