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# Prevalence & Risk Factors for Perinatal Stroke: A Population-Based Study

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## Abstract

**Objectives:** The study objective was to calculate the birth prevalence of perinatal stroke and examine risk factors in term infants. Some risk factors are present in healthy infants, making it difficult to determine at-risk infants.

**Study Design:** Prospective population-based perinatal stroke data were compared to the Australian general population data using chi-squared and Fisher's exact tests and multivariable logistic regression analysis.

**Results:** Sixty perinatal stroke cases were reported between 2017 and 2019. Estimated stroke prevalence was 9.6/100,000 live births/year including 5.8 for neonatal arterial ischemic stroke and 2.9 for neonatal hemorrhagic stroke. Eighty seven percent had multiple risk factors. Significant risk factors were cesarean section ($p = 0.04$), 5-min Apgar score <7 ($p < 0.01$), neonatal resuscitation ($p < 0.01$) and nulliparity ($p < 0.01$).

**Conclusions:** Statistically significant independent risk factors do not fully explain the cause of perinatal stroke, because they are not a direct causal pathway to stroke. These data now require validation in a case-control study.

## Keywords

perinatal stroke, risk factors, stroke prevalence

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Perinatal stroke includes acute symptomatic perinatal stroke presenting in the perinatal period from 20 weeks of gestation to 28 days postnatal age and presumed perinatal stroke presenting after 28 days of age.[1-3] The focus of this paper is on acute symptomatic perinatal stroke. The subtypes of acute symptomatic perinatal stroke are neonatal arterial ischemic stroke (NAIS), neonatal cerebral sinovenous thrombosis (CSVT) and neonatal hemorrhagic stroke (NHS).[4]

The incidence of perinatal stroke has been inconsistently reported in the literature due to a lack of a population register, heterogeneity of data sources, reporting bias in non-population clinical samples and inconsistent terminology for stroke subtypes.[5] Diagnostic criteria discrepancies also influence reported incidence rates. The incidence of perinatal stroke is 25–40/100,000 live births, compared to the incidence of childhood stroke 2–3/100,000 children in the United States.[6,7] The global incidence of perinatal arterial ischemic stroke ranges from 1/2800 to 1/5000 live births.[1,8,9] Prior studies in Australia have quoted the incidence of arterial ischemic stroke as 1.8/100,000 children per year and CSVT as 0.34/100,000 children per year, although the true incidence of perinatal stroke remains unknown.[10,11]

Risk factors for perinatal stroke, underlying etiologies and pathophysiology depend on stroke subtype.[12] Most epidemiological studies are based on retrospective data or small heterogenous samples aggregated into group means, which limits the identification of precise risk factors.[7,13,14] Moreover, some of these risk factors are present in the general population, leading to uncertainties in etiology and prevention strategies.

The aim of this study was to determine the prevalence and identify risk factors for perinatal stroke in full term infants compared to the general Australian population.

## Methods

### Study Design

This was a 2-year study conducted between 1 July 2017 and 30 June 2019. Acute symptomatic perinatal stroke cases were reported prospectively by specialist physicians including neonatologists, pediatricians, or neurologists to the Australian Paediatric Surveillance Unit (APSU). The APSU is a national resource that facilitates active surveillance of rare childhood diseases.[15] It is closely affiliated with the University of Sydney's Faculty of Medicine and Health Sciences and the Sydney Children's Hospital Network. A data questionnaire designed by the investigators (BR, NB and IN) was submitted by reporting physicians with deidentified data to the APSU. Data included postal zip code, risk factors for stroke, clinical presentations, investigations, management, and outcomes of stroke. Diagnosis of stroke was based on the reporting neonatologist, pediatrician or neurologist and independently confirmed by brain MRI reports by three authors (BR, CM and NB). MRI images were not sought to lower respondent burden and reduce the likelihood of missing data. Results were reported according to the revised STROBE statement.[16]

For consistency of reporting and analysis, risk factors for stroke were categorized into maternal, pregnancy, intrapartum and neonatal groups, as follows based on previous studies.[17-20]

(a) Maternal risk factors included: ethnicity, age, consanguinity, genetic or hematological abnormalities, miscarriage, still birth and neonatal death history, and history of stroke in other children.
(b) Pregnancy risk factors included: gravida, parity, multiple births, type of conception, gestational diabetes, hypertension, and history of illicit drugs, smoking and alcohol.
(c) Intrapartum risk factors included: infections, group B streptococcus (GBS) colonization, prolonged rupture of membrane, meconium-stained liquor, placental abnormalities, mode of delivery and history of difficult delivery.
(d) Neonatal risk factors included: sex, gestational age, birth weight, head circumference, Apgar scores, resuscitation, cord blood gas, history of receiving vitamin K, sepsis, meningitis, congenital heart disease (CHD), hypoglycemia, central vascular catheterization and hematological or coagulation abnormalities.

