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Perinatal Stroke

Arterial ischemic stroke and cerebral sinovenous thrombosis: epidemiology, risk factors, and clinical presentation

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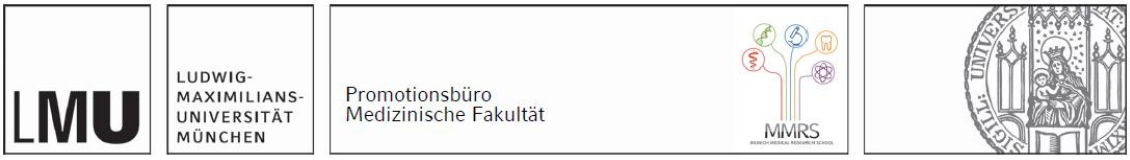

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Contents

Abbreviations

AIS	Arterial ischemic stroke
BAQ	Bavarian Institute for Quality Assurance of Hospital Care 'Bayerische Arbeitsgemeinschaft für Qualitätssicherung in der stationären Versorgung'
CI	Confidence interval
CRC	Capture-Recapture Calculation
cUS	Cranial ultrasound
CSVT	Cerebral sinovenous thrombosis
CT	Computed tomography
ESPED	German Paediatric Surveillance Unit 'Erhebungseinheit für Seltene Pädiatrische Erkrankungen in Deutschland'
GA	Gestational age
HD	Data of hospital discharge documentation
HELLP	Haemolysis, elevated liver enzymes, and a low platelet count
ICD / ICD-10	International Classification of Disease, 10. Revision, German Modification (ICD-10-GM)
IQR	Interquartile range
LGA	Large for gestational age
MRI	Magnet Resonance Imaging
MRV	Magnetic resonance venography
NRW	North–Rhine–Westphalia
na	Not applicable
nCSVT	Neonatal cerebral sinovenous thrombosis
OPS	German modification of the International Classification of Health Interventions (ICHI) 'Operationen- und Prozedurenschlüssel'
OR	Odds ratio
PAIS	Perinatal arterial ischemic stroke
PPIS	Presumed perinatal arterial ischemic stroke
SD	Standard deviation
SGA	Small for gestational age
VLBW	Very low birthweight infant
wks	Weeks
10P	Tenth percentile
90P	Ninetieth percentile

List of publications related to the thesis

Publication I

Sorg A-L, von Kries R, Klemme M, Gerstl L, Felderhoff-Müser U, Dzietko M. Incidence Estimates of Perinatal Arterial Ischemic Stroke in Preterm- and Term-Born Infants: A National Capture-Recapture Calculation Corrected Surveillance Study. *Neonatology 2021:1–7.*

Publication II

Sorg A-L, von Kries R, Klemme M, Gerstl L, Beyerlein A, Lack N et al. Incidence and risk factors of cerebral sinovenous thrombosis in infants. *Dev Med Child Neurol 2021*.

Publication III

Sorg A-L, Klemme M, von Kries R, Felderhoff-Müser U, Flemmer AW, Gerstl L et al. Clinical Diversity of Cerebral Sinovenous Thrombosis and Arterial Ischaemic Stroke in the Neonate: A Surveillance Study. *Neonatology 2021:1–7.*

Author's contribution to the related works

The Department of Neonatology and the Department of Paediatric Neurology in the University Paediatric Hospital of the Ludwig-Maximilians-University Munich, the Institute of Social Paediatrics and Adolescent Medicine of the Ludwig-Maximilians-University Munich, the Department of Neonatology in the Paediatric Hospital of the University Duisburg-Essen, and the German Surveillance Unit for Rare Disease in Childhood (Erhebungseinheit für Seltene Pädiatrische Erkrankungen in Deutschland — ESPED) collaborative conducted the nationwide, hospital-based study of stroke in children from 2015 to 2017.

The author of the thesis, Anna-Lisa Sorg, joined the study team at the beginning of 2018 when the case reporting period of the surveillance study was completed, and most of the questionnaires were returned to ESPED. The ESPED office conducted the monthly survey from 2015 to 2017 in the paediatric hospitals in Germany, gathered the case reports and monitored the return of the corresponding questionnaires. Anna-Lisa Sorg was accountable for data transmission to an electronic database, quality control, data completeness checking and maintenance. She communicated between the ESPED office and the study team, including reporting incomplete questionnaires to ESPED, which contacted the representatives in the clinics to add the missing information.

Together with the supervisor Rüdiger von Kries, Anna-Lisa Sorg was primarily involved in the idea, design, and planning of the follow-up studies intended for incidence estimations (corrected for incomplete ascertainment) and risk factor analyses. In particular, Anna-Lisa Sorg selected the study design and methods, managed data acquisition, merged the different data sources, performed data curation, and all analyses. For the three publications related to this dissertation, Anna-Lisa Sorg was in charge of the conception of the research questions and data management. Anna-Lisa Sorg reviewed existing literature, conducted all data analyses, and was responsible for data interpretation, drafting the manuscripts (including all figures and tables), and the publishing processes.

About the three publications, the co-authors, in particular Mark Dzietko and Rüdiger von Kries, support the dissertation by reviewing the manuscripts and supporting the data interpretation with their expertise. Lucia Gerstl was in charge of the idea and conception of the ESPED study, including the study-specific questionnaire. Mark Dzietko, Ursula Felderhoff-Müser, and Mathias Klemme were responsible for revising the study-specific questionnaire and the case validation processes. Nicholas Lack provided the BAQ data for the nested case-control study in Publications II and IV, and Andreas Beyerlein conducted the control selection and matching process.

The manuscript draft for Publication IV of this dissertation originated from the author's master's thesis. Since the revision and publication process was within the dissertation period, and the content is relevant for the thesis, it has been included in the appendix.

Summary (English)

With the rise of sophisticated imaging techniques in clinical settings, the number of diagnoses of perinatal strokes increased in recent decades. A perinatal stroke occurs in-utero or in the neonatal period and is causal for several neurological deficits. There are different types of perinatal stroke, with the two most common arterial ischemic stroke and cerebral sinovenous thrombosis. So far, information on the incidence of the subtypes, risk factors or specifics of the clinical presentation is limited. Previous data often originate from settings without extensive use of modern cerebral imaging. Additionally, most studies excluded preterm born infants. Thus, although there are reports of perinatal stroke in preterm born infants, the incidence in this group remains unknown.

Timely diagnosis is essential to improve outcomes. This requests knowledge of risk factors, early signs, clinical presentation, the disease's characteristic course, and whether co-morbidities, such as prematurity, lead to different symptomatology or course. Previous studies analysed the subtypes of perinatal stroke separately. For in-depth understanding, however, it is important to identify differences in risk factors and clinical presentation by comparing the subtypes. Furthermore, there is a great need for research into neuroprotective strategies. Reliable epidemiological data, providing information on the incidence, timing of diagnosis, and risk groups may facilitate the design of future clinical trials.

This cumulative thesis reports the results of a nationwide, hospital-based study in Germany (2015-2017), including estimations of incidences of the two most common types of perinatal stroke – arterial ischemic stroke and cerebral sinovenous thrombosis – along with analyses of risk factors and clinical presentations. Incidence estimates were adjusted for under-reporting using a second data source (hospital discharge diagnoses) and the Capture-Recapture methodology, which enable valid estimations for the frequency of disease from incomplete data sources. In addition, simultaneous and uniform data collection of the two types of perinatal stroke enables the comparison of arterial ischemic stroke and cerebral sinovenous thrombosis in neonates.

