



# Incidence and risk factors of cerebral sinovenous thrombosis in infants

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## ABBREVIATIONS

CSVT	Cerebral sinovenous thrombosis
ESPED	German Paediatric Surveillance Unit

**AIM** To describe the incidence of term and preterm neonatal cerebral sinovenous thrombosis (CSVT) and identify perinatal risk factors.

**METHOD** This was a national capture-recapture calculation-corrected surveillance and nested case-control study. Infants born preterm and at term with magnetic resonance imaging-confirmed neonatal CSVT were identified by surveillance in all paediatric hospitals in Germany (2015–2017). Incidence was corrected for underreporting using a capture-recapture method in one federal state and then extrapolated nationwide. We reviewed PubMed for comparisons with previously reported incidence estimators. We used a population-based perinatal database for quality assurance to select four controls per case and applied univariate and multivariable regression for risk factor analysis.

**RESULTS** Fifty-one newborn infants (34 males, 17 females; 14 born preterm) with neonatal CSVT were reported in the 3-year period. The incidence of term and preterm neonatal CSVT was 6.6 (95% confidence interval [CI] 4.4–8.7) per 100 000 live births. Median age at time of confirmation of the diagnosis was 9.95 days (range 0–39d). In the univariate analysis, male sex, preterm birth, hypoxia and related indicators (umbilical artery pH <7.1; 5-minute Apgar score <7; intubation/mask ventilation; perinatal asphyxia), operative vaginal delivery, emergency Caesarean section, and pathological fetal Doppler sonography were associated ( $p < 0.05$ ) with neonatal CSVT. Multivariable regression yielded hypoxia (odds ratio=20.3; 95% CI 8.1–50.8) as the independent risk factor.

**INTERPRETATION** Incidence of neonatal CSVT was within the range of other population-based studies. The results suggest that hypoxia is an important perinatal risk factor for the aetiology of neonatal CSVT.

Although cerebral sinovenous thrombosis (CSVT) in newborn infants (hereafter termed 'neonatal CSVT') is a rare event, infants are at the highest risk since more than half of all CSVTs in childhood are diagnosed during the neonatal period.<sup>1–3</sup> The true rate of neonatal CSVT is still unknown and possibly underestimated. Due to improved quality of imaging modalities, it may be increasingly diagnosed. Population-based studies are rare and may be fraught with incomplete underreporting of cases unless corrected for underreporting.

It is assumed that the combination of different maternal, perinatal, and neonatal risk factors contribute to the thrombotic process based on the classic Virchow triad: vascular lesions, impaired blood flow, and hypercoagulability.<sup>3</sup> However, little is known about the actual impact of these

risk factors on the aetiology of neonatal CSVT. Identification of risk factors may help to enhance the understanding of the underlying pathophysiology; comprehensive understanding of risk factors is required for evidence-based prevention, treatment, and clinical management. Several risk factors have so far been suggested in register studies.<sup>3–11</sup> However, to identify relevant risk factors, a comparison with a representative population of newborns without impairment is needed, which to our knowledge has not been done yet.

We investigated the epidemiology and risk factors of neonatal CSVT in a population-based study using a second ascertainment source for incidence estimation and a case-control design of four population-based controls for each case for the investigation of risk factors.

## METHOD

### Study design and case definition

In 2015 to 2017, the German paediatric surveillance unit, which monitors rare diseases in childhood, performed a nationwide active surveillance of perinatal stroke in all 345 German paediatric hospitals, which were requested to report any case of CSVT in infants ( $\leq 28$  postnatal days or calculated date of birth, any gestational age) and to complete an anonymous questionnaire respectively. Case ascertainment via ESPED (German Paediatric Surveillance Unit; Erhebungseinheit für Seltene Pädiatrische Erkrankungen in Deutschland) was reported previously in detail.<sup>12,13</sup> The questionnaire asked for data on clinical symptoms, potential risk factors, diagnostic procedure, localization, and therapy. Any reported cases of neonatal CSVT in infants born at term and preterm including symptomatic and subclinical cases were eligible. This analysis was confined to cases with a confirmatory magnetic resonance imaging (MRI) scan. Questionnaires were independently reviewed by a study team of three neonatologists and one paediatric neurologist to validate the diagnosis of neonatal CSVT.

### Incidence estimation

Underreporting of cases is a known weakness of surveillance systems, but capture-recapture methodology using a second independent data source provides a means for valid incidence estimation despite underreporting.<sup>14</sup> To bill treatment fees, clinics have to provide several items of information to assert the claims, including the International Classification of Diseases (ICD) codes for the diagnoses related to medical treatment.

The German Modification of the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) published by the World Health Organization is the basis of the payment system for outpatient and inpatient care and is used for hospital diagnosis statistics and quality assurance purposes in Germany.<sup>15</sup> This information (called hospital discharge documentation) is collected centrally in each clinic in an electronic data system. Generally applicable coding guidelines and specially trained staff provide a uniform coding system in all hospitals. Hospital discharge documentation was used as the second data source in this study.

