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

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This article is commented on by Chabrier and Sebire on page 413–414 of this issue.

AIM To identify maternal, obstetric, and neonatal risk factors related to perinatal arterial ischaemic stroke (PAIS) diagnosed within 28 days after birth and to understand the underlying pathophysiology.

METHOD For case and control ascertainment, we used active surveillance in 345 paediatric hospitals and a population-based perinatal database for quality assurance of hospital care. We analysed complete cases of PAIS using logistic regression. Multivariate analysis was guided by a directed acyclic graph.

RESULTS After exclusion of records with missing data, we analysed 134 individuals with PAIS and 576 comparison individuals. In univariate analysis, male sex, preterm birth (<37wks gestational age), small for gestational age (SGA), low umbilical artery pH (<7.1), low 5-minute-Apgar score (<7), multiple pregnancies, hypoxia, intubation/mask ventilation, nulliparity, Caesarean section, vaginal-operative delivery, chorioamnionitis, and oligohydramnios were associated with an increased risk. Mutual adjustment yielded male sex (odds ratio [OR] 1.81; 95% confidence interval [CI] 1.20–2.73), multiple birth (OR 3.22; 95% CI 1.21–8.58), chorioamnionitis (OR 9.89; 95% CI 2.88–33.94), preterm birth (OR 1.86; 95% CI 1.01–3.43), and SGA (OR 3.05; 95% CI 1.76–5.28) as independent risk factors.

INTERPRETATION We confirmed the increased risk in males and the role of chorioamnionitis and SGA for PAIS, pointing to the importance of inflammatory processes and fetal–placental insufficiency. Multiple birth and preterm birth were additional risk factors.

Perinatal arterial ischaemic stroke (PAIS) has been identified as a cause of unexplained clinical conditions in newborn infants.1 It is an important cause of chronic neurological disability, including unilateral cerebral palsy, and it is the second most underlying cause of seizures in the neonate.2–4

The aetiology of PAIS, however, remains unclear. Identification of risk factors helps to enhance understanding of the underlying pathophysiology as well as to characterize high-risk populations.

Although previous studies have identified several risk factors, their interdependence and role in the causal pathway of PAIS are poorly understood.3–12 Most available studies are either small, often restricted to term infants, lack an adequate comparison group, or do not control for interdependencies between potential risk factors.

A recently published meta-analysis depicted some of these limitations and identified pre-eclampsia, oligohydramnios, intrapartum fever, birth asphyxia, hypoglycaemia, and small for gestational age (SGA) as the most likely relevant risk factors.8 Since this study was not based on a data analysis of individual patients, however, no uniform analysis could be applied. Non-uniform adjustment of the included studies might account for biased assessments.

On the basis of prospectively ascertained cases of PAIS with extensive documentation of potential risk factors, we had the opportunity to investigate risk factors for cases in infants born both preterm and at term, with four population-based comparison individuals for each case. On the basis of these data, we validated risk factors described in previous studies and had the chance to identify hitherto unknown potential causes. In addition, we investigated

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potential causal pathways of risk factors in the development of PAIS.

**METHOD**

**Study design**

We conducted a case–control study, with patients with PAIS recruited from the German paediatric surveillance system (ESPED) and comparison individuals from the Bavarian Working Group for Quality Assessment (BAQ). Four comparison individuals per case were randomly selected with same birth year as the only selection criterion.

**Case definition**

A cerebral arterial ischaemic infarction confirmed by any imaging technique within 28 days after birth diagnosed as PAIS by the responsible physician was considered as a case.

**Case ascertainment**

ESPED, an established active surveillance system in 345 paediatric hospitals, was used for case identification. Physicians were asked to report cases of PAIS on a monthly basis (including a null option) from 1st January 2015 to 31st December 2017. Report of a case prompted an anonymous questionnaire, which was answered on the basis of pre- and postnatal medical documentation by the notifying physician. In more than 95% of all reported cases, questionnaires were returned. Case reports were independently validated by a paediatric neurologist (LG) and three neonatologists (MK, MD, UF-M). A focus was on diagnostic criteria for PAIS and to differentiate PAIS from other forms of stroke (haemorrhagic stroke, cerebral venous sinus thrombosis). For inconclusive statements, the notifying physician was asked to provide further information. Our main analysis was confined to 134 of 161 reported cases, with no missing values on relevant covariates (Table S1, online supporting information).