The first publication includes data of 145 newborn infants with arterial ischemic stroke. Nineteen of these infants were born prematurely. The incidence adjusted for under-reporting using the Capture-Recapture methodology was 22 (95% confidence interval (CI) 17, 27) per 100,000 live-born infants. This corresponds to 131-209 diagnoses annually among 773,100 live births in Germany. The incidence in preterm infants was higher compared to the incidence in term born infants (32 (95% CI 15, 49) and 21 (95% CI 16, 26) per 100,000). The higher incidence seems to be due to subclinical cases, as there was no difference in incidence confining the calculation to symptomatic cases. Infants born prematurely are exposed to significantly more risk factors that contribute to a stroke but are less likely to show specific symptoms such as seizures.

The second publication shows an incidence of cerebral sinovenous thrombosis in newborn infants of 6.6 (95% CI 4.4, 8.7) per 100,000 live births, also using the Capture-Recapture methodology.

To date, there is no study analysing risk factors of cerebral sinovenous thrombosis in neonates using a control group. Comparison with a control group derived from the Bavarian Perinatal Survey yielded associations to sex, preterm birth, hypoxia, operative vaginal delivery, emergency caesarean section, and pathological fetal Doppler assessment. Hypoxia was an independent risk factor with an odds ratio of 20.3 (95% CI 8.1, 50.8).

The third publication provides a comparison of the two forms of perinatal stroke. Arterial ischemic stroke was almost three times more common in neonates than cerebral sinovenous thrombosis. While the diagnosis of arterial ischemic stroke was usually made within a few hours around birth, cerebral sinovenous thrombosis was generally diagnosed within the first days of life. Prematurity and symptoms suggesting perinatal asphyxia were more often reported in infants with cerebral sinovenous thrombosis.

In conclusion, the results on the actual incidence related to case ascertainment in a country with high medical standards of perinatal care may be useful in planning future clinical trials on neuroprotective and therapeutic strategies. Furthermore, these findings specified and confirmed the risk factors and clinical presentation of the two most common forms of perinatal stroke. In particular, the findings highlighted that perinatal stroke is also a relevant disorder in preterm born infants. Symptoms of preterm born infants with stroke are highly non-specific and often confounded by co-morbidities of prematurity. So far, the awareness of perinatal stroke has been limited in this risk group. The identified differences in perinatal stroke subtypes may help to disentangle the underlying causal pathways of perinatal stroke.

Summary (German)

Mit zunehmender Verfügbarkeit hochentwickelter bildgebender Verfahren wurden perinatale Schlaganfälle in den letzten Jahrzehnten immer häufiger diagnostiziert. Ein perinataler Schlaganfall tritt intrauterin oder in der Neugeborenenperiode auf und ist ursächlich für verschiedene neurologische Störungen. Es gibt verschiedene Arten des perinatalen Schlaganfalls, wobei die beiden häufigsten der arterielle ischämische Schlaganfall und die zerebrale Sinusvenenthrombose sind. Bislang gibt es wenig fundierte Kenntnisse zur Inzidenz der Subtypen, zu Risikofaktoren oder zu den Besonderheiten des klinischen Bildes. Bisherige Daten wurden häufig ohne umfassenden Einsatz moderner zerebraler Bildgebung erhoben. Zudem wurden in den meisten Studien Frühgeborene ausgeschlossen. Obwohl es Berichte über perinatale Schlaganfälle bei Frühgeborenen gibt, ist die Inzidenz in dieser Gruppe nach wie vor unbekannt.

Eine rechtzeitige Diagnose ist entscheidend für ein verbessertes Outcome. Dies erfordert genaue Kenntnisse über Risikofaktoren, frühe Anzeichen, das klinische Erscheinungsbild, den charakteristischen Krankheitsverlauf und darüber, ob Komorbiditäten wie Frühgeburtlichkeit zu einer veränderten Symptomatik oder einem anderen Verlauf führen. Bisherige Studien untersuchten die Subtypen des perinatalen Schlaganfalls getrennt. Für ein vertieftes Verständnis ist es jedoch wichtig die Subtypen hinsichtlich Risikofaktoren und klinischem Erscheinungsbild zu vergleichen und Unterschiede zu identifizieren. Darüber hinaus besteht ein großer Bedarf an Forschung zu neuroprotektiven Strategien. Verlässliche epidemiologische Daten, die Aufschluss über die Häufigkeit, den Zeitpunkt der Diagnose und Risikogruppen geben, könnten die Konzeption solcher klinischen Studien zukünftig erleichtern.

Diese kumulative Dissertation berichtet die Ergebnisse einer deutschlandweiten, krankenhausbasierten Studie (2015-2017), die die Schätzung der Inzidenzen der beiden häufigsten Formen des perinatalen Schlaganfalls – der arteriell ischämische Schlaganfall und die zerebrale Sinusvenenthrombose – ebenso wie die Untersuchung von Risikofaktoren und der klinischen Erscheinungsbilder beinhaltet. Die Inzidenzschätzungen wurden unter Verwendung einer zweiten Datenquelle (Krankenhausentlassungsdiagnosen) mittels der Capture-Recapture Methodik auf Untererfassung bereinigt, welche valide Schätzungen der Krankheitshäufigkeit aus unvollständigen Datenquellen ermöglicht. Darüber hinaus ermöglichte die zeitgleiche und einheitliche Datenerhebung der beiden Formen den Vergleich des arteriellen ischämischen Schlaganfalls und der zerebralen Sinusvenenthrombose bei Neugeborenen.

Die erste Publikation beinhalt Daten von insgesamt 145 neugeborenen Kindern mit arteriell ischämischen Schlaganfall. Neunzehn dieser Kinder kamen zu früh zur Welt. Die durch die Capture-Recapture Methodik auf Untererfassung bereinigte Inzidenz lag bei 22 (95% Konfidenzintervall (CI) 17, 27) pro 100.000 Lebendgeborene. Dies entspricht 131-209 Diagnosen bei jährlich 773.100 Lebendgeburten in Deutschland. Die Inzidenz bei zu früh geborenen Kindern war höher als die Inzidenz bei reif geborenen Kindern (32 (95% CI 15, 49) und 21 (95% CI 16, 26) pro

100.000). Die höhere Inzidenz scheint auf subklinische Fälle zurückzuführen zu sein, da sich bei der Beschränkung auf symptomatische Fälle kein Unterschied in der Inzidenz zeigte. Frühgeborene Kinder waren mehr Risikofaktoren ausgesetzt, die einen Schlaganfall begünstigen, zeigten aber weniger häufig spezifische Symptome wie beispielsweise Krampfanfälle.

In der zweiten Publikation ist, ebenfalls durch Anwendung der Capture-Recapture Methodik, gezeigt, dass die Inzidenz der zerebralen Sinusvenenthrombose bei Neugeborenen bei 6,6 (95% CI 4,4, 8,7) pro 100.000 Lebendgeburten lag. Bislang gibt es keine Studie in der Risikofaktoren für eine zerebrale Sinusthrombose bei Neugeborenen unter Verwendung einer Kontrollgruppe untersucht wurden. Der Vergleich mit einer aus der Bayerischen Perinatalerhebung stammenden Kontrollgruppe ergab Assoziationen zu Geschlecht, Frühgeburt, Hypoxie, vaginal-operativer Entbindung, notfallmäßigem Kaiserschnitt und pathologischem fetalem Doppler Untersuchung. Hypoxie erwies sich als unabhängiger Risikofaktor mit einem Odds Ratio von 20,3 (95% CI 8,1, 50,8).