### Participants

Inclusion criteria were:

1. Term infants (37-42 weeks of gestation) with perinatal stroke in Australia
2. Perinatal stroke presenting from birth to 28 days of age
3. Infants born between 2017 and 2019.

Exclusion criteria were:

1. Perinatal stroke presenting after 28 days of age
2. Strokes secondary to head injury
3. Preterm infants (<37 weeks of gestation)
4. CSVT alone.

### Stroke Types

Inconsistent classification of stroke in young children in the literature is one of the major hurdles in aggregating and interpreting data. Some of the classifications are based on: a) age when stroke occurs (eg fetal stroke, perinatal stroke, neonatal stroke, and pediatric or childhood stroke); b) type of stroke (eg ischemic or hemorrhagic), and c) nature of blockage of blood vessel causing stroke (eg arterial ischemic stroke, CSVT, hemorrhagic stroke or periventricular venous infarction).

Dunbar and Kirton's classification of acute symptomatic perinatal stroke, including arterial or venous and ischemic or hemorrhagic subtypes, was used in this study.[4]

Arterial stroke included:

1. Neonatal arterial ischemic stroke (NAIS) – defined as focal ischemic infarction in one or more arterial territories, occurring more commonly in term infants with acute clinical presentation of stroke in the first 28 days of age.

Venous stroke included:

1. Neonatal hemorrhagic stroke (NHS) – a focal bleed within the brain parenchyma in term infants in the first 28 days of age.
2. Cerebral sinovenous thrombosis (CSVT) – includes presence of thrombus in one or more cerebral veins or dural sinuses plus parenchymal venous infarction in cerebral venous territory, occurring in term infants presenting with seizures in the first days of life.

### Statistical Analysis

Birth prevalence rates of acute symptomatic perinatal stroke in Australia were calculated by dividing the number of cases by the number of live births, annually, which was determined from the Australian Bureau of Statistics population dataset.[21] The term 'incidence' was used for whole population data and 'prevalence' was used for non-population data.

Frequencies and percentages were calculated for maternal and neonatal risk factors across stroke subtype groups. When missing data occurred (reported in Table 1), the denominator for each variable was adjusted as appropriate. Differences in maternal and neonatal risk factors between stroke subtypes were tested using chi-squared tests, or Fisher's exact tests where group sizes were $n < 5$. Odds ratios and associated 95% confidence intervals for the associations between risk factors and stroke subtypes were also calculated where possible. Multivariable logistic regression models were conducted for the stroke subtype outcomes to identify independent risk factors.

Total population level data was obtained from the Australian Institute of Health and Welfare's (AIHW) Australia's Mothers and Babies report, which is based on 2019 data from the National Perinatal Data Collection, the National Maternal Mortality Data Collection, and the National Perinatal Mortality Data Collection.[22] The prevalence of maternal and neonatal risk factors in the stroke population was compared with their overall population prevalence using chi-squared tests and z-tests of proportions. For all statistical analyses, significance was set at $p < 0.05$.

## Statement on Ethics

This study was approved by the Sydney Children's Hospital Network Human Research Ethics Committee (Ethics approval no: 2019/ETH06281).

## Results

### Patient Population

Sixty acute symptomatic perinatal strokes met all three inclusion criteria (Table 2).

The acute symptomatic perinatal stroke subtypes and birth prevalence are shown in Figure 1.

### Risk Factors for Stroke

Risk factors were identified in 95% (57/60) of acute symptomatic perinatal strokes, and 87% (52/60) had multiple risk factors. In the univariate analysis (Table 3), mode of delivery and meconium-stained liquor were identified as having significant associations with stroke subtype. Specifically, birth via cesarean section was significantly more prevalent among NAIS compared to NHS, with 61.7% of NAIS infants born via cesarean section compared to 29.4% of NHS (OR for NAIS vs NHS 3.77; 95% CI 1.00, 17.04). Meconium-stained liquor was more common in NAIS than in NHS; 34.3% versus 5.6% (OR for NAIS vs NHS 8.59; 95% CI 1.07, 400.21). Group B streptococcal colonization and central vascular catheterization were different between the perinatal stroke