Request of hospital discharge data was confined to paediatric hospitals of one federal state (North-Rhine Westphalia) reflecting 22% of all births in Germany. All 65 paediatric hospitals in North-Rhine Westphalia were asked to electronically scan their hospital discharge diagnoses data system for cases of neonatal CSVT during the study period with the use of the ICD-10, German Modification code G08 (diagnoses are coded according to the ICD-10, German Modification). Far wider than the instructions within the ICD-10, German Modification is the comprehensive system of rules pertaining to the ICD-10. This basic information also applies to the ICD-10, German

### What this paper adds

- The population-based incidence estimation for neonatal cerebral sinovenous thrombosis (CSVT) in Germany is 6.6 per 100 000 live births.
- Preterm birth and complicated delivery were identified as risk factors for neonatal CSVT.
- Mutual multivariable adjustment revealed hypoxia as an independent risk factor associated with neonatal CSVT.

Modification. However, priority is given to section-specific encoding guidelines.<sup>15</sup> The ICD-10, German Modification is close to the ICD-10 and there is no difference in the ICD code in the first three digits. Identified cases were matched to those reported via the ESPED in North-Rhine Westphalia. All cases ascertained by review of the hospital discharge diagnoses were validated by two neonatologists (MD and UF) based on the anonymized patients' discharge summaries including MRI reports. Hospitals providing hospital discharge data ( $n=36$  out of 65) are representative of all hospitals in North-Rhine Westphalia regarding the number of hospital beds, annual admissions, birth rates, and distribution of centres in terms of level of care.

Identification of common cases in both data sources was made by linking date of birth, sex, birthweight, date of hospital admission, place and name of the notifying hospital, and the first three digits of the postal code of the place of residence. Capture-recapture uses Bayesian probability theory to estimate the true number of cases. The calculation of the total number of neonatal CSVT cases and the 95% confidence intervals (CIs) were performed using Chapman's nearly unbiased estimator.<sup>16</sup>

For nationwide incidence estimation, we extrapolated the results of North-Rhine Westphalia for Germany by assuming that the proportions of matches for ESPED and hospital discharge in North-Rhine Westphalia reflect the respective proportions for the whole of Germany. The annual number of live births provided by the German Federal Statistical office was used to calculate the incidence rate for neonatal CSVT.<sup>17</sup>

### Search strategy

To compare our incidence estimate to those reported in the literature, we performed a review to identify all studies reporting the incidence of neonatal CSVT in PubMed on 3rd October 2020. We used the search terms: 'sino\*' [Title/Abstract] OR 'sinus\*' [Title/Abstract] OR 'venous\*' [Title/Abstract] AND 'thrombosis' [Title/Abstract] AND 'cerebral' [Title/Abstract] AND 'child\*' OR 'neonate' OR 'infant' OR 'newborn' OR 'perinatal' NOT (case report). The asterisk represents any group of characters, including no character, after the search term. We further limited the search to full text availability and scanned reference lists for relevant publications.

### Risk factor analysis

To assess the underlying aetiology of neonatal CSVT, the study aimed to investigate risk factors by comparison to control infants in a case-control study. We randomly

selected four controls per case from the data set of the Bavarian Working Group for Quality Assessment (Bayrische Arbeitsgemeinschaft für Qualitätssicherung). The Bavarian Working Group for Quality Assessment data set, which has been described previously,<sup>12</sup> comprises all deliveries in obstetric units of the federal state of Bavaria. The Bavarian Working Group for Quality Assessment is part of a nationwide benchmarking network for the assessment of clinical performance in German hospitals. Medical and paramedical hospital staff routinely record data electronically.

Control infants were matched to cases with neonatal CSVT on birth year only. The risk factor analysis is based on 48 ESPED cases and 192 controls. ESPED is an ongoing case ascertainment system. Three cases were reported after control selection and could not be included in the risk factor analysis. Only 48 of 51 cases could be examined. Comparison of risk factors in case and control infants was based on the available case analysis.

Clinical experience suggests differences in risk factors and clinical presentation of neonatal CSVT between infants born preterm and at term. Therefore, we stratified the univariate analyses by preterm birth as sensitivity analysis.

### Variable definition

Description of the risk factors as documented in ESPED and the Bavarian Working Group for Quality Assessment was given previously.<sup>12</sup> Infants born before 37 completed weeks of gestation are defined as born preterm, small for gestational age with a birthweight below the 10th centile, and large for gestational age with a birthweight above the 90th centile.<sup>18</sup> A 5-minute Apgar score below 7 and an umbilical artery blood pH below 7.1 were considered as indicators for perinatal acidosis. Hypoxia was defined by any of the following: a 5-minute Apgar score below 7; an umbilical artery blood pH below 7.1; a diagnosis of perinatal asphyxia; or the need for intubation or mask ventilation during initial care. A history of abortion and miscarriage was assumed when the number of preceding pregnancies exceeded the number of live births. Mothers 18-years-old or younger or 35-years-old or older were considered as high-risk pregnancies. Reported maternal diagnoses of pre-eclampsia, eclampsia, HELLP syndrome (haemolysis, elevated liver enzymes, and a low platelet count), or pregnancy-induced hypertension were grouped as the variable

‘hypertensive pregnancy disorder’. Operative vaginal delivery consisted of ventouse and forceps deliveries.