**Comparison group selection**

The BAQ is part of a nationwide benchmarking network for assessment of clinical performance in German hospitals. The BAQ data set, which has previously been described, comprises all deliveries in obstetric units of the federal state of Bavaria. Data are routinely electronically recorded by medical and paramedical hospital staff. Four comparison individuals per case, in total 644, were randomly selected and matched for birth year only. Full information was available for 576 comparison individuals (Table S1).

**Variable definition for risk factors in cases of PAIS and comparison individuals**

All risk factors as documented in ESPED and BAQ are shown in Table S2 (online supporting information). For all variables with a null option the data were used as recorded. For variables without a null option we assumed absence of the risk factor if no information was given.

**What this paper adds**

- Chorioamnionitis and small for gestational age (SGA) precede perinatal arterial ischaemic stroke (PAIS).
- Chorioamnionitis and SGA are independent risk factors for PAIS.
- Inflammatory processes and fetal–placental insufficiency are the likely underlying mechanisms.
- Multiple birth and preterm birth are additional risk factors.

We defined SGA as birthweight below the 10th centile and large for gestational age as birthweight above the 90th centile. Preterm delivery was defined as birth before 37 completed weeks of gestation. Maternal age was classified according to general standards: mothers 18 years and younger or 35 years and older were considered as having high-risk pregnancy. We defined a 5-minute Apgar score below 7 as critical and an umbilical artery blood pH below 7.1 as an indicator for acidosis in newborn infants. History of abortion and miscarriage was assumed when the number of preceding pregnancies exceeded the number of births. We defined a hypertensive pregnancy disorder by pre-eclampsia, eclampsia, HELLP syndrome (haemolysis, elevated liver enzymes, and a low platelet count), or documentation of pregnancy-induced hypertension only. Vaginal-operative delivery combined ventouse and forceps deliveries.

**Statistical analysis**

For univariate analysis, we calculated odds ratios with 95% confidence intervals and p-values based on $\chi^2$ testing or Fisher’s exact test.

We plotted a directed acyclic graph (DAG) to illustrate the temporal sequence of risk factors to identify potential causality, mediation, or reverse causality. Variable selection for the multivariate statistical models was guided by the DAG.

Three different multivariate logistic regression models were calculated. Model 1 was based on a priori considerations and a univariate $p$-value of at least 0.2. We included only variables definitely preceding the outcome (thus potentially causal). For model 2, we added putative mediators such as preterm birth and SGA, which might be both independent risk factors and/or in the causal pathway of preceding risk factors. Model 3 used the variables included in model 2 with backward selection and $p<0.05$ as the cutoff for retention to obtain a parsimonious model.

**Sensitivity analyses**

**First sensitivity analysis**

Since cases of PAIS were from all over Germany whereas comparison individuals were from Bavaria only, we compared characteristics of cases and their role in univariate risk analysis in Bavarian (infants reported from a Bavarian hospital) with non-Bavarian cases.

**Second sensitivity analysis**

Perinatal asphyxia can be a consequence of PAIS, as we assumed in the DAG and in the main analysis. However, in some cases of neonatal stroke, perinatal asphyxia can...
also be causative or in the causal pathway. To verify whether this influenced the identified risk factors, we included hypoxia/respiratory disorder as a preceding risk factor in the multivariate models.

**Third sensitivity analysis**
Magnetic resonance imaging (MRI) and computed tomography are the criterion standard for diagnosis. The validity of ultrasound for diagnosis of PAIS is controversial. To make use of all available data we included the cases of PAIS diagnosed by ultrasound in the main analysis, but we performed a separate analysis by excluding all cases not receiving MRI or computed tomography for diagnosis.

**Fourth sensitivity analysis**
According to current knowledge, it is assumed that PAIS differs in many aspects in infants born moderately and very preterm compared with those born near term and at term. To take this aspect into account, we also show the results of the models for preterm birth defined before 35 completed weeks of gestation instead of the cut-off at 37 weeks of gestation.

Because PAIS is a rare event, the odds ratio can be considered as an indicator of relative risk. We used a significance level of 5% for all analyses without adjustment for multiple testing. All statistics were calculated using SAS version 9.4 (SAS Institute, Cary, NC, USA) and R 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria). The program code is available online (https://osf.io/wxfeq/).