**Table 1.** Missing (unknown) data for NAIS and NHS.

| Risk factors | NAIS (n=36) | NHS (n=18) |
|---|---|---|
| **Maternal risk factors** | | |
| Racial background: Unknown | 2 (5.6%) | 3 (16.7%) |
| Age: Unknown | 5 (15.6%) | 4 (22.2%) |
| Consanguinity Unknown | 2 (5.6%) | 1 (5.6%) |
| Hematological/ Genetic abnormalities: Unknown | 32 (88.9%) | 15 (83.3%) |
| History of miscarriage or still birth or neonatal deaths Unknown | 1 (2.8%) | 2 (11.1%) |
| History of stroke in other children Unknown | 0 (0.0%) | 1 (5.6%) |
| **Pregnancy risk factors** | | |
| Gravida: Unknown | 4 (12.5%) | 1 (5.6%) |
| Parity: Unknown | 4 (12.5%) | 1 (5.6%) |
| Multiple births Unknown | 0 (0.0%) | 0 (0.0%) |
| Type of conception: Unknown | 1 (2.8%) | 3 (16.7%) |
| Pregnancy complications: Unknown | 1 (2.8%) | 1 (5.6%) |
| Medications for hypertension, diabetes, thyroid disease Unknown | 1 (2.8%) | 1 (5.6%) |
| History of smoking Unknown | 2 (5.6%) | 1 (5.6%) |
| History of alcohol Unknown | 2 (5.6%) | 3 (16.7%) |
| History of illicit drugs Unknown | 2 (5.6%) | 2 (11.1%) |
| **Intrapartum risk factors** | | |
| Infections: Unknown | 1 (2.8%) | 1 (5.6%) |
| Prolonged rupture of membranes (>24 hours) Unknown | 1 (2.8%) | 1 (5.6%) |
| Meconium-stained liquor Unknown | 1 (2.8%) | 0 (0.0%) |
| Chorioamnionitis/Abno-rmal histopathology Unknown | 1 (2.8%) | 1 (5.6%) |
| Mode of delivery: Unknown | 2 (5.6%) | 1 (5.6%) |
| History of difficult delivery Unknown | 4 (12.5%) | 2 (11.1%) |
| Type of difficult delivery: Unknown | 1/4 (25.0%) | 0/2 (0.0%) |
| **Neonatal risk factors** | | |
| Gender: Unknown | 0 (0.0%) | 0 (0.0%) |

(continued)

**Table 1.** Continued.

| Risk factors | NAIS (n=36) | NHS (n=18) |
|---|---|---|
| Birth weight: | 1 (2.8%) | 3 (16.7%) |
| Unknown | 3 (8.3%) | 3 (16.7%) |
| Birth weight percentile | | |
| Unknown | | |
| Head circumference: | 9 (25.0%) | 9 (50.0%) |
| Unknown | | |
| 5-minute Apgar score | 2 (5.6%) | 3 (16.7%) |
| Unknown | | |
| 10-minute Apgar score | 23 (63.9%) | 7 (38.9%) |
| Unknown | | |
| Received vitamin K | 3 (8.3%) | 1 (5.6%) |
| Unknown | | |
| Resuscitation at birth | 2 (5.6%) | 1 (5.6%) |
| Unknown | | |
| Abnormal cord blood gas | 22 (61.1%) | 12 (66.7%) |
| Unknown | | |
| Infection (sepsis / meningitis) | 14 (38.9%) | 5 (27.8%) |
| Unknown | | |
| CHD | 16 (44.4%) | 11 (61.1%) |
| Unknown | | |
| Hypoglycemia | 14 (38.9%) | 5 (27.8%) |
| Unknown | | |
| Central vascular catheterisation | 6 (18.8%) | 5 (27.8%) |
| Unknown | | |
| Hematological abnormalities: | 32 (88.9%) | 15 (83.3%) |
| Unknown | | |

*n - number, NAIS - neonatal arterial ischemic stroke, NHS - neonatal hemorrhagic stroke

**Table 2.** Patient characteristics.

| | Acute symptomatic Perinatal Stroke (<28 days of age) |
|---|---|
| Total | 60 |
| Gestational age (weeks) range (mean) | 37–42 (39) |
| Birth weight (grams) range (mean) | 2114–4470 (3294) |
| Male:Female | 35:25 |

n – number.

subtypes, with 17.1% of NAIS having a GBS infection compared to none in the NHS, and 20.0% of NAIS having central vascular catheterization compared to 46.2% in the NHS, although these differences did not reach statistical significance. Both NAIS and NHS had more males than females, but the ratio of males to females was not statistically significant (OR 1.25; 95% CI 0.34, 4.56).