Congenital thrombophilia is a known risk factor for neonatal CSVT. We asked the treating physicians what kind of prothrombotic diagnostics they had performed and whether these values were within normal limits or pathological. Unfortunately, this information was not available in the control data set and could not be included in the univariate analysis.

### Statistical analysis for risk factor analysis

In the univariate analysis, we calculated odds ratios (ORs) and 95% CIs with Firth’s bias correction; *p*-values were based on  $\chi^2$  or Fisher’s exact test.

To identify the most relevant independent risk factors, we performed a mutual multivariable analysis with Firth’s bias correction including all variables with a univariate *p*<0.2.

We used a significance level of 5% for all analyses. All statistics were calculated using SAS v9.4 (SAS Institute, Cary, NC, USA). The data supporting the findings and the programme code of this study are available from the corresponding author upon reasonable request.

The ethics committee of the Ludwig-Maximilians-University of Munich gave ethical approval (no. 42 15 [05-04-2015]). Due to anonymous reporting in the ESPED and because Bavarian Working Group for Quality Assessment data are anonymous, routinely documented data, informed consent was not required.

## RESULTS

### Incidence of neonatal CSVT

In the 3-year study period, 60 cases of neonatal CSVT were reported from all German paediatric hospitals to the ESPED. Nine were excluded because diagnosis was based on ultrasound only. All remaining cases (*n*=51, 34 males, 17 females) were confirmed by MRI scan.

Ten of the 51 cases (20%) were born and treated in North-Rhine Westphalia and formed the basis for the capture-recapture calculation. We identified nine cases of neonatal CSVT with ICD-10, German Modification code G08 from hospital discharge lists, which were validated using discharge summaries and MRI reports. Three out of nine were identical with reports in the ESPED (Fig. S1, online supporting information). Based on seven cases reported only in the ESPED database, six only in the

**Table 1:** Capture-recapture estimation of nationwide neonatal cerebral sinovenous thrombosis incidence (extrapolation based on the proportion of matches in the ESPED and hospital discharge documentation in North-Rhine Westphalia)

	Exclusively ESPED	Exclusively hospital discharge cases <sup>a</sup>	Number of matches <sup>a</sup>	Capture-recapture estimated total number of cases, <i>n</i>	95% CI	Incidence rate (95% CI)
North-Rhine Westphalia	7	6	3	27	12–41	5.2 (2.3–8.2) per 100 000 live births
Nationwide <sup>a</sup>	36	31	15	152	103–201	6.6 (4.4–8.7) per 100 000 live births

<sup>a</sup>Extrapolated from the North-Rhine Westphalia survey. ESPED, German Paediatric Surveillance Unit; CI, confidence interval.

**Table 2:** Prothrombotic risk factors in infants with neonatal cerebral sinovenous thrombosis (*n*=48)

Prothrombotic risk factor	Number of cases with performed tests (%)	Pathological test result (%)
Antithrombin deficiency	38 (79)	4 (11)
Protein C deficiency	29 (60)	2 (7)
Protein S deficiency	29 (60)	2 (7)
Factor V Leiden	18 (38)	3 (17)
Prothrombin mutation	11 (5)	2 (27)
Plasminogen activator inhibitors	2 (4)	–
Homocysteine increase	10 (21)	–
Lipoprotein(a)	13 (27)	–
Lupus	12 (25)	–
Anticoagulant		
Activated protein C resistance	13 (27)	3 (23)
Anti-cardiolipin antibodies	10 (21)	–
Antiphospholipid antibodies	10 (21)	–

hospital discharge database, and three cases identified in both data sets, the capture-recapture method yielded an estimated incidence of neonatal CSVT in North-Rhine Westphalia of 5.2 (95% CI 2.3–8.2) per 100 000 live births.

Extrapolating the results of the North-Rhine Westphalia region, data yielded a nationwide incidence for neonatal CSVT of 6.6 (95% CI 4.4–8.7) per 100 000 live births (Table 1). Study data indicated an increased incidence of neonatal CSVT in infants born preterm (see the risk factor analysis). However, due to an insufficient number of cases and the capture-recapture methodology in one federal state, no valid incidence estimates were possible with regard to gestational age.