Anonymous reporting in ESPED made parental consent unnecessary. Ethical approval was obtained by the ethics committee of the Ludwig-Maximilians-Universität München, number 42-15 (05–04–2015). For the BAQ data, ethics approval or informed consent was not necessary because they were used for a secondary analysis of anonymous routine data.

**RESULTS**
As shown in Table S1, the proportion of missing values was similar in the PAIS and comparison groups for all infant variables, whereas there were more missing values for maternal items in the ESPED data set. In both the PAIS and comparison groups, most of the excluded individuals had only one missing variable. Thus, the analysed data set allowed a meaningful assessment of risk factors.

The variable definition was almost identical in the PAIS and comparison groups, most of the excluded items in the ESPED data set. In both the infant variables, whereas there were more missing values was similar in the PAIS and comparison groups (Table S2).

Most cases of PAIS (n=117, 87%) presented with clinical symptoms, whereas PAIS was an incidental finding in 13% (n=17). One hundred and twenty-one (90%) cases were identified by MRI, one case by computed tomography, and 12 cases by ultrasound. Most cases had seizures as a leading symptom (n=69, 51%) and 86% (n=115) of the cases were diagnosed within the first week of life (median 3d). There were substantially more males (68% vs 32%), 16% were born preterm, nine cases were twins, and 21 cases had birth asphyxia (Table 1).

### Table 1: Maternal and infant characteristics of the cases of perinatal arterial ischaemic stroke (PAIS) (n=134)

| Variable                  | PAIS (n=134) |
|---------------------------|--------------|
| Sex (male:female ratio)   | 2:1          |
| Gestational age, wks      | 39 (30–41)   |
| Gestational age <32wks    | 2 (1.5)      |
| Gestational age 32 to <37wks | 20 (14.9) |
| Gestational age ≥37wks    | 112 (83.5)   |
| Birthweight, g            | 3215 (1410–4830) |
| Head circumference at birth, cm | 34 (25–38) |
| Maternal age, y           | 30 (20–45)   |
| Multiple births           | 9 (6.7)      |
| Maternal obesity          | 12 (9.0)     |
| 1min Apgar score          | 8 (10–10)    |
| 5min Apgar score          | 9 (10–10)    |
| 10min Apgar score         | 10 (1–10)    |
| Umbilical artery pH       | 7.25 (6.93–7.60) |
| White ethnicity           | 127 (96)     |
| Age at time of diagnosis, d | 3 (0–27) |
| No underlying diseases    | 59 (51)      |
| Underlying diseases*      | 65 (49)      |
| Perinatal asphyxia        | 21 (16)      |
| Newborn sepsis            | 10 (7)       |
| Heart defect              | 7 (5)        |
| Polyclaglobulina          | 4 (3)        |
| Meconium aspiration       | 2 (1)        |
| Genetic disorder          | 2 (1)        |
| Haematological disease    | 2 (1)        |
| Others                    | 2 (1)        |
| Cerebrovascular disease   | 1 (1)        |
| Conspicuous family history | 17 (13)     |

Quantitative variables are expressed as median (minimum–maximum). Categorical variables are expressed as n (%). *Multiple underlying diseases are possible. **Stroke, thrombosis, cardiovascular events, or other conspicuous events in family history.

**Univariate risk factor analysis**
Table 2 summarizes the univariate analysis in 134 cases of PAIS and 576 comparison individuals. Infants with PAIS were more often males and from multiple births. Preterm birth was associated with a 2.38 (95% confidence interval [CI] 1.37–4.12) times higher risk for PAIS. Cases were more likely to have an Apgar score less than 7 at 5 minutes (odds ratio [OR] 41.7; 95% CI 9.51–182.9) and an umbilical artery pH of 7.1 or below (OR 5.10; 95% CI 2.55–10.20). In 15.7% of cases of PAIS, hypoxia or respiratory disorder was diagnosed compared with 1.2% in the comparison group (OR 15.10; 95% CI 6.27–36.35). In addition, more infants diagnosed with PAIS required intubation or mask ventilation during initial care (n=25, 19% vs n=29, 5%; OR 4.33; 95% CI 2.44–7.67). Maternal age and history of abortion or miscarriage did not differ significantly between groups. Mothers of infants with stroke were more likely to be nulliparous. Obstetric and peripartum characteristics associated with PAIS included Caesarean and vaginal-operative delivery, chorioamnionitis, and oligohydramnios.