Die dritte Publikation zeigt den Vergleichs der beiden Formen des perinatalen Schlaganfalls. Ein arteriell ischämischer Schlaganfall kam bei Neugeborenen fast dreimal häufiger vor als die zerebrale Sinusvenenthrombose. Während die Diagnose des arteriell ischämischen Schlaganfalls meist innerhalb weniger Stunden nach der Geburt gestellt wurde, erfolgte die Diagnose einer zerebralen Sinusvenenthrombose häufig erst innerhalb der ersten Lebenstage. Frühgeburtlichkeit, sowie Symptome, die auf eine perinatale Asphyxie hindeuten, wurden bei Neugeborenen mit einer der zerebralen Sinusvenenthrombose häufiger berichtet.

Zusammenfassend lässt sich sagen, dass die Ergebnisse über die tatsächliche Inzidenz in Bezug auf die Erfassung von Fällen in einem Land mit hohen medizinischen Standards der perinatalen Versorgung bei der Planung künftiger klinischer Studien zu neuropräventiven und therapeutischen Strategien nützlich sein können. Darüber hinaus wurden die Risikofaktoren und das klinische Bild der beiden häufigsten Formen des perinatalen Schlaganfalls präzisiert und bestätigt. Insbesondere wurde deutlich, dass der perinatale Schlaganfall auch bei Frühgeborenen eine relevante Erkrankung darstellt. Die Symptome von Frühgeborenen mit Schlaganfall sind sehr unspezifisch und werden oft durch Komorbiditäten der Frühgeburt überlagert. Bislang ist das Problembewusstsein für einen perinatalen Schlaganfall bei dieser Risikogruppe noch begrenzt. Die festgestellten Unterschiede bei den Subtypen des perinatalen Schlaganfalls könnten zur Entschlüsselung der zugrundeliegenden Ursachen des perinatalen Schlaganfalls beitragen.

1 Introduction

While there are numerous studies on strokes in adults, stroke was not recognised as a relevant health care problem in neonates for a long time though it is related to life-long motor and neurological impairment. Perinatal stroke is associated with cerebral palsy, epilepsy, intellectual disabilities, developmental and behavioural disorders.[1] Despite advances in neonatal care, there are no preventive strategies, and therapeutic options are still limited. The pathophysiology is multifactorial and may be related to a wide variety of events in the pre-, peri- and postnatal period. The development of a stroke can be influenced by maternal characteristics but also by infantile conditions or even by a combination of these events. The details of the aetiologies, however, remains unclear. In most cases, no cause can be defined. The research focus on the identification of risk factors helps to enhance understanding of the underlying pathophysiology as well as to characterize high-risk populations. Clinical management focuses on timely diagnosis and early rehabilitative measurements to improve the outcomes.

Implementation of diagnostic and treatment guidelines in clinical practice requires detailed knowledge of risk factors, early signs, and the disease's characteristic course. In this context, it is also relevant to know about different symptomatology or course according to co-morbidities, such as prematurity. With predominantly non-specific symptoms, a precise description of the characteristics and the clinical presentation of the disease is important. Efforts should aim to avoid delay in diagnosis or even failure to diagnose perinatal strokes in the neonatal period. These objectives guided the analyses of the publications included in this dissertation.

Along with increasing disease awareness and improving timely diagnosis of perinatal stroke in perinatal care, future research should focus on the possibilities of neuroprotective strategies. The implementation of neuroprotective strategies requires evidence of efficacy from clinical trials. The design of such studies depends on reliable epidemiological data, providing information on the incidence, timing of diagnosis, and certain risk groups such as preterm born infants, which have been mostly excluded from previous studies[2, 3] or neglected in interpretation even though the proportion of preterm born infants in previous study cohorts was higher than expected[4].

As much of the previous data do not reflect the current setting mainly due to improved imaging, their extent of generalisability to today's practice is limited. The publications covered in this dissertation make a relevant scientific contribution by using contemporary acquired data to present incidence estimates for the two most common types of perinatal stroke – arterial ischemic stroke and cerebral sinovenous thrombosis. The incidence of perinatal arterial ischemic stroke was estimated for preterm born infants, a unique estimate to date. Additionally, the findings of comparing perinatal stroke subtypes may help to disentangle the poorly understood underlying causal pathways of perinatal stroke.

2 Background

2.1 Definition

Perinatal stroke is a focal vascular brain injury occurring in the fetal or neonatal period (until the 28th corrected postnatal day).[5] It is defined as 'a group of heterogeneous conditions in which there is focal disruption of cerebral blood flow secondary to arterial or cerebral venous thrombosis or embolisation.'[6] Although it was first suggested in the early 19th century that stroke in the perinatal period may be causal for neurological deficits such as cerebral palsy,[7] strokes as a relevant disorder in newborns was not recognised until the late 20th century with advances in medical imaging.[8] Recent research has demonstrated that the neonatal period is associated with the highest risk of stroke in childhood, or even is 'the most focused lifetime risk for stroke'.[1, 6, 9] Stroke in neonates and older children differ in frequency, aetiology, presentations, and therapeutic interventions.[10]

Timing of the cerebrovascular injury is usually hard to gauge, and often the onset cannot be clearly determined.[6] Therefore, the definition refers to the time of diagnosis and differentiates between acute perinatal stroke, diagnosed in the neonatal period, and presumed perinatal stroke. The latter is diagnosed retrospectively, at a later age in infancy, typically presented as hemiparetic cerebral palsy, but imaging indicates that the vascular injury might have occurred in the neonatal period.[11] Signs of perinatal stroke were not recognised in these children during the neonatal period and therefore failed to receive precise diagnostics.

Apart from the classification as acute or presumed, imaging criteria further subdivide perinatal stroke into arterial or venous and ischemic or haemorrhagic.[12, 11] This thesis focused on two acute subtypes of perinatal stroke – arterial ischemic stroke and cerebral sinovenous thrombosis.

2.2 Subtypes of perinatal stroke relevant to the publications

2.2.1 Perinatal arterial ischemic stroke

Perinatal arterial ischemic stroke (PAIS) accounts for approximately 70% of the cases of perinatal stroke.[13] It is a vascular occlusion of one or more brain arteries, typically in the left middle cerebral artery,[14] characterised by focal cerebral ischemia and infarction with subsequent impairment of blood supply and oxygenation of brain tissue.[15] Typically, patients present with seizures in the first days of life.[14] International guidelines uniformly support MRI (magnetic resonance imaging) as the standard diagnostic tool.[16]

There are different ideas for the pathophysiology of PAIS. According to the current knowledge, scientists consider a thromboembolic event arising from the placenta to be the most probable.[12] Indeed, placenta abnormalities are frequently observed by pathologists.[17] Placental programming of PAIS is supported by a strong association between amniotic inflammation processes and

PAIS.[18] An analysis of the thesis' author also showed this association (see Publication IV, Appendix A) since maternal chorioamnionitis multiplied the risk of PAIS by ten compared to controls (OR 9.89; 95% CI 2.88, 33.94).[19] Peripartum hypoxia and neonatal infections are further discussed causes of PAIS.[18, 20–22] Several risk factor studies support these hypotheses and identified further maternal and neonatal risk factors.[23] Despite partly inconsistent results, it is assumed that intrauterine growth retardation, small for gestational age, and hypertensive pregnancy disorders increase the risk of PAIS.[2, 3, 24–26] Determinants such as male sex, arteriopathy, dehydration, and complications during birth are additionally associated with PAIS.[14, 27–29] Aetiology of PAIS is complex and multifactorial. Risk factor analyses with mutual adjustment, and the disaggregation of individual causal pathways, as attempted by means of a directed acyclic graph in the author's previous work,[19] may allow identifying the most relevant risk factors and provide indications of possible interactions several risk factors.