We screened the titles and abstracts of 69 publications (Fig. S2, online supporting information). Of these, six papers pertained to the incidence of neonatal CSVT (Table S1, online supporting information).<sup>1,7,19–22</sup> These studies reported a broad range of incidence estimates between 0.82 and 40.7 per 100 000 live births, which probably reflects differences in study periods, data sampling, and case definition. One study was hospital-based,<sup>22</sup> two were multicentre,<sup>7,21</sup> and three were population-based.<sup>1,19,20</sup> Two studies included infants born preterm in the incidence calculation.<sup>19,20</sup>

### Case characteristics

A detailed case description is shown in Table S2 (online supporting information). Of the 48 neonatal CSVT cases (*n*=32, 67% males) examined in the risk factor analysis, 14 (29.2%) were born preterm with a mean gestational age of 32<sup>+6</sup> weeks (range 28<sup>+5</sup>–36<sup>+3</sup> wks). Three of these infants born preterm were twins. All but two were white, one was Asian, and one African. Median age at time of confirmation of diagnosis was 9.95 days (range 0–39d). One patient,

who was 39 days old at confirmation of diagnosis, was born at 28<sup>+5</sup> weeks of gestation. Diagnosis was made before the calculated date of birth. Median age at diagnosis (12d) in the group of infants born preterm was significantly higher compared to infants born at term (7d, *p*=0.02).

Sixty per cent (29 out of 48) of all infants with CSVT and more frequently cases of preterm birth (13 out of 14, 93% infants born preterm vs 18 out of 34, 53% infants born at term) needed intensive medical care. Seven cases (five born at term and two born preterm) received chest compressions during initial care. Twenty-seven per cent (13 out of 48, nine born at term and four born preterm) suffered from perinatal asphyxia, 17% (8 out of 48, five born at term and three born preterm) developed intraventricular haemorrhage, and 13% (6 out of 48, five born at term and one born preterm) had sepsis.

The most common clinical symptom was seizure, observed in 31 (65%) cases, which was equally frequent in infants born preterm and at term. Other reported symptoms were hypotonia (31%, 15 out of 48), insufficient sucking (31%, 15 out of 48), lethargy (23%, 11 out of 48), apnoea (23%, 11 out of 48), respiratory dysfunction (21%, 10 out of 48), pathological limb movement (21%, 10 out of 48), hypoglycaemia (13%, 6 out of 48), and electrolyte imbalance (6%, 3 out of 48). Table S3 (online supporting information) shows the symptoms for infants born preterm and at term separately, with no major differences noted. In seven infants (four of them born preterm), no clinical neurological symptoms attributed to stroke were reported. Seven had seizures as the only presenting symptom.

Established prothrombotic risk factors are shown in Table 2. The results reveal that in clinical practice, complete prothrombotic screening is not performed in every case. In 7 out of 48 (15%) of cases, only a basic coagulation diagnostic (e.g. quick/partial thromboplastin time) was performed but no testing for specific prothrombotic risk factors was carried out. In 11 out of 48 cases (23%), at least one established prothrombotic risk factor was found. Most had a single prothrombotic risk factor and only three cases presented with combined risk factors. Antithrombin deficiency was detected in 4 out of 38 (11%) tested cases, protein C and protein S deficiency in 2 out of 29 (7%) each, Factor V Leiden in 3 out of 18 (17%), prothrombin mutation in 2 out of 11 (18%), and activated protein C resistance in 3 out of 13 (23%).

Eighty-four per cent (26 out of 31) of infants with seizures were treated with phenobarbital (*n*=15), levetiracetam (*n*=5), or both medications (*n*=2). In four cases, the anti-seizure medication used was not specified. Most infants (45 out of 48) received anticoagulation with heparin (31 low-molecular-weight, four unfractionated, nine both, one not specified). Forty-two infants were discharged with low-molecular-weight heparin. Four patients were treated with antiviral therapy, 22 with antibiotics, and seven received treatment for hypothermia.

The most frequently affected vessel was the superior sagittal sinus (*n*=25 infants born at term, *n*=9 infants born



**Table 3:** Univariate analyses of maternal and neonatal characteristics in infants with cerebral sinovenous thrombosis (CSVT) versus infants in the comparison group