**DAG**
Figure 1 illustrates likely pathways. All variables with univariate p<0.02 were taken into account. The temporal sequence of risk factors and outcome of PAIS is arranged from left to right. The causal pathway between sex and nulliparity and PAIS is unlikely to be mediated.
by other risk factors which is indicated by a direct arrow to PAIS. Obstetric risk factors definitely precede PAIS and might have a direct effect as well as an indirect effect mediated by preterm birth and/or SGA. Covariates of the ‘asphyxia at delivery complex’ (low umbilical artery pH or Apgar score, hypoxia/respiratory disorder, and intubation/mask ventilation) are depicted on the right, as well as Caesarean or vaginal-operative delivery, because these might also be possible consequences of PAIS (indicated by arrows between PAIS and asphyxia/delivery mode).

Multivariate risk factor analysis

After adjusting for all variables preceding the outcome (model 1), male sex, multiple births, and chorioamnionitis remained as risk factors associated with PAIS (Table 3).

Adjustment for preceding risk factors changed the odds ratio for preterm birth from 2.38 (95% CI 1.37 – 4.12) in the univariate analysis to 1.57 (95% CI 0.82 – 3.03) (model 2). The odds ratio of SGA changed only slightly after adjustment from 2.84 (95% CI 1.68 – 4.85) in the univariate analysis to 2.95 (95% CI 1.68 – 5.19). In general, comparing results of models 1 and 2, the odds ratios for other risk factors did not change substantially, except for multiple births (decreasing) and chorioamnionitis (increasing) (Table 3).

All variables significantly associated in model 2 and preterm birth remained independently associated with PAIS in multivariate backward analysis (model 3 and Table 3).

Sensitivity analysis

First sensitivity analysis

To exclude bias due to confinement in Bavarian comparison individuals, we evaluated the characteristics of Bavarian with non-Bavarian cases of PAIS (Table S3, online supporting information) and performed separate univariate analysis for these groups (Table S4, online supporting information). Except for Caesarean section, all risk factors were comparable in the univariate analysis.

Second sensitivity analysis

Inclusion of hypoxia/respiratory disorder as an explanatory variable (being either a generic risk factor or in the causal pathway of other risk factors), the analysis basically confirmed the identified risk factors in the main models. The odds ratio for hypoxia/respiratory disorder was 13.7 (95% CI 5.5 – 34.4) in model 3 (data available on request).

Third sensitivity analysis

For cases of PAIS confirmed by MRI or computed tomography, we found a similar risk factor pattern except for preterm birth (no longer significant) and oligohydramnios (emerging as significant) (Table S5, online supporting information).

Fourth sensitivity analysis

Defining preterm birth as less than 35 weeks of gestation increased the risk of PAIS from 1.86 (95% CI 1.01 – 3.43) in the main analysis to 3.81 (95% CI 1.70 – 8.52), whereas multiple births as an independent risk factor was no longer
in the parsimonious model 3 (Table S6, online supporting information).

**DISCUSSION**

On the basis of a substantial number of cases, we identified male sex, chorioamnionitis, multiple births, preterm birth, and SGA as independent risk factors for PAIS. Male sex, chorioamnionitis, and SGA were also identified in a recent meta-analysis by Li et al.\(^8\) Confirmation in our study adds to the body of evidence since these three factors were only analysed in three\(^{10,11,14}\) and two\(^{6,7}\) studies with a limited number of cases of PAIS respectively. Lee et al.\(^{14}\) were the first to suggest chorioamnionitis as an independent risk factor. The inflammatory process characterizing chorioamnionitis might promote thromboembolism and increase the risk for emboli to the fetal brain or impair the placental function, leading to PAIS.\(^7,15\) Furthermore, the role of cerebral focal vasculitis as a remote consequence of fetal inflammation has been reported as triggering ischaemic injuries in the neonate.\(^15\) There seems to be an important role of inflammatory processes in the placental–fetal interrelationship promoting causal pathways of PAIS. This concept is further supported by the well-established association between chorioamnionitis and cerebral palsy.\(^8,16\)

In addition, multiple births and preterm birth were identified as independent risk factors. After adjustment for preterm birth, the effect estimator for multiple births decreased, suggesting that part of the multiple effect is mediated by preterm birth. Indeed, 6 out of 9 cases of PAIS associated with multiple deliveries were preterm, whereas only one twin was also SGA. Although part of the effect of multiple births might be mediated by preterm
birth, an additional independent direct effect seems likely. Similarly, a role of multiple births in cerebral palsy, a common outcome of PAIS, has been suggested by others.17–19

The unadjusted estimate for preterm birth suggested a higher risk in infants born preterm. As depicted in the DAG, some of this risk might rather be related to the role of preterm birth in the causal pathway of preceding risk factors. A genuine effect of preterm birth is suggested in model 3. A role of preterm birth in the pathophysiology of PAIS is also suggested by van der Aa et al.,20 who claim that maturational changes of the vascular system might account for this phenomenon.