We used multivariable logistic regression models for stroke subtypes, with categorial variables included in the model when they were sufficiently populated ($n \geq 1$ in the smallest level) and univariate analysis yielded a p-value lower than 0.20. Only 3 variables (mode of delivery, meconium-stained liquor and central vascular catheterization) met these criteria. When included together in the model, all 3 variables showed significant association with stroke subtype. Meconium-stained liquor was associated with higher odds of NAIS (adjusted OR for NAIS vs NHS 52.41; 95% CI 2.04, 1348.50). In particular, central vascular catheterization (3 infants with umbilical vessel catheter, 2 with femoral catheter and 1 with peripherally inserted central catheter) was associated with a higher likelihood of NHS, though, none of the infants with central catheters had received anticoagulant treatment. Small sample size with the catheters precluded drawing firm conclusions (adjusted OR for NAIS vs NHS 0.05; 95% CI 0.00, 0.58). Normal vaginal delivery was similarly associated with higher odds of NHS (adjusted OR for NAIS vs NHS 0.15; 95% CI 0.02, 0.93), while cesarean section was associated with higher odds of NAIS (adjusted OR for NAIS vs NHS 6.91; 95% CI 1.07, 44.54).

The risk factors for perinatal stroke and its subtypes were also compared with those that are present in the general population, from the AIHW total population data (Table 4). After controlling for risks in the general population, significant risk factors for perinatal stroke included: previous history of miscarriage or still birth or neonatal death ($p < 0.01$); cesarean section ($p = 0.04$); low Apgar score ($p < 0.01$); neonatal resuscitation ($p < 0.01$), and nulliparity ($p < 0.1$).

## Discussion

### *Prevalence of Perinatal Stroke*

The estimated birth prevalence of acute symptomatic perinatal stroke in this population-based study was 9.6/100,000 live births per year, compared with 0.54–18.60/100,000 live births reported in studies from USA and 15.87/100,000 live births reported in a Canadian population-based study and in a perinatal stroke registry.[23-25] Our estimates were based on prospective reports from the entire country, and controlled for by birth prevalence in each state. Standardized stroke classification reporting was conducted by specialist physicians.[26,27]

In our study the birth prevalence of NAIS was 5.8/100,000 live births per year compared with 10.2/100,000 live births in Canada, 7.0/100,000 in Germany, 1.3/100,000 in Denmark with a global pooled incidence of 24.6/100,000 live births.[28,29] The birth prevalence of NHS in our study was 2.9/100,000 live births per year, which was significantly lower than a retrospective study that quoted 6.2/100,000 and 10.5–15.9/100,000 annually from a combined retrospective prospective study.[30,31]. The two countries with the highest stroke prevalence in the literature have registers, suggesting possible under-reporting in our method and other countries.

### *Epidemiology*

*Risk Factors Associated with Stroke Subtypes.* Our study found no difference in the risk factors between ischemic (NAIS) and hemorrhagic strokes (NHS), except for higher numbers