	Neonatal CSVT group, <i>n</i>		Comparison group, <i>n</i>		OR (95% CI)	<i>p</i>
	<i>n</i>	(%)	<i>n</i>	(%)		
<b>Infant characteristics</b>						
Male sex	48	32 (66.7)	192	95 (49.5)	2.0 (1.0–3.9)	<b>0.03</b>
Preterm birth	48	14 (29.2)	192	18 (9.4)	4.0 (1.8–8.8)	<b>&lt;0.001</b>
SGA (birthweight <10th centile)	48	6 (12.5)	192	18 (9.4)	1.4 (0.5–3.8)	0.52
LGA (birthweight >90th centile)	48	5 (10.4)	192	23 (12.0)	0.9 (0.3–2.5)	1.00
<b>Hypoxia</b>						
Umbilical artery pH ≤7.1	48	25 (52.1)	192	12 (6.3)	15.7 (7.0–35.2)	<b>&lt;0.001</b>
Apgar score (5 min) <7	43	13 (30.2)	192	4 (2.1)	18.5 (5.8–59.3)	<b>&lt;0.001</b>
Perinatal asphyxia	43	12 (27.9)	191	0 (0)	151.9 (7.8–∞)	<b>&lt;0.001</b>
	48	13 (27.1)	192	2 (1.0)	29.0 (6.9–122.2)	<b>&lt;0.001</b>
Intubation/mask ventilation during initial care	48	20 (41.7)	178	8 (4.5)	14.4 (5.8–35.7)	<b>&lt;0.001</b>
Multiple births	48	3 (6.3)	192	7 (3.7)	1.9 (0.5–7.5)	0.42
<b>Maternal factors</b>						
Age ≤18y or ≥35y	46	18 (39.1)	192	58 (30.2)	1.5 (0.8–2.9)	0.24
History of abortions or miscarriage	40	7 (17.5)	192	42 (21.9)	0.8 (0.3–1.9)	0.54
Gestational diabetes	48	5 (10.4)	192	9 (4.7)	2.4 (0.8–7.6)	0.13
Hypertensive pregnancy disorders	48	5 (10.4)	192	5 (2.6)	4.3 (1.2–15.6)	<b>0.03</b>
Nulliparity	41	28 (68.3)	192	99 (51.6)	2.0 (1.0–4.0)	0.05
<b>Obstetric and peripartum characteristics</b>						
Spontaneous delivery <sup>a</sup>	43	12 (27.9)	192	113 (58.9)	1	
Operative vaginal delivery		5 (11.6)		14 (7.3)	3.4 (1.1–11.0)	<b>&lt;0.001</b>
Planned Caesarean section		5 (11.6)		32 (16.7)	1.5 (0.5–4.6)	
Emergency Caesarean section		21 (48.8)		33 (17.2)	5.8 (2.6–13.0)	
Pathological fetal Doppler sonography	48	3 (6.3)	192	1 (0.5)	9.8 (1.1–85.4)	<b>0.03</b>
Chorioamnionitis	48	1 (2.1)	192	0 (0)	12.3 (0.1–∞)	0.20
Oligohydramnios	48	0 (0)	192	3 (1.6)	0.6 (0.02–17.3)	1.00
Polyhydramnios	48	1 (2.1)	192	1 (0.5)	4.0 (0.2–65.6)	0.36
Umbilical cord abnormalities	48	4 (8.3)	192	14 (7.3)	1.2 (0.4–3.9)	0.76

Bold type indicates statistical significance with  $p < 0.05$ .  $p$ -values were obtained using  $\chi^2$  or Fisher's exact test. <sup>a</sup>Reference category. OR, odds ratio; CI, confidence interval; SGA, small for gestational age; LGA, large for gestational age.

preterm), followed by the transverse sinus ( $n=16$  infants born at term,  $n=8$  infants born preterm), straight sinus ( $n=8$  infants born at term,  $n=1$  infant born preterm), and inferior sagittal sinus ( $n=3$  infants born at term,  $n=1$  infant born preterm). In 21 cases ( $n=16$  infants born at term,  $n=5$  infants born preterm), multiple sinuses were involved. In four cases ( $n=3$  infants born at term,  $n=1$  infant born preterm), no localization was reported.

One infant born extremely preterm (born 28<sup>+6</sup>wks of gestation) with suspected genetic muscular disease died 15 days after birth. All other patients were discharged. In some cases, neurological symptoms like hypotonia (25%, 12 out of 48), insufficient sucking (7 out of 48, 15%), pathological limb movement (8 out of 48, 17%), and opisthotonos (1 out of 48, 2%) were observed at the time of discharge.

### Risk factor analysis

Table 3 shows the univariate analysis in 48 cases of neonatal CSVT and 192 control infants. Male sex, preterm birth, and indicators for hypoxia (umbilical artery blood pH ≤7.1, 5-minute Apgar score <7, intubation/mask ventilation during initial care, and perinatal asphyxia) were significantly associated with neonatal CSVT. Maternal complications significantly associated with neonatal CSVT included emergency Caesarean

section, operative vaginal delivery, and pathological fetal Doppler sonography.

At least one perinatal risk factor (preterm birth, hypoxia, emergency Caesarean section, or operative vaginal delivery) was present in 40 (83%) cases but only in 65 (34%) of the controls ( $p < 0.001$ ). After multivariable mutual adjustment, only hypoxia with an OR of 10.4 (95% CI 3.9–27.7) was a strong independent risk factor.

In the stratified univariate analysis by preterm birth, 14 infants born preterm and 18 controls born preterm were compared, as well as 34 infants born at term versus 174 controls born at term (Tables S4 and S5, online supporting information). Other than the delivery mode (with 75% delivered by emergency Caesarean section in infants born preterm vs 33% in the infants born preterm control group), no risk factors could be identified in the analysis of the cohort born preterm, which is most likely due to the small number of cases. Further adjustment by gestational age is needed in future investigations of risk factors in infants born preterm. Univariate risk factor analysis of infants born at term only revealed comparable results to the overall analysis.