Regarding the observed risk for multiple pregnancies, Benders et al.21 suggested that twin-to-twin transfusion might be causally related to PAIS. In our data, however, there was only one case with twin-to-twin transfusion syndrome.

A unique feature of our analysis is the consideration of causal pathways using the DAG approach. A DAG is used to model probabilities, connectivity, and causality by illustrating the temporal sequence of risk factors, thus taking a-priori knowledge and assumptions into account. The importance of considering the origin, the causal pathway, and the consequence of PAIS is intuitively evident. The conceptualization of potential causal pathways in DAG graphs, however, is rather new.22,23 Most importantly, covariates that might also be a consequence of PAIS do not meet the prerequisites for risk factors. Several papers have included Apgar score, umbilical artery pH, birth asphyxia, and the delivery mode as risk factors in their models.5–7 These papers did not consider that indicators of perinatal asphyxia might also be a consequence of PAIS or in the causal pathway of other risk factors, as outlined in Figure 1. The concept that factors such as low Apgar scores, low umbilical artery pH, or Caesarean section might rather be a consequence of PAIS has previously been suggested by Wu et al.11 and Lee et al.14 They reported on infants presenting with a clinical picture of birth asphyxia subsequently being diagnosed with a focal arterial infarction confirmed by brain imaging. This reminds us that the clinical diagnosis of birth asphyxia is not specific for any single pathogenetic mechanism of brain injury and might be misleading, especially in the setting of PAIS.

We acknowledge that indicators of perinatal asphyxia and delivery mode might have some predictive value for PAIS without necessarily being true risk factors.

Male sex and nulliparity are definitely preceding risk factors. The predominance of male infants in patients with PAIS has been reported in most of the published studies.7–24–26 The role of sex in PAIS has been linked to the general vulnerability related to male sex or hormonal status, which potentially influences the susceptibility to ischaemic events in males.24,27,28 Nulliparity was analysed, because others described an increased risk of PAIS in infants of nulliparous women.6–8,14 We confirmed this in our univariate analysis, but not after multiple adjustment. Indeed, other studies have pointed to limited convincing pathophysiological plausibility to explain the association of nulliparity and PAIS, and suggested that this covariate might rather be a statistical predictor than causally relevant.14

SGA was identified as a strong risk factor. SGA, as shown in Figure 1, might be an intermediate variable reflecting several preceding disorders in pregnancy.11,29 These preceding conditions, however, do not fully explain the effect of SGA. Our data thus strengthen previous findings of SGA as an independent risk factor for PAIS.6,8,11

Some maternal and pregnancy disorders reported in other studies could not be confirmed by our data, such as hypertensive pregnancy disorders, oligohydramnios, or gestational diabetes.8,14,30 Our definition of hypertensive pregnancy disorders might not be optimal, because we did not differentiate between pre-eclampsia, HELLP, and maternal hypertension in the ESPED survey. Thus, an association of pre-eclampsia and PAIS cannot be excluded, despite the lack of proof in the current study. Darmency-Stamboul et al.10 showed an association of PAIS and gestational diabetes, but pathophysiological plausibility has been questioned. In our data, gestational diabetes was not more frequent in infants with PAIS than in comparison individuals, confirming a published meta-analysis.8 Benders et al.21 identified hypoglycaemia as an independent risk factor for PAIS. Unfortunately, we could not address this risk factor in our analysis because the database for the comparison individuals did not provide this information. In addition, fetal periventricular infarction might be misinterpreted as presumed PAIS, and has often been included in previous studies,10,16 suggesting that obstetric rather than peripartum risk factors play a role. Presumed PAIS was not included in our study. This might explain why several previously described risk factors including prepartum complications were not identified as risk factors in our study.