So far, there is no standard therapy, and management focuses on supportive care measures and neuroprotection.[10] Some innovative therapeutic approaches, such as erythropoietin to prevent cell death or stem cell therapy, which has been shown to stimulate neurogenesis in animal models,[12, 30, 31] have already been investigated in a few laboratory trials but not yet in clinical trials.

2.2.2 Neonatal cerebral sinovenous thrombosis

Although less common, neonatal cerebral sinovenous thrombosis (nCSVT) also significantly contributes to morbidity and mortality in perinatal stroke.[13, 32] Cerebral sinovenous thrombosis, most common in neonates,[33] is defined as a loss of blood flow secondary to occlusion in a cerebral vein or sinus.[34] nCSVT often occurs in the superficial venous system of the brain and commonly involves multiple sinuses.[34, 35] With mostly diffuse and subtle symptoms, diagnosis is difficult and requires a high level of paediatric experience.[34] This might explain often delayed diagnoses, as indicated in Publication III.

There are far fewer studies on nCSVT than PAIS, and some findings are based only on case series. In particular, studies on risk factor studies are missing, but as in any thrombotic process, risk factors are associated with the classical Virchow triad: vascular lesions, impaired blood flow, and hypercoagulability.[34] Available evidence of risk factors of nCSVT is discussed in Publication III and is extended by a case-control study missing in this research field so far. Besides some maternal and obstetrical determinants, nCSVT was associated with hypoxia, infection, dehydration, mechanical compression, or clustered medical complications.[32, 36]

2.3 Outcomes of perinatal stroke

Perinatal stroke is a common cause of severe neurological disorders in childhood, accounting for life-long disability, including a high degree of therapeutic and rehabilitative treatments. Many children with perinatal stroke have an abnormal neurological outcome of varying severity,[37–39] often having multiple adverse outcomes.[37, 39] The rate of adverse sequelae tends to be higher than the rate caused by similar lesions occurring later in childhood.[1] The most commonly described cause of hemiparetic cerebral palsy is a perinatal stroke.[37, 40, 41] More than half of the children with a stroke in the fetal or neonatal period present with motor deficits, about a third with cerebral palsy later in life.[11, 42, 43] This adversely affects the quality of life and self-esteem.[44] Although not all infants presenting with seizures as an acute symptom have recurrent seizures, the risk of childhood epilepsy is increased.[37, 45] Further long-term effects are language delays, visual deficits, behavioural problems or cognitive disorders,[1, 37–39] identifiable in up to 60% of the children with perinatal stroke.[1] Some deficits become apparent years after the cerebral injury, typically not until school age.

Findings to the effect of perinatal stroke on cognitive impairment are inconsistent, probably due to different outcome measures and testing times. Some studies report normal cognitive development in the majority of children with perinatal stroke.[1, 46] Others point to an increased risk of cognitive disorders, particularly affecting those who subsequently develop childhood epilepsy.[1]

Furthermore, perinatal stroke has been shown to affect family health. In families where the children had moderate or severe outcomes, the proportion of depressive syndromes was increased, family functioning was impaired, quality of life was reduced, and marital distress was greater.[47, 48] Parental feelings such as fear, guilt, or shame may occur and sometimes last for a long time, as the definitive cause of the stroke often cannot be clarified. It is described that emotional problems such as depression, attention problems, or mood changes may be increased in children after stroke, although not well studied yet.[1]

Besides, perinatal stroke also has a considerable socioeconomic impact with large and long term direct medical costs.[49] A study from Northern California found 15-fold higher five-year health care costs in children with stroke than controls.[49] There are no studies on this in a German setting, but given the long-term health care needs of the children, the burden of disease may be substantial.

2.4 Particularities of perinatal stroke

2.4.1 Subclinical cases of perinatal arterial ischemic stroke

Per definition, besides neuroimaging evidence, acute stroke is a clinical event related to specific symptoms.[16] But in neonates, classic stroke symptoms are difficult to identify. Symptoms can be subtle and diffuse and do not immediately make paediatricians think of stroke. Awareness is rising, but the incidence is likely to be still underestimated. For some children, diagnosis is made beyond the neonatal period, when symptoms of stroke such as hemiparesis occur. The precise timing of stroke cannot be determined, but imaging assessments suggest that the stroke presumably occurred during the perinatal period.[12] This is why this particular subcategory of perinatal stroke is called 'presumed perinatal arterial ischemic stroke – PPIS'.[6]

Some children in our study were reported as having a perinatal arterial ischemic stroke but diagnosed coincidentally on imaging performed for other medical reasons. Either these infants had no symptoms, at least not at the time of imaging, or it was impossible to determine the origin of the symptoms because of co-morbidities. These cases were categorised as subclinical or asymptomatic strokes. Due to a high degree of non-specific symptoms, distinguishing between symptomatic and subclinical infarctions in neonates is complicated and relies on the paediatricians' assessment. This problem is particularly relevant in preterm born infants, as many stroke symptoms such as apnea, poor feeding, or respiratory difficulties are typical in prematurity. Scientists are divided as to include these children or not. It might be argued that these cases probably would belong to the PPIS group if they had not received imaging for other reasons by showing up with symptoms later in life. However, in our opinion, such speculation does not justify the exclusion of these children from the analysis.

So far, the clinical significance of subclinical perinatal infarcts is unclear. Small, subclinical embolic infarcts may be common in the perinatal period and are thought to have little impact on the neurological prognosis. Moreover, the occurrence of symptoms might also depend on the localisation of the infarct.[35] Therefore, we followed the definition by classifying the stroke by time of diagnosis irrespective of symptoms and included subclinical cases. This makes it important to think about 'confounding by indication', which is discussed in section 4.3.4 of this dissertation.

2.4.2 Perinatal stroke in preterm infants

Stroke is also a disorder in preterm born infants (infants born before 37 completed weeks of gestation),[50] but may differ from a stroke in term infants. As initial analyses showed that the number of observed preterm born cases was significantly higher than the expected number (see results of Publication IV), preterm born infants with perinatal stroke became a focus of subsequent analyses. Most previous reports of perinatal stroke have excluded preterm born infants,[6] probably because, as described, it is hard to distinguish symptomatic and subclinical cases, sometimes without any apparent clinical manifestation in this group.[4, 51]

However, this symptomatology could be a special feature of perinatal stroke in preterm infants and not a reason to exclude this group from research. Meanwhile, the scientific community is aware that there is also a risk of perinatal stroke for preterm born infants,[24, 50] but there are very few studies, most with small sample sizes. Therefore, little is known about the risk factors and clinical characteristics of perinatal stroke in preterm born infants. This thesis focuses on preterm infants in detail where appropriate. The first publication presents an incidence estimate and discusses different theories of increased risk of perinatal stroke in preterm infants.

2.5 Relevance of epidemiological data

Acquiring data of a sufficient number of cases is a major challenge of studies on rare diseases such as perinatal stroke. It is difficult to attain a reasonable number of cases to address scientific questions. Due to data availability, studies are mostly retrospective in design using hospital-based cohorts with long past observations periods. Long observation periods can be difficult as clinical care settings usually change significantly over time. The results do not necessarily represent the overall population and the current situation. Furthermore, some important measures, such as incidence or trend monitoring, cannot be calculated from hospital cohorts. Epidemiological studies are hypothesis-generating, aim to test research questions with a 'view to the interests of the population as a whole', seek to describe specific characteristics of a disease, determine the strength of associations and help to distinguish them from random effects.[52]

Obtaining comprehensive information on the morbidity of rare diseases requires population-based study cohorts. In countries such as Germany, without an available standard health data registry, the design of such population-based cohort studies on rare diseases poses significant challenges. As long as reporting to a disease registry is not mandatory, cases are probably not entirely recorded. Therefore, it is essential to determine the degree of under-reporting using epidemiological methods and adjust the incidence calculations accordingly. Variations in the interpretation of the case and outcomes definitions are likely, requiring strategies for validating the diagnosis. Furthermore, non-comparable settings and differing clinical protocols need to be taken into account in interpreting the results of epidemiological studies.