### DISCUSSION

In this population-based surveillance study, we observed a neonatal CSVT incidence of 6.6 per 100 000 live births

after correction for underreporting. In the univariate analysis, we identified significant associations to neonatal CSVT for several risk factors. Hypoxia was independently associated with neonatal CSVT in the multivariable model.

There are only a few published population-based estimates for neonatal CSVT incidence. The largest study, which included children up to the age of 16 years, was conducted by the Canadian Pediatric Ischemic Stroke Registry and also used correction for underreporting; however, it did not apply capture-recapture.<sup>10</sup> Incidence estimates for infants with neonatal CSVT of 40.7 per 100 000 live births have been reported in a subsequent review paper by Shroff and deVeber,<sup>1</sup> however, they did not provide information on the imaging techniques used. The high incidence of neonatal CSVT suggested in this paper, on a cohort of infants diagnosed between 1992 and 1997, might be caused by diagnoses not necessarily based on up-to-date imaging techniques.

The study by Berfelo et al.,<sup>7</sup> although confined to 6 out of 10 level III neonatal care units, provides population-based estimates because of a defined catchment area and population. The yearly neonatal CSVT incidence in the Netherlands ranged from 1.4 (95% CI 0.04–8.01) per 100 000 live births in 2000 to 12 (95% CI 5.20–23.73) per 100 000 live births in 2007. Since data were sourced from a database that is likely to be complete, underreporting is unlikely. All cases were validated with MRI. However, the authors chose to report yearly incidence estimates excluding infants born preterm. Therefore, the results cannot easily be compared to our estimate, although the range of annual point estimates of incidence includes our findings.

The study by Grunt et al.<sup>19</sup> included infants born preterm in the incidence estimate. Like our study, it was based on physician reporting. The lower point estimate of 3.4 per 100 000 live births might have been caused by the absence of a secondary source to adjust for underreporting. The population-based study by Tuckuviene et al.<sup>20</sup> with a low incidence estimate of 0.82 (95% CI 0.39–1.71) per 100 000 live births included only seven neonatal cases.

The synopsis of the available incidence reports based on population-based settings suggests that the estimate of 6.6 (4.4–8.7) per 100 000 live births might reflect the incidence for neonatal CSVT to be expected in high-income populations with imaging facilities that use MRI on a regular basis.

Some of the identified risk factors have already been suggested in previous studies but not yet confirmed with a control group.<sup>11,23</sup> Male sex is a risk factor as described previously for other types of perinatal stroke.<sup>12</sup> The pathophysiological role of sex in the aetiology of stroke is not yet clear. The influence of hormones has been discussed as a potential cause.<sup>24</sup>

All of Virchow's criteria may be relevant in neonatal CSVT. Compression of the large venous sinuses or distension of vessel walls during delivery could have a potential impact on brain perfusion and perhaps trigger neonatal CSVT. Hypoxia is associated with impaired cerebral blood

flow and hypercoagulopathy. Hypoxia, defined as low umbilical artery blood pH, low Apgar score, a diagnosis of perinatal asphyxia, or the need for ventilation during initial care, was indeed identified as a strong risk factor in our study. The International Paediatric Stroke Study, as well as others, reported a high percentage of infants with hypoxia, acidosis, and resuscitation among newborns with CSVT.<sup>8–10,25,26</sup>

In the univariate analysis, emergency Caesarean section was another strong risk factor and is likely a precursor of perinatal complications. Therefore, emergency Caesarean section might be a predictor for the development of neonatal CSVT. Previous reports hinted to a high proportion of complicated deliveries among infants with neonatal CSVT.<sup>5,7,27,28</sup>

Maternal complications like gestational hypertension, pre-eclampsia, gestational diabetes, or chorioamnionitis were previously assumed to be related to neonatal CSVT.<sup>5,9</sup> It is unclear whether failure to confirm these risk factors in our data is related to lack of power; chorioamnionitis was diagnosed in only one mother and in none of the controls. In the study by Wu et al.,<sup>9</sup> 20% (6 out of 30) of all mothers of infants with neonatal CSVT had chorioamnionitis. Although plausible explanations regarding the association of these risk factors with the development of neonatal CSVT are conceivable, the impact of maternal determinants in the aetiology of neonatal CSVT might be less relevant than previously suggested.

In addition, preterm birth was identified as a risk factor in the univariate analysis but may also be a precursor of perinatal and postnatal complications. A higher risk for neonatal CSVT in infants born preterm has already been described;<sup>29</sup> however, data about infants with neonatal CSVT born preterm are scarce.