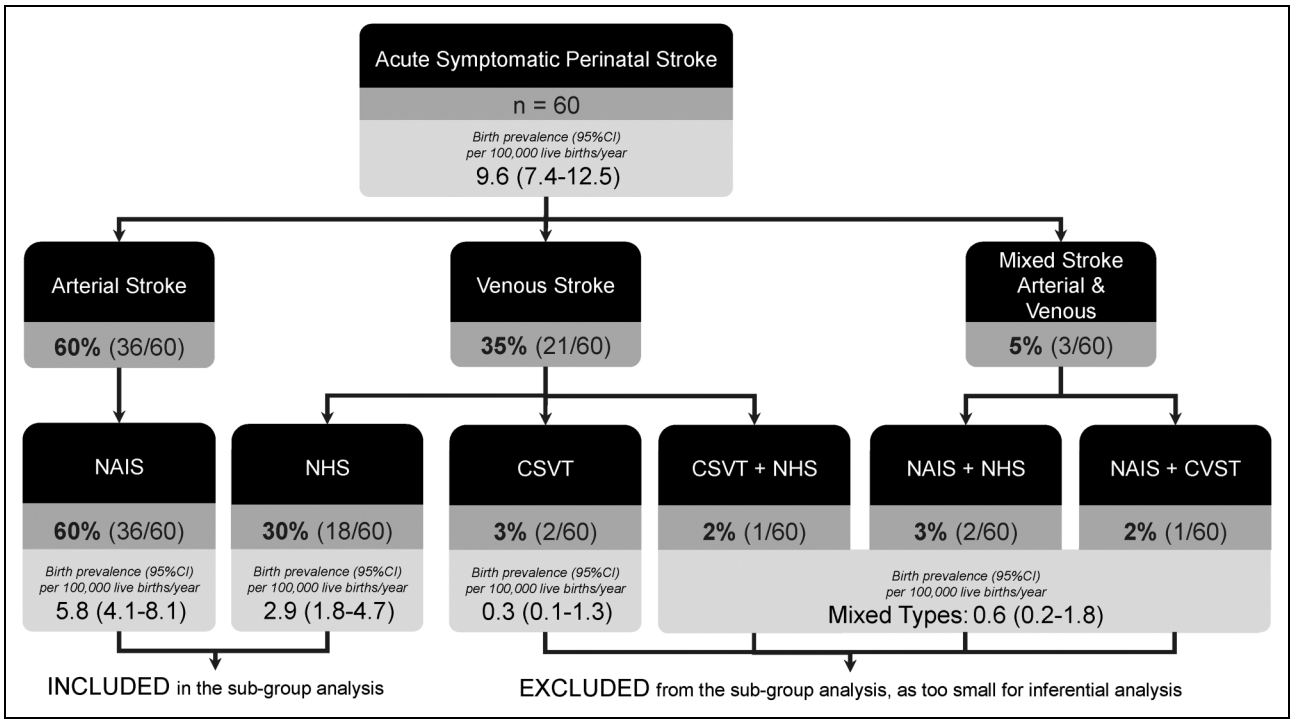


**Figure 1.** Types and birth prevalence of acute symptomatic perinatal stroke ($n = 60$).

**Table 3.** Risk factors for acute symptomatic perinatal stroke subtypes ($n > 2$).

| Risk factors | NAIS ($n = 36$) | NHS ($n = 18$) | OR (NAIS vs NHS) | p value |
|---|---|---|---|---|
| **Maternal risk factors** | | | | |
| Racial background: | | | | |
| Pacific Islander | 1 (2.9%) | 0 (0.0%) | NA | 1.00 |
| Indigenous Australian | 0 (0.0%) | 1 (6.7%) | NA | 0.30 |
| Caucasian | 26 (76.5%) | 10 (66.7%) | 1.61 (0.33, 7.32) | 0.50 |
| Asian | 4 (11.8%) | 3 (20.0%) | 0.54 (0.08, 4.25) | 0.70 |
| Others | 3 (8.8%) | 1 (6.7%) | 1.35 (0.10, 76.11) | 1.00 |
| Age: | | | | |
| <20 years | 0 (0.0%) | 0 (0.0%) | NA | 0.50 |
| 20–39 years | 30 (96.8%) | 13 (92.9%) | 2.26 (0.03, 186.77) | |
| ≥40 years | 1 (3.2%) | 1 (7.1%) | | |
| Consanguinity | 0 (0.0%) | 1 (5.9%) | NA | 0.38 |
| Hematological/ Genetic abnormalities: | | | | |
| Factor V Leiden | 1 (25.0%) | 0 (0.0%) | NA | 1.00 |
| Protein C & S | 1 (25.0%) | 0 (0.0%) | NA | 1.00 |
| Homocysteine | 0 (0.0%) | 0 (0.0%) | NA | 1.00 |
| Prothrombin | 0 (0.0%) | 0 (0.0%) | NA | 1.00 |
| AT III | 1 (25.0%) | 0 (0.0%) | NA | 1.00 |
| Fibrinogen | 1 (25.0%) | 0 (0.0%) | NA | 1.00 |
| Normal | 3 (75.0%) | 2 (66.7%) | NA | |
| History of miscarriage or still birth or neonatal deaths | 3 (8.6%) | 0 (0.0%) | NA | 0.54 |
| History of stroke in other children | 0 (0.0%) | 0 (0.0%) | NA | 1.00 |
| **Pregnancy risk factors** | | | | |
| Gravida: | | | | |
| Primigravida | 18 (56.2%) | 10 (58.9%) | 0.90 (0.23, 3.44) | 1.00 |
| Multigravida (>2) | 14 (43.8%) | 7 (41.1%) | | |
| Parity: | | | | |

(continued)