The study underlying the analyses of the publications in this dissertation faced these challenges and used a specific questionnaire to collect data on perinatal strokes for three years, including all paediatric hospitals in Germany. The corresponding methods used to deal with the challenges described are outlined in the following.

3 Study design and data sources

The publications in this dissertation are based on three data sets. The primary data set derives from a surveillance study and included information on cases with PAIS and nCSVT. The German Surveillance Unit for Rare Disease in Childhood (Erhebungseinheit für Seltene Pädiatrische Erkrankungen in Deutschland — ESPED) monitored strokes in children from January 2015 to December 2017. Along with ascertaining PAIS and nCSVT cases, ESPED monitored childhood arterial ischemic stroke in children aged 28 days to18 years. These data were analysed separately.

Following a British model, ESPED was established in Germany almost 30 years ago and has become an established national clinical surveillance system.[53] All paediatric hospitals are routinely contacted once a month and asked to report the number of paediatric patients hospitalised with one of up to twelve different rare diseases.[54] The median response rate to the ESPED survey is 94% (Range 72-98%). The questionnaires return rate is 91% (Range 36-100%).[53]

ESPED asked all 345 paediatric hospitals in Germany every month during the study period whether they had treated a newly diagnosed case of PAIS or nCSVT. When the paediatricians reported a case, they were asked to complete a study-specific questionnaire on the responding child. An ESPED representative at each site forwarded the anonymised patient information to ESPED and from there to the study team in Munich. The questionnaire requested case characteristics such as date of birth, sex, gestational age, family ethnicity, maternal and obstetrical history, anthropometric measurements at birth, symptoms, co-morbidities, information on diagnostic and clinical management, as well as on therapy and clinical-neurological findings at discharge.

A data set with ICD-coded hospital discharge diagnoses is the second data source for the incidence estimations of PAIS and nCSVT, presented in Publications I and II. These data allow the correction for under-reporting in the ESPED data. Medical controlling departments of paediatric hospitals of one federal state in Germany, North-Rhine-Westphalia (NRW), were invited to participate in hospital discharge data collection. Medical controllers were asked to report all hospitalised cases with a discharge diagnosis of ICD code I63 'Cerebral infarction', I64 'Stroke, not specified as haemorrhage or infarction', or G08 'Intracranial intraspinal phlebitis and thrombophlebitis' between 2015 and 2017.[55] Only children with a 'Major Diagnostic Category 15 - Pregnancy, Childbirth and Puerperium' were included to confine the data to neonates.

Risk factor analyses in case-control studies (Publications II and IV) are based on the third data set. These data were extracted from data provided by the Bavarian Working Group for Quality Assessment (BAQ), gathered for obligatory nationwide benchmarking to assess the clinical performance of obstetrical departments. The data set included maternal and neonatal information on all deliveries in Bavarian obstetric units. We randomly drew four children as controls per case with the same birth years.

4 Methodological specifications

4.1 Diagnostic challenge – the requirement of an MRI-confirmation

Strokes in the neonatal period are difficult to recognise, requiring appropriate neuroimaging.[37] MRI, including diffusion-weighted MRI and MR angiography, is the gold standard.[56] Cranial ultrasound (cUS) is helpful for initial screening, though a negative cUS does not preclude perinatal stroke. A study by Olivé et al. revealed a sensitivity of cUS for PAIS of 87% (95% CI 0.79, 0.95) if performed by a person experienced in cUS.[57] Sensitivity is higher in specialised centres than community hospitals (47% vs 12%)[58] and higher in experts than non-experts (87% vs 72%).[57] Sensitivity depends not only on the physician's ability to perform the cUS but also on the timing of the cUS. Sensitivity was lower with early scans than later scans.[59] Due to technological progress, sensitivity has been increasing in recent decades. The specificity of cUS used within 6 hours of age is estimated at 60% studied on infants with hypoxic-ischemic encephalopathy.[60] Reviewing the cases reported in ESPED yielded that in 11% (25/220), the diagnosis was based only on a pathological cUS, without confirmation by MRI. Due to the inaccuracy of cUS as the only diagnostic tool for perinatal stroke, the 25 cases without MRI confirmation were excluded.

Complete ascertainment of all perinatal stroke cases is almost impossible since some infants with mild or no symptoms escape neuroimaging in the neonatal period. Universal neuroimaging in the neonatal period would be the only way to identify all cases of perinatal stroke, which is not justified without clear benefits demonstrated in appropriate studies. All studies focusing on perinatal stroke are fraught with this source of bias.[37] Therefore, it is critical to facilitate the identification of children needing neuroimaging, which is enhanced by the findings of these publications.

4.2 International classification of diseases and perinatal stroke

The International Classification of Diseases (ICD) is an international tool for systematically classifying diseases.[61] Electronic medical records of diagnoses according to the ICD are primarily administrative but offer a wealth of data for clinical research. However, to use this data for clinical research, scrutiny of the accuracy of ICD codes for identifying infants with stroke is needed. In Germany, physicians record patient diagnoses data to claim the treatment fees from the health insurance providers. There is no national patient registry pooling data of all patients, as in other European countries. Data is only available via the hospital itself or the more than 100 different German health insurance providers. For logistic reasons, we limit the ICD data acquisition to the paediatric hospitals of one federal state. NRW is the largest of the 16 federal states with 65 paediatric hospitals. Thirty-five provided ICD discharge diagnoses for validation of the ESPED data. As neither data source needs to be complete to estimate the incidence using the Capture-Recapture methodology, it had no impact that some hospitals have not been participating (see 4.3.2).

A hospital discharge diagnosis of ICD code I63 and I64 was used in our study to identify infants with PAIS and G08 with nCSVT. To minimise false positives, we did not include ICD P91 'cerebral ischemia in the newborn' in our case definition of PAIS. This procedure may result in some unidentified cases, but this is not an issue since the Capture-Recapture approach accounts for the incompleteness of the data sources.

Walås et al. reported a positive predictive value of 96% (95% CI 0.91, 1.0) of the ICD I63 and I64 for perinatal ischemic stroke in the Swedish Medical Birth Register.[62] Nevertheless, to reduce false positives, a case validation process is essential, which was done by two experienced neonatologists through reviewing anonymised discharge letters. There were no false positives in the six nCSVT cases with G08. The accuracy of the PAIS ICD diagnosis in our study was lower than in the Swedish study. Thirty-two patients treated in hospitals in NRW 2015 to 2017 had a discharge diagnosis I63 or I64. Eighteen remained after reviewing discharge letters.

The planned revision of the ICD (ICD-11) will address the lack of case ascertainment of rare diseases in ICD databases. In this revised version, there will be an extra chapter for 'neonatal cerebral ischemia' (KB00) with specific codes for PAIS (KB00.0) and nCSVT (KB00.1), which will facilitate future studies using these data.[63] ICD-11 will come into force on 1 January 2022 with a flexible transition period of 5 years. The date of implementation in Germany is unclear.[64]

4.3 Incidence calculation in rare disease

4.3.1 Difficulties

Determining the probability of a disease, expressed by the incidence, is part of every basic description of a disease. Incidence calculation is a tool to monitor changes, define disease burden, and make decisions about the distribution of limited healthcare services and resources. It is also an important scientific outcome variable to test certain hypotheses. Incidence data are needed to identify differences in risk between population groups. The formula for calculating incidence is simple if the number of new cases in a given period and the number of people at risk are known.[65]

Reliable data are available for the denominators of the incidence calculation. The denominators, the number of live births in the year 2015-2017 and numbers of these infants born prematurely were extracted from the official population data of the German Federal Statistical Office and the German Institute for Quality Assurance and Transparency in Health Care. There were 2,314,590 live-born infants in Germany in the 3-year study period, of whom 505,721 (22%) were resident in North-Rhine-Westfalia.[66] 8.44% of these children were born prematurely.[67]

The challenge in incidence calculation is the lack of information on the actual number of cases due to failure to comply with reporting, recall bias of study participants, and lack of standardised criteria.[68] Data sources recording the same group of patients only partially overlap,[69] indicating that no single data source can provide reliable incidence estimates. The incompleteness of data

results in an underestimation of the incidence. In addition, methodological peculiarities must be taken into account in incidence calculation for small samples.