Sepsis, meningitis, dehydration, and cardiac disease were identified in a number of cases, suggesting a potential role for the aetiology of neonatal CSVT.<sup>5,10,30,31</sup> Neonatal sepsis was a common complication in our cases. Unfortunately, the control data set in our analysis includes only perinatal data. Therefore, we could not verify these potential risk factors.

### Study strengths

These are the most recent estimates for neonatal CSVT incidence from a high-income country in a contemporary health care setting with comprehensive access to modern imaging techniques. The population-based design with correction of underreporting by a second data source and availability of an appropriate control group are the unique and substantial strengths of the study. Limiting analysis to MRI-confirmed cases and a considerable study size further support the relevance of the results.

### Study limitations

On-site case validation and independent neuroimaging evaluation from the reporting hospitals to review the original data was not possible due to the study structure of the

ESPED and data protection regulations in Germany. Physician awareness guided diagnostic procedures, the inclusion of patients, and interpretation of neuroimaging results. However, we had access to discharge records or questionnaires with detailed case descriptions including imaging, which were used to validate data regarding plausibility. Through the ESPED centre, it was also possible to make enquiries with the treating physicians.

The basis of the capture-recapture calculation and nationwide extrapolation of incidence are based on the data from only one federal state. The number of patients in a confined area is limited due to the rareness of the disease. In particular, the small number of matches limits the precision of the estimate.

We cannot definitely rule out that some of the control infants might be individuals with neonatal CSVT; however, the probability is low. Even if we assume the highest reported incidence of neonatal CSVT (40.7 per 100 000 live births), the probability that at least one neonatal patient with CSVT was included in the control group is 7.5%.

We could have analysed perinatal and maternal risk factors. Congenital thrombophilia and postnatal risk factors could not be addressed. The cause of neonatal CSVT in the affected child is likely to be an interplay of a number of risk factors from different domains.

Finally, the criterion to include all variables with a univariate  $p < 0.2$  in the multivariate analysis was determined arbitrarily.

## CONCLUSION

The most probable estimate for the contemporary incidence of neonatal CSVT in high-income countries is 6.6 per 100 000 live births. Hypoxia is the most important perinatal risk factor for the aetiology of neonatal CSVT.

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## DATA AVAILABILITY STATEMENT

The data that support the findings, as well as the program code of this study, are available from the corresponding author upon reasonable request.

## SUPPORTING INFORMATION

The following additional material may be found online:

**Table S1:** Studies concerning the incidence of CSVT in infants

**Table S2:** Maternal and infant characteristics of the cases of neonatal CSVT

**Table S3:** Frequency of symptoms in infants born at term and infants born preterm for neonatal CSVT cases

**Table S4:** Univariate analyses of maternal and neonatal characteristics in infants born preterm with neonatal CSVT versus infants born preterm

**Table S5:** Univariate analyses of maternal and neonatal characteristics in infants with neonatal CSVT born at term versus control infants born at term

**Figure S1:** Graphical representation of the capture-recapture methodology performed in North-Rhine Westphalia.

**Figure S2:** Flow chart of the literature review conducted using PubMed.

## REFERENCES

- Shroff M, deVeber G. Sinovenous thrombosis in children. *Neuroimaging Clin N America* 2003; **13**: 115–38.
- Kersbergen KJ, Groenendaal F, Benders MJNL, de Vries LS. Neonatal cerebral sinovenous thrombosis: neuroimaging and long-term follow-up. *J Child Neurol* 2011; **26**: 1111–20.
- Ramenghi LA, Cardillo V, Rossi A. Neonatal cerebral sinovenous thrombosis. *Handb Clin Neurol* 2019; **162**: 267–80.
- Sébire G, Tabarki B, Saunders DE, et al. Cerebral venous sinus thrombosis in children: risk factors, presentation, diagnosis and outcome. *Brain* 2005; **128**: 477–89.
- Fitzgerald KC, Williams LS, Garg BP, Carvalho KS, Golomb MR. Cerebral sinovenous thrombosis in the neonate. *Arch Neurol* 2006; **63**: 405–9.
- Kenet G, Waldman D, Lubetsky A, et al. Paediatric cerebral sinus vein thrombosis. A multi-center, case-controlled study. *Thromb Haemost* 2004; **92**: 713–8.
- Berfelo FJ, Kersbergen KJ, van Ommen CHH, et al. Neonatal cerebral sinovenous thrombosis from symptom to outcome. *Stroke* 2010; **41**: 1382–8.
- Shevell MI, Silver K, O’Gorman AM, Watters GV, Montes JL. Neonatal dural sinus thrombosis. *Pediatr Neurol* 1989; **5**: 161–5.
- Wu YW, Miller SP, Chin K, et al. Multiple risk factors in neonatal sinovenous thrombosis. *Neurology* 2002; **59**: 438–40.
- deVeber G, Andrew M, Adams C, et al. Cerebral sinovenous thrombosis in children. *N Engl J Med* 2001; **345**: 417–23.
- Chabrier S, Husson B, Dinomais M, Landrieu P, Nguyen The Tich S. New insights (and new interrogations) in perinatal arterial ischemic stroke. *Thromb Res* 2011; **127**: 13–22.
- Sorg A-L, von Kries R, Klemme M, et al. Risk factors for perinatal arterial ischaemic stroke: a large case-control study. *Dev Med Child Neurol* 2020; **62**: 513–20.
- Gerstl L, Weinberger R, Heinen F, et al. Arterial ischemic stroke in infants, children, and adolescents: results of a Germany-wide surveillance study 2015–2017. *J Neurol* 2019; **266**: 2929–41.
- Hook EB, Regal RR. Capture-recapture methods in epidemiology: methods and limitations. *Epidemiol Rev* 1995; **17**: 243–64.
- Federal Institute for Drugs and Medical Devices. ICD-10-GM [Internet]. Available at: URL: <https://www.dimdi.de/dynamic/en/classifications/icd/icd-10-gm/> (accessed 6 January 2021).
- Chapman DG. Some properties of the hypergeometric distribution with applications to zoological sample censuses. Berkeley, CA: University of California Press, 1951.
- Statistisches Bundesamt (Destatis). Statistisches Bundesamt Deutschland. GENESIS-Online [Internet]. Available at: [https://www-genesis.destatis.de/genesis/online;jsessionid=FFF2C900F1350C21C97FB22F20A8991.tomcat\\_GO\\_1\\_3?operation=previous&levelindex=2&le](https://www-genesis.destatis.de/genesis/online;jsessionid=FFF2C900F1350C21C97FB22F20A8991.tomcat_GO_1_3?operation=previous&levelindex=2&le)