**Table 3.** Continued.

| Risk factors | NAIS ($n = 36$) | NHS ($n = 18$) | OR (NAIS vs NHS) | p value |
|---|---|---|---|---|
| One | 21 (65.5%) | 12 (70.6%) | 0.80 (0.17, 3.29) | 1.00 |
| ≥ Two | 11 (34.5%) | 5 (29.4%) | | |
| Multiple births: Twins/triplets | 1 (2.8%) | 0 (0.0%) | NA | 1.00 |
| Type of conception: | | | | |
| Natural | 32 (97.0%) | 15 (100.0%) | NA | 1.00 |
| In-vitro fertilization | 1 (30.0%) | 0 (0.0%) | | |
| Pregnancy complications: | | | | |
| Gestational diabetes mellitus | 5 (14.3%) | 1 (5.9%) | 2.70 (0.27, 137.10) | 0.65 |
| Pregnancy hypertension | 2 (5.7%) | 1 (5.9%) | 1.00 (0.05, 62.40) | 1.00 |
| Medications for hypertension, diabetes, thyroid disease | 7 (20.0%) | 1 (5.9%) | 3.91 (0.44, 171.20) | 0.25 |
| History of smoking | 2 (5.9%) | 1 (5.9%) | 1.00 (0.05, 62.60) | 1.00 |
| History of alcohol | 1 (2.9%) | 0 (0.0%) | NA | 1.00 |
| History of illicit drugs | 1 (2.9%) | 0 (0.0%) | NA | 1.00 |
| **Intrapartum risk factors** | | | | |
| Infections: | | | | |
| Group B streptococcus colonization | 6 (17.1%) | 0 (0.0%) | NA | 0.16 |
| HSV infection | 0 (0.0%) | 1 (5.9%) | NA | 0.33 |
| Parvovirus infection | 0 (0.0%) | 1 (5.9%) | NA | 0.33 |
| Prolonged rupture of membranes (>24 h) | 1 (2.9%) | 0 (0.0%) | NA | 1.00 |
| Meconium-stained liquor | 12 (34.3%) | 1 (5.6%) | **8.59 (1.07, 400.21)** | **0.04** |
| Chorioamnionitis/Abnormal histopathology | 2 (5.0%) | 0 (0.0%) | NA | 1.00 |
| Mode of delivery: | | | | |
| Normal vaginal delivery | 7 (20.6%) | 8 (47.1%) | 0.30 (0.07, 1.24) | 0.10 |
| Instrumental (vacuum, forceps) | 6 (17.7%) | 4 (23.5%) | 0.70 (0.13, 3.98) | 0.71 |
| Cesarean section (elective and emergency) | 21 (61.7%) | 5 (29.4%) | **3.77 (1.00, 17.04)** | **0.04** |
| Breech | 0 (0.0%) | 0 (0.0%) | NA | 1.00 |
| History of difficult delivery | 4 (12.5%) | 3 (18.8%) | 0.63 (0.09, 4.90) | 0.67 |
| Type of difficult delivery: | | | | |
| Shoulder dystocia | 0 (0.0%) | 0 (0.0%) | NA | 1.00 |
| Multiple vacuum attempts and/or failed vacuum | 0 (0.0%) | 1 (50.0%) | NA | 1.00 |
| **Neonatal risk factors** | | | | |
| Sex: | | | | |
| Male | 22 (61.1%) | 10 (55.6%) | 1.25 (0.34, 4.56) | 0.77 |
| Female | 14 (38.9%) | 8 (44.4%) | | |
| Birth weight: | | | | |
| <2500 g | 4 (11.4%) | 1 (6.7%) | 1.78 (0.16, 95.18) | 1.00 |
| Small for gestational age (<$10^{th}$ percentile) | 4 (12.1%) | 2 (13.3%) | 0.90 (0.11, 11.12) | 1.00 |
| Large for gestational age (>$90^{th}$ percentile) | 3 (9.1%) | 1 (6.7%) | 1.39 (0.10, 78.64) | 1.00 |
| Head circumference: | | | | |
| <$10^{th}$ percentile | 3 (11.1%) | 0 (0.0%) | NA | 0.56 |
| ≥$90^{th}$ percentile | 6 (22.2%) | 1 (11.1%) | 2.24 (0.21, 118.02) | 0.65 |
| 5-min Apgar score <7 | 5 (14.7%) | 4 (26.7%) | 0.48 (0.09, 2.90) | 0.43 |
| 10-min Apgar score <7 | 1 (7.7%) | 2 (18.2%) | 0.39 (0.01, 8.62) | 0.58 |
| Received vitamin K | 33 (100.0%) | 17 (100.0%) | NA | 1.00 |
| Resuscitation at birth | 17 (50.0%) | 8 (47.1%) | 1.12 (0.30, 4.25) | 1.00 |
| Abnormal cord blood gas | 11 (37.9%) | 4 (28.6%) | 1.78 (0.11, 22.86) | 0.61 |
| Infection (sepsis / meningitis) | 7 (31.8%) | 2 (15.4%) | 1.91 (0.31, 20.98) | 0.70 |
| Congenital heart disease | 9 (45.0%) | 2 (33.3%) | 1.61 (0.18, 21.67) | 1.00 |
| Hypoglycemia | 3 (13.6%) | 1 (7.7%) | 1.53 (0.11, 85.80) | 1.00 |
| Central vascular catheterization | 6 (20.0%) | 6 (46.2%) | 0.30 (0.06, 1.51) | 0.14 |
| Hematological abnormalities: | | | | |
| Factor V Leiden | 1 (25.0%) | 1 (33.3%) | 0.37 (0.01, 34.82) | 0.51 |
| Protein C & S | 3 (75.0%) | 0 (0.0%) | NA | 0.52 |
| Homocysteine | 1 (25.0%) | 0 (0.0%) | NA | 1.00 |
| Prothrombin | 0 (0.0%) | 0 (0.0%) | NA | 1.00 |
| AT III | 1 (25.0%) | 0 (0.0%) | NA | 1.00 |
| Fibrinogen | 2 (50.0%) | 0 (0.0%) | NA | 1.00 |