Diagnostic procedures, imaging quality, awareness among professionals, and even the disease definition have changed over time, making the comparison with incidence estimates published in the past difficult. Contemporary, transnational, longitudinal, population-based studies would be helpful to generate reliable data. Some countries established patient registries gathering health care data of all participants, facilitating incidence calculation. However, since these do not exist in countries with strict data protection regulations such as Germany, other methodological means need to be applied to estimate the *true* incidence based on incomplete data.

Presupposing all cases are reported, ESPED is designed to capture all cases completely. In mandatory surveillance systems, as is the case for some infectious diseases in Germany, it can be assumed that almost all cases are recorded. However, reporting to ESPED is voluntary, and in the hustle and bustle of everyday business and ever-growing hospital structures, likely, some cases will not be recorded. This is reflected as incidence estimates from ESPED data are typically lower than estimates from other population-based studies.

4.3.2 Adjustment for under-reporting: Capture-Recapture Calculation

Incomplete case ascertainment is a limitation of most rare disease surveillance systems and necessitates adjustment. One established method is the Capture-Recapture Calculation (CRC)[70–72] originating from zoology to estimate animal populations' size. 'Wildlife biologists recognised long ago that it would be impossible to count every fish by capturing them all and that the identification of all the fish is not necessary to an accurate estimate of their numbers.'[73] The CRC can offset random under-reporting, not due to systematic recording errors.[74] It requires at least two independent data sources, each recording the number of patients with the disease of interest. Personal identifiers enable the identification of duplicates in these data sources. Based on the number of cases in the first data source, the number of cases in the second data source, and the number of duplicate cases, the total number can be estimated.[73] The first source of data for incidence estimations of PAIS and nCSVT is the ESPED data of NRW. The second is the ICD discharge data of the paediatric hospitals in NRW. In a second step, to obtain nationwide incidences, we extrapolated the results of the CRC incidence calculation in NRW, which is explained in more detail in the next chapter. The application of the CRC requires fulfilling the following criteria.[69, 74, 75]

The first criterion is the possibility to identify the same cases in different sources by either personal identifiers or a combination of unique variables such as age, sex, or date of birth.[76] Because of mostly anonymised data sets, several identifying variables are needed. Sufficient identifiers (date of birth, sex, date of admission, first three digits of the postal code, hospital of treatment, birth weight) were available to identify duplicates in the ESPED and hospital discharge data set. If several of these identifiers match, it is safe to assume the same patient. For this dissertation, cases are deemed identical if they match at least five of the mentioned variables.

The second criterion demands the same case definition in all sources. As previously mentioned, we excluded ICD P91 since several forms of cerebral haemorrhage are coded with this digit. However, ICD I63 and I64 also need to be validated, which was done using anonymised discharge letters according to the same criteria and by the same persons as for ESPED cases. Therefore, by applying the same criteria, including only MRI confirmed cases and having the same people for case validation, it is reasonable to assume that the same case definition is met.

The third criterion requires that data collection of all sources has to be in the same area and at the same time. To ensure a closed population, we included all hospitals in NRW for ICD data acquisition that the ESPED coordination office monthly contacted. So, both data sources originate from paediatric hospitals and refer to the same patient population. The criterion of the same time for data acquisition also applies since only children born in 2015-2017 were included in both sources.

The independence of the two sources is the fourth criterion. Reporting of a case in ESPED must not depend on the reporting of the case in the ICD data. A positive dependency will result in an underestimation; negative dependency will overestimate the incidence. The following points suggest the likely independence of the data sources. In each hospital, there is one physician responsible for reporting to ESPED. Conversely, the ICD data was retrieved by the medical controlling department after completion of data acquisition in ESPED. The hospitals were only informed about the validation project following the ESPED study. The relatively few duplicates also indicate independence. Nevertheless, the dependence of the two data sources cannot be definitively ruled out and might be a potential limitation. A similarly designed study by Weiß et al.[77] asked the hospitals' ESPED representatives whether they consult the ICD database to prepare their ESPED reports. As 5 of 28 ESPED representatives (18%) consulted the hospital discharge database in this survey, the CRC estimates in this dissertation may also be slightly underestimated.[77]

The last criteria is the equality in the chance – catchability – of patients being recorded in a data source, no matter of any characteristics such as disease severity, age, sex, or place of residence.[75] Differences in catchability may lead to a biased incidence estimate, which can be both under- and overestimated as a result.[75] To note, it is about the probability of being recorded within a data source. The two data sources may well have different 'catchabilities'. In this study, there were no indications of unequal chances in catchability. If so, a stratified analysis could correct this bias. Stratified analysis was performed for preterm birth to test whether prematurity increased the probability of being reported in ESPED. There was no difference in the sum of the stratified CRC estimators to the raw CRC estimator, providing no evidence of different 'catchabilities'. Nevertheless, the low number of cases in this context should be noted.

In conclusion, it is necessary to review the plausibility of the CRC incidence estimates, which can be done either with another data source or by comparison with other international data. The CRC-based incidence estimates of PAIS and nCSVT, presented in this dissertation, are consistent with internationally published incidence estimates of other population-based studies.[5, 78–80]

4.3.3 Statistics of the CRC and incidence estimation

In zoology, the size of an animal population is estimated by capturing a sample, tagging, releasing, afterwards capturing a second sample and determining the proportion of recaptured, tagged animals.[73] For at least 50 years, this method has also been used in epidemiology to determine disease incidences.[81] The assumption is that the ratio of tagged to untagged animals in the recaptured sample is transferable to the population. In the context of human diseases tagging means to be recorded on a list of cases and 'evaluation the degree of overlap among incomplete lists of cases.'[82]

The CRC presented in this dissertation calculated the incidence using data of a sub-region of Germany. We assumed that the ratio of duplicate cases in both data sources to cases identified in only one of these data sources in the entire population is the same as the ratio in our sample in NRW. Since ESPED covers all paediatric hospitals in Germany, this assumption enables the estimation of the number of cases of PAIS and nCSVT, respectively, for overall Germany. The benefit of this approach is a reliable incidence estimate that has been corrected for under-reporting without the effort and cost of collecting two data sources for a large region. The disadvantage is that the number of rare disease cases reduces gradually as the region for data collection shrinks.

Since small sample sizes lead to a bias in the initial CRC estimator for population size, which lacks finite moments,[83] applying the Chapman estimator reduces the bias in the estimator.[84] More information on the underlying statistical formula is provided in the appendix.

4.3.4 Confounding by indication

Some clinical determinants such as prematurity or vaginal-operative delivery lead to more cerebral imaging per child independent of the perinatal stroke's clinical symptoms. In addition, correct diagnosis of perinatal stroke is strongly related to the skill and experience of the person performing the scan. These factors increase the likelihood of a stroke being diagnosed in the neonatal period, causing confounding. Elimination of the confounding is possible by adjusting for these factors, provided the availability of this information.