- velid=1534941870245&step=2 (accessed 6 January 2021).
18. Voigt M, Rochow N, Schneider KTM, et al. New percentile values for the anthropometric dimensions of singleton neonates: analysis of perinatal survey data of 2007–2011 from all 16 states of Germany [Article in German]. *Z Geburtshilfe Neonatol* 2014; **218**: 210–7.
  19. Grunt S, Mazenauer L, Buerki SE, et al. Incidence and outcomes of symptomatic neonatal arterial ischemic stroke. *Pediatrics* 2015; **135**: e1220–e1228.
  20. Tuckuviene R, Christensen AL, Helgestad J, Johnsen SP, Kristensen SR. Paediatric arterial ischaemic stroke and cerebral sinovenous thrombosis in Denmark 1994–2006: a nationwide population-based study. *Acta Paediatr* 2011; **100**: 543–9.
  21. Heller C, Heinecke A, Junker R, et al. Cerebral venous thrombosis in children: a multifactorial origin. *Circulation* 2003; **108**: 1362–7.
  22. Machado V, Pimentel S, Pinto F, Nona J. Perinatal ischemic stroke: a five-year retrospective study in a level-III maternity [Article in Portuguese]. *Einstein (Sao Paulo)* 2015; **13**: 65–71.
  23. Yang JYK, Chan AKC, Callen DJA, Paes BA. Neonatal cerebral sinovenous thrombosis: sifting the evidence for a diagnostic plan and treatment strategy. *Pediatrics* 2010; **126**: e693–e700.
  24. Sheiner E, Levy A, Katz M, Hershkovitz R, Leron E, Mazor M. Gender does matter in perinatal medicine. *Fetal Diagn Ther* 2004; **19**: 366–9.
  25. Jordan LC, Rafay MF, Smith SE, et al. Antithrombotic treatment in neonatal cerebral sinovenous thrombosis: results of the International Pediatric Stroke Study. *J Pediatr* 2010; **156**: 704–10.
  26. Ramenghi LA, Govaert P, Fumagalli M, Bassi L, Mosca F. Neonatal cerebral sinovenous thrombosis. *Semin Fetal Neonatal Med* 2009; **14**: 278–83.
  27. Rutherford MA, Ramenghi LA, Cowan FM. Neonatal stroke. *Arch Dis Child Fetal Neonatal Ed* 2012; **97**: F377–F384.
  28. Hunt RW, Badawi N, Laing S, Lam A. Pre-eclampsia: a predisposing factor for neonatal venous sinus thrombosis? *Pediatr Neurol* 2001; **25**: 242–6.
  29. Raets MMA, Sol JJ, Govaert P, et al. Serial cranial US for detection of cerebral sinovenous thrombosis in pre-term infants. *Radiology* 2013; **269**: 879–86.
  30. Carvalho KS, Bodensteiner JB, Connolly PJ, Garg BP. Cerebral venous thrombosis in children. *J Child Neurol* 2001; **16**: 574–80.
  31. Nwosu ME, Williams LS, Edwards-Brown M, Eckert GJ, Golomb MR. Neonatal sinovenous thrombosis: presentation and association with imaging. *Pediatr Neurol* 2008; **39**: 155–61.