**Table 4.** Comparison of risk factors of perinatal stroke with AIHW total population data.

| Variable | AIHW Data % | Perinatal Stroke Data n (%) | p-value | NAIS ($n = 36$) | p-value | NHS ($n = 18$) | p-value |
|---|---|---|---|---|---|---|---|
| Maternal age: | | | | | | | |
| <20 years | 1.9% | 0 (0%) | 0.64 | 0 (0.0%) | 0.91 | 0 (0.0%) | 1.00 |
| 20–39 years | 93.6% | 48 (96.0%) | 0.69 | 30 (96.8%) | 0.72 | 13 (92.9%) | 1.00 |
| 40 + years | 4.5% | 2 (4.0%) | 1.00 | 1 (3.2%) | 1.00 | 1 (7.1%) | 1.00 |
| Smoking | 10.2% | 4 (7.3%) | 0.62 | 2 (5.9%) | 0.58 | 1 (5.9%) | 0.91 |
| Alcohol | 5.0% | 1 (1.8%) | 0.44 | 1 (2.9%) | 0.87 | 0 (0.0%) | 0.77 |
| Delivery: | | | | | | | |
| NVD | 64% | 16 (28.6%) | **<0.01** | 7 (20.6%) | **<0.01** | 8 (47.1%) | 0.23 |
| CS | 36% | 28 (50.0%) | **0.04** | 21 (61.8%) | **<0.01** | 5 (29.4%) | 0.75 |
| Forceps | 10.1% | 5 (8.9%) | 0.94 | 3 (8.8%) | 1.00 | 1 (5.9%) | 0.86 |
| Vacuum | 13.1% | 7 (12.5%) | 1.00 | 3 (8.8%) | 0.63 | 3 (17.7%) | 0.84 |
| Breech | 4.1% | 0 (0.0%) | 0.23 | 0 (0.0%) | 0.44 | 0 (0.0%) | 0.81 |
| GDM | 11.0% | 7 (12.3%) | 0.92 | 5 (14.3%) | 0.73 | 1 (5.9%) | 0.77 |
| PIH | 2.0% | 3 (5.3%) | 0.20 | 2 (5.7%) | 0.33 | 1 (5.9%) | 0.78 |
| LBW | 6.6% | 6 (10.9%) | 0.31 | 4 (11.4%) | 0.42 | 1 (6.7%) | 1.00 |
| SGA | 9.4% | 7 (13.2%) | 0.47 | 4 (12.1%) | 0.81 | 2 (13.3%) | 0.33 |
| 5-min Apgar <7 | 2.0% | 9 (16.7%) | **<0.01** | 5 (14.7%) | **<0.01** | 4 (26.7%) | **<0.01** |
| Resuscitation | 19% | 25 (45.5%) | **<0.01** | 17 (50.0%) | **<0.01** | 8 (47.1%) | **<0.01** |
| Parity | | | | | | | |
| One | 43% | 35 (64.8%) | **<0.01** | 21 (65.5%) | **0.02** | 12 (70.6%) | **0.04** |
| ≥ Two | 57% | 19 (35.2%) | | 11 (34.5%) | | 5 (29.4%) | |

of cesarean section ($p = 0.04$) and meconium-stained liquor ($p = 0.04$) in NAIS compared to NHS (Table 3). There were 11 infants with CHD: 9 had NAIS and 2 had NHS. No equivalent studies were found in the published literature for comparison. Previous studies have reported maternal infection in the perinatal and postnatal period as important risk factors, but these were not significant in our sample.[32-34]

Maternal illicit drug use is associated with stroke. In our study, one mother had a history of buprenorphine and her baby had NAIS.[35,36] The other risk factors in this case were low birth weight, small for gestational age, emergency cesarean section and Apgar score <7, requiring oxygen for resuscitation.

We confirm a male predominance (male:female ratio 1.4:1.0), similar to a high male incidence (male:female ratio 1.5:1.0) quoted in the literature.[29,37] The cause for male dominance was not clear, though studies have indicated an association between elevated endogenous testosterone and risk of cerebral thromboembolism.[38] Previous meta-analyses have suggested male predominance was not associated with a greater vulnerability of males to adverse neonatal outcome.[20]

In our study cohort we had no genetic findings and no reports of sickle cell anemia, a known risk factor.[34,39] It was not clear whether this was due to a unique Australian phenomenon, ethnicity of the participants, insufficient data entry, or an artefact of the sample size.