Confounding by indication occurs when the indication for treatment or a part of a diagnostic procedure acts as a confounder.[85] In this dissertation, the frequency or quality of cerebral imaging may potentially confound the effect of risk factors on the outcome. The indication for the exposure causes the statistical association between exposure and outcome, being the actual cause of the outcome, not the assessed exposure.[86] For example, the association of vaginal-operative delivery and perinatal stroke may be, at least partial, confounded since cerebral imaging indicated by vaginal-operative delivery can lead to a diagnosis of perinatal stroke. It is difficult to disentangle the causal pathways. This issue is relevant in cases where no stroke symptoms triggered cerebral imaging, but the perinatal stroke was incidentally detected in cerebral imaging for other clinical indications. The first publication had to deal with this issue due to asymptomatic cases in PAIS. As we do not have information on the indication, frequency, and quality of neonatal imaging, we performed a stratified analysis: symptomatic and asymptomatic/subclinical cases were considered

separately in the incidence estimation as we assumed that symptoms indicated imaging, irrespective of other pre-existing determinants.

Standards for clinical indication of cerebral imaging in infants vary depending on the hospitals' policies. One way to address the described bias would be to implement a standard imaging protocol. Thus, equal numbers of cerebral imaging, at equal points during the hospital stay, of comparable quality would be ideal. However, it may not be feasible under realistic conditions.

In future studies, incidence estimation could be refined by including data on the indication of the primary imaging of a child and the number of performed imaging in general in the hospital. This, for example, would allow the incidence to be weighted according to the general rate of pathological imaging per centre to minimise the discussed bias.

Regardless, all presented risk factors have a plausible causal relationship, and we assumed that the level of the estimator, but not the relationship at all, might be biased by unmeasured factors. The comparison of the two subtypes of perinatal stroke (Publication III) is not affected by this issue since it is assumable that the indication, frequency and quality of the performed imaging is the same in the respective subgroups.

4.4 Identification of risk factors

Risk factors are events or circumstances increasing an individual's likelihood of developing a disease.[65] Mathematical methods of risk assessments intent to predict this likelihood as a probability term, using 1.0 as a base.[65] Associations identified in observational studies can be due to different reasons and do not necessarily infer causality.[87]

Risk assessment in perinatal stroke research aims to improve timely diagnostics, risk communication, disease awareness, and outcome prediction. Any interpretation of an increase in risk needs to be made with regard to the generally low risk of rare diseases. The aetiology of perinatal stroke is not yet fully understood.[8, 88] Single risk factors are more likely to contribute to the onset of perinatal stroke than to cause it. The disease is a cumulative effect of multiple risk factors.

Considerations of possible causal processes, addressing the relationship between a determinant and the disease and the relationships among various determinants, should precede any risk factor analysis. Statistical association indicates causality but is not a sufficient criterion. Associated determinants may be early signs of the disease and therefore associated per se. These are predictors of the disease but not causal. One critical aspect of interpreting risk factor data in perinatal stroke is that it is usually hard to determine the exact timing of the stroke retrospectively. It is helpful to make causal assumptions prior to analysis and, at best, to display the underlying relations visually (for example, see the causal pathway in Publication IV).

Some studies descriptively report case characteristics, naming these *risk factors* without including a control group. Risk factors are not provable without comparing the frequency of exposure within a patient group to persons without the disease. We combined different data sets and thus provided

control groups for the risk factor analyses. Nevertheless, the analyses were limited to the available data of the control group, which meant that not all risk factors of interest could be examined. This was indicated accordingly in the publications. Small sample sizes are challenging for risk factor analyses of rare diseases, as the statistical power might be too low to detect risk factors. Therefore, the sample size always needs to be taken into account in interpreting the results. Trials with larger sample sizes in rare diseases will only be feasible if pooling multiple data sets. Alternatively, a worldwide disease registry would be reasonable, as it is already for other rare diseases.

4.5 Identification of differences in the subtypes of perinatal stroke

Although recognising perinatal stroke and classifying subtypes rests on neuroimaging,[9] a comparison of the subtypes may help find predictors indicating perinatal stroke at an early stage and thus initiate faster diagnostics. Timely identification will lead to early interventions and the infants' referral to specialised centres (Paediatric Stroke Units), providing high-quality care and increasing the infants' chance of a good outcome. Since infants with strokes diagnosed beyond the neonatal period have a worse outcome with more frequent cerebral palsies,[89] the importance of timely diagnostic and early rehabilitation measures is apparent. Furthermore, the findings of the comparison may help to disentangle the poorly understood underlying causal pathways of perinatal stroke. The risk factors and specific characteristics of the subtypes of perinatal stroke identified in the publication of this thesis provide relevant supporting information.

5 Conclusion and outlook

Although awareness of perinatal stroke in science and clinical care has increased in recent decades, the implementation of clinical guidelines for diagnostics and therapy is still pending. Guidelines require contemporary epidemiological data about the disease. In this dissertation, the publications provide epidemiological data from Germany, gathered between 2015 and 2017, concerning incidence, risk factors and clinical presentations of PAIS and nCSVT.

Using the Capture-Recapture methodology, the incidence of PAIS was 22 per 100,000 infants, with a significantly increased incidence in preterm born infants of 32 per 100,000. However, the incidence of preterm and term born infants was equal, excluding subclinical cases. As outcome data are scarce, there is little information on the relevance of these subclinical cases. Clinical seizures are observed less frequently in preterm born infants, complicating recognising early signs of perinatal stroke and hindering timely diagnosis. To date, there are only a few studies dedicated to the risk of stroke in preterm born infants or the relationship of prematurity of the brain and the occurrence of strokes. These issues ought to become more focused in future research.

The analyses also showed that PAIS is about three times more common than nCSVT, with an incidence of 6.6 per 100,000 infants. While inflammatory processes could play a dominant role in the pathogenesis of PAIS, an association between determinants indicating perinatal asphyxia and nCSVT suggest that hypoxia contributes to the aetiology of nCSVT. These results are further indications for understanding the aetiology of perinatal stroke.

The results of the analyses may increase paediatricians' awareness of the disease and therefore could support a higher rate of timely diagnosis. Improving the quality of care for infants with perinatal strokes requires the implementation of guidelines for diagnosis and therapy. These guidelines might support the standardisation of possible differences in care to reduce the burden of disease. The Society for Neonatology and Paediatric Intensive Care Medicine (GNPI), along with other paediatric societies, has announced the launch of such a guideline for Germany by June 2022. Presumably, the results of these publications are also helpful in this context.

Future research activities should address the cumulative effect of multiple risk factors, possibilities of therapeutic interventions and neuroprotective strategies. Postnatal examination of the placenta and umbilical cord could provide interesting insights to reveal pathological pathways further. The presented findings support generating hypotheses and designing studies on these topics. Establishing an international registry would be useful to expand data availability, as would the national and international enhancement of collaboration between experts. In order to pool resources in Germany, ensure dissemination of up to date disease information and enable multidisciplinary discussions of cases, the establishment of reference centres has proven to be effective in rare diseases. Efforts are underway to establish such a centre at the university hospital in Munich.

Publication I

Incidence Estimates of Perinatal Arterial Ischemic Stroke in Preterm- and Term-Born Infants: A National Capture-Recapture Calculation Corrected Surveillance Study

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Mark Dzietko

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Publication II

Incidence and risk factors of cerebral sinovenous thrombosis in infants

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Publication III

Clinical Diversity of Cerebral Sinovenous Thrombosis and Arterial Ischaemic Stroke in the Neonate: A Surveillance Study

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Appendix A: Publication IV

Risk factors for perinatal arterial ischaemic stroke: a large case-control study

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Appendix B: Methodological background of the CRC

The Capture-Recapture approach aims to estimate the actual number of cases (N) – total population of infants with PAIS or newborns with nCSVT 2015-2017 in Germany – in a defined population by using the number of cases determined by different, at least two, incomplete data sources (here: $cases_A$: number of reported cases in ESPED 2015-2017 and $cases_B$: number of cases identified in healthcare ICD data 2015-2017) and the number of cases present in both of these data sources (here: $cases_{AB}$). CRCs in these analyses primarily estimate the number of cases for NRW (N_{NRW}) and extrapolate these results nationwide (N).

Formula to estimate the total number of cases for NRW (N_{NRW})

$$N_{NRW} = \frac{cases_{A_{NRW}} + cases_{B_{NRW}}}{cases_{AB_{NRW}}} \quad [1]$$

This formula is adapted with a correction factor for small samples (Chapman).

$$N_{NRW} = \left(\frac{(cases_{A_{NRW}}+1)*(cases_{B_{NRW}}+1)}{cases_{AB_{NRW}}+1}\right)-1 \quad [2]$$

With variance ($var(N_{NRW})$) estimated by

$$var(N_{NRW}) = \frac{(cases_{A_{NRW}}+1)*(cases_{B_{NRW}}+1)*(cases_{A_{NRW}}-cases_{AB_{NRW}})*(cases_{B_{NRW}}-cases_{AB_{NRW}})}{(cases_{AB_{NRW}}+1)^2*(cases_{A_{BNRW}}+2)} \quad [3]$$

95% confidence intervals for N ($N_{CI_{NRW}}$)are based on

$$N_{CI_{NRW}} = N_{NRW} \pm 1.96 * \sqrt{var\ (N_{NRW})} \quad [4]$$

Extrapolation:

Number of cases from source A ($cases_A$) is the number of cases reported in ESPED and is given for overall Germany.

The number of cases present in both sources ($cases_{AB}$) is calculated by

$$cases_{AB} = cases_A * \frac{cases_{AB_{NRW}}}{cases_{A_{NRW}}} \quad [5]$$

The number of cases of the second data source ($cases_B$) is calculated by

$$cases_B = \frac{cases_{AB} * cases_{B_{NRW}}}{cases_{B_{NRW}}} \quad [6]$$

[7]

According to the second formula, the actual number of cases (N) is calculated by

$$N = \left(\frac{(cases_A+1)*(cases_B+1)}{cases_{AB}+1}\right) - 1 = \left(\frac{(cases_A+1)*\left(\frac{cases_{AB}*cases_{B_{NRW}}}{cases_{B_{NRW}}}+1\right)}{cases_A*\frac{cases_{AB_{NRW}}}{cases_{A_{NRW}}}+1}\right)\text{-}1$$

Variance and 95% confidence intervals for N are calculated according to formulas 3 and 4.

Appendix C: List of additional publications

Sorg A-L, Obermeier V, Armann J, Klemme M, von Kries R. Rückgang von Infektionen durch Streptokokken der Gruppe B bei Neugeborenen: Analyse von Krankenversicherungsdaten 2005 bis 2017. Klin Padiatr 2020.

Sorg A-L, Obermeier V, Liese JG, von Kries R. Incidence trends of parapneumonic pleural effusions/empyema in children 2009 to 2018 from health insurance data: Only temporal reduction after the introduction of PCV13. Vaccine 2021.

Sorg A-L, Kaiser V, Becht S, Simon A, von Kries R. Impact of School Closures on the Proportion of Children in the COVID-19 Pandemic: An Example from the Winter Lockdown in Germany. Klin Padiatr 2021.

Gerstl L, Weinberger R, Heinen F, Bonfert MV, Borggraefe I, Schroeder AS et al. Arterial ischemic stroke in infants, children, and adolescents: results of a Germany-wide surveillance study 2015-2017. J Neurol 2019.

Olivieri M, **Sorg A-L**, Weinberger R, Kurnik K, Bidlingmaier C, Juranek S et al. Recanalisation strategies in childhood stroke in Germany. Sci Rep 2021; 11(1).

Bonfert MV, Jelesch E, Hartmann J, Koenig H, Warken B, Meuche A et al. Test-Retest Reliability and Construct Validity of the German Translation of the Gait Outcome Assessment List (GOAL) Questionnaire for Children with Ambulatory Cerebral Palsy. Neuropediatrics 2021.

Poets CF, Abadie V, Breugem C, Wallis C, Abel F, Chalouhi C et al. Managing infants with craniofacial malformations - Where to go next? Semin Fetal Neonatal Med 2021:101289.

Not yet published publications

Sorg A-L, von Kries R, Borggraefe I. Cognitive disorders in childhood epilepsy: a comparative longitudinal study using administrative healthcare data. *(recently accepted in Journal of Neurology)*

Sorg A-L, Bergfeld L, Jank M, Corman VM, Semmler I, Görtz A et al. SARS-CoV-2 Antibodies in Children: A One-Year Seroprevalence Study From June 2020 to May 2021 in Germany: PREPRINT. SSRN Library 2021. Available from: http://dx.doi.org/10.2139/ssrn.3965378
(under review in nature communications)

Sorg A-L, Hufnagel M, Doenhardt M, Diffloth N, Schroten H, von Kries R et al. Risk of Hospitalization, severe disease, and mortality due to COVID-19 and PIMS-TS in children with SARS-CoV-2 infection in Germany: PREPRINT. medrxiv 2021. Available from: https://www.medrxiv.org/content/early/2021/11/30/2021.11.30.21267048
(to be submitted to European Journal of Pediatrics)

Congress papers

Sorg A-L, Klemme M, Hasbargen U, Armann J, von Kries R, Obermeier V. Inzidenz der Neugeborenenseptikaemien durch Streptokokken der Gruppe B und Escherichia Coli – Analyse von Krankenversicherungsdaten der Barmer GEK von 2005 bis 2017: 45. Jahrestagung der Gesellschaft für Neonatologie und Pädiatrische Intensivmedizin gemeinsam mit der 27. Jahrestagung der Deutschen Gesellschaft für Pädiatrische Infektiologie, 23.–25. Mai 2019, Leipzig. Monatsschr Kinderheilkd 2019; 167(S3):S161.

Sorg A-L, Klemme M, von Kries R, Obermeier V. Inzidenz der Neugeborenenseptikämien durch Streptokokken der Gruppe B und Escherichia Coli: Analyse von Krankenversicherungsdaten der Barmer GEK von 2005 bis 2017: Gemeinsame Jahrestagung der Deutschen Gesellschaft für Kinder- und Jugendmedizin (DGKJ), der Deutschen Gesellschaft für Sozialpädiatrie (DGSPJ), der Deutschen Gesellschaft für Kinderchirurgie (DGKCH), des Berufsverbandes Kinderkrankenpflege Deutschland (BeKD) und der Gesellschaft für Neuropädiatrie (GNP). Monatsschr Kinderheilkd 2019; 167(S4):197–278.

Sorg A-L, von Kries R, Klemme M, Gerstl L, Felderhoff-Müser U, Dzietko M. Incidence and clinical characteristics of perinatal arterial ischemic stroke in preterm and term born infants – CRC corrected active surveillance data from Germany 2015 – 2017. In: 29. Deutscher Kongress für Perinatale Medizin. Deutsche Gesellschaft für Perinatale Medizin (DGPM) – „Hinterm Horizont geht's weiter, zusammen sind wir stark“. Georg Thieme Verlag KG; 2019 (Zeitschrift für Geburtshilfe und Neonatologie).

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