*Risk Factors Compared to Population Data.* Some risk factors were significantly higher in the stroke cases compared to the babies from the control AIHW group (Table 4), for example history of miscarriage, still birth and neonatal death, and cesarean section, consistent with previous studies.[40] However, risks such as miscarriage, still birth and neonatal death were aggregated in the AIHW data, and could not be analyzed individually. This was problematic because still birth and neonatal death are presumed individual risk factors for stroke. Elective and emergency cesarean sections were reported collectively in AIHW population data, whereas in our study 7% had elective cesarean section and 40% had emergency cesarean section. Emergency cesarean sections are likely to be ascribed to fetal compromise, which is presumed to be a risk factor for stroke.

The 5-min Apgar score <7 and neonatal resuscitation were significant risk factors. Similar findings have been reported in previous studies.[41] Though emergency cesarean section, low 5 min Apgar score, meconium stained liquor and neonatal resuscitation were coded as risk factors, these variables in combination could be signs and symptoms of a perinatal stroke in progress. Hence infants with these signs and symptoms should have a brain MRI to detect stroke as early as possible.

Nulliparity was another statistically significant risk factor. An association between nulliparity and adverse neonatal outcomes have been reported in the literature,[42] although the correlation between nulliparity and perinatal stroke requires more research.

In this study there was no association between neonatal infection, CHD and hypoglycemia because of the lack of information on these in the AIHW data set. A well powered case-control study is warranted to further examine the relationship between these risks.

The strength of our study was the prospective comparison with Australian population data since some of the risk factors were also found in healthy infants and infants with other disabilities. The limitation of this study was the inability to obtain MRI images and the diagnosis of perinatal stroke

was therefore based on the physician's report and the MRI brain report, which may have clinical interpretation differences. Other limitations include possible under-reporting due to different ethics requirements in different Australian jurisdictions; the Covid pandemic causing burden of notifications from busy clinicians; and potentially delayed recognition of perinatal stroke (beyond 28 days of age) in some cases. Under-reporting could potentially have been overcome by a longer study. Also, a full population ascertainment reporting to a national pediatric stroke register with timely early diagnosis will be critical to substantiate the risk factors and true incidence.

In conclusion, this Australian population-based study reported the birth prevalence of acute symptomatic perinatal stroke, including for the subtypes. This was the first study to compare the risk factors for perinatal stroke with the Australian population data (AIHW) and elucidate the significant risk factors for perinatal stroke. Infants with perinatal stroke had low Apgar scores and more frequent caesarean sections. These risk factors are common to many neonatal disorders and do not fully explain the etiology of perinatal stroke.

Dilemmas remain. Hence, a prospective case control study is now needed to elucidate the etiology. Further research may also include placental pathology and the role of genetic factors to allow more precise investigation into the causal pathway and enabling preventative measures, earlier diagnosis, and individualized neuroplasticity treatment.

## Abbreviations

| | |
|---|---|
| AIHW | Australian Institute of Health and Welfare |
| APPIS | Arterial Presumed Perinatal Ischemic Stroke |
| APSU | Australian Paediatric Surveillance Unit |
| AT III | Antithrombin III |
| CHD | Congenital Heart Disease |
| CI | Confidence Interval |
| CS | Cesarean Section |
| CSVT | Cerebral Sinovenous Thrombosis |
| GDM | Gestational Diabetes Mellitus |
| HSV | Herpes Simplex Virus |
| LBW | Low Birth Weight |
| MRI | Magnetic Resonance Imaging |
| n | Number |
| NAIS | Neonatal Arterial Ischemic Stroke |
| NHS | Neonatal Hemorrhagic Stroke |
| NVD | Normal Vaginal Delivery |
| PIH | Pregnancy Induced Hypertension |
| PPHS | Presumed Perinatal Hemorrhagic Stroke |
| PVI | Periventricular Venous Infarction |
| SGA | Small for Gestational Age |

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## Author Contributors

Dr Bithi Roy, Prof Iona Novak and Prof Nadia Badawi conceptualized and designed the study and designed the data collection instruments.

Dr Bithi Roy collected data, carried out the initial analyses, drafted the initial manuscript, and revised the manuscript.

Prof Iona Novak critically analyzed and reviewed and revised the manuscript for important intellectual content.

Prof Nadia Badawi assisted in data collection, and critically reviewed and revised the manuscript for important intellectual content.

Clinical Prof Karen Walker and Dr Catherine Morgan assisted in data collection, and critically reviewed and revised the manuscript for important intellectual content.

Annabel Webb carried out the initial analyses, and critically analyzed and revised the manuscript.

Dr Carlos Nunez collected and curated the data and critically reviewed and revised the manuscript.

Prof Guy Eslick critically analyzed, critically reviewed, and revised the manuscript.

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All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

## Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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## Ethical Approval

All information and data described in this observational study are aligned with the Sydney Children's Hospital Network Human Research Ethics Committee. There was no required written IRB consent for this study in our institution.

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