**Sensitivity analyses**

**First sensitivity analysis**

Confinement to comparison individuals from Bavaria only might account for bias. However, we demonstrated only a small difference between Bavarian and non-Bavarian children, accounting for almost identical univariate risk estimates. The only significant association observed pertained to the delivery mode, which we consider to be a chance finding, the more so as it would not be significant after correction for multiple testing. This assumption is further supported by almost identical overall rates of Caesarean section in Bavaria (31.9% in 2017) compared with the other federal states of Germany (30.2% in 2017, range 24.0–37.2%).31

**Second sensitivity analysis**

Even assuming a role of hypoxia/respiratory disorder in the causal pathway changed the effect estimates of the identified risk factors compared with the main model only slightly. Whether the high odds ratio of hypoxia/respiratory disorder reflects a genuine risk or reverse causation is unclear.
Third sensitivity analysis
We showed that inclusion of cases of PAIS diagnosed by ultrasound only did not bias the results substantially. The failure to detect a significant risk related to preterm birth was most probably caused by the low statistical power, because there was a high proportion of infants with PAIS born preterm diagnosed with ultrasound only.

Fourth sensitivity analysis
Some authors have shown that PAIS differs in many aspects in infants born very or moderately preterm. Using a different cut-off for gestational age to compare infants born very or moderately preterm with near-term/term-born infants in our study increased the risk related to preterm birth. Most of the risk related to preterm birth seems to be caused by very early and moderate gestational age.

Limitations
Our case ascertainment was based on surveillance. Reporting by the treating physician was not mandatory and thus might have been incomplete. Incomplete reporting, however, is unlikely to differ by risk factors. We lacked cerebral imaging for case validation, but asked the physician to report the findings of the imaging. These were carefully scrutinized and in case of uncertainty or implausibility were further validated from medical documentation. Recall bias is unlikely because almost all risk factors were abstracted from documentation during pregnancy or delivery. Absence of null options for some variables was identical in both data sources.

In theory there might have been individuals with PAIS in the comparison group. The probability, however, is low. With an expected PAIS incidence of between 1 in 3000 and 1 in 2500 infants, the probability that at least one individual with PAIS was included in the comparison group is about 12% to 27%. The criterion to include all variables with a univariate \( p \)-value of less than 0.2 in the multivariate analysis was determined arbitrarily.

That congenital heart disease is associated with PAIS has been well described in the literature. Although we found 5% of infants had both PAIS and congenital heart disease, we did not have access to this information for our comparison group, making further analysis impossible.

Strengths
These limitations are offset by several strengths of our study. These include study size, the population-based setting, selection of an appropriate comparison group, and mutual adjustment guided by a priori considerations concerning causal pathways. The period of case ascertainment was confined to 3 years only, ensuring a comparable framework of clinical and health policies and available structures for imaging.

CONCLUSION
The role of chorioamnionitis and SGA for PAIS was confirmed, pointing to the importance of inflammatory processes and fetal–placental insufficiency. Multiple births and preterm birth were identified as additional risk factors. The effect of multiple births is likely to be related to placental- or preterm-birth-linked complications. Preterm birth is likely to have an additional independent effect on PAIS. Our data further support the theory of a multifactorial pathogenesis, with a combination of prenatal, perinatal, and neonatal risk factors being involved in the aetiology of PAIS.

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SUPPORTING INFORMATION
The following additional material may be found online:
- Table S1: Missing values
- Table S2: Variable coding in the German paediatric surveillance system and the Bavarian Working Group for Quality Assessment
- Table S3: Sensitivity analysis: comparison of Bavarian with non-Bavarian cases of perinatal arterial ischaemic stroke
- Table S4: Sensitivity analysis: separate univariate analyses of Bavarian and non-Bavarian cases of perinatal arterial ischaemic stroke
- Table S5: Sensitivity analysis: multivariate models excluding cases with no magnetic resonance imaging or computed tomography for diagnosis of perinatal arterial ischaemic stroke
- Table S6: Sensitivity analysis: preterm birth defined as less than 35 completed weeks of gestation

REFERENCES
1. Nelson KB, Lynch JK. Stroke in newborn infants. Lancet Neurol 2004; 3: 110–8.
2. Estan J, Hope P. Unilateral neonatal cerebral infarction in full term infants. Arch Dis Child Fetal Neonatal Ed 1997; 76: F88–90.
3. Wu YW, Groen LA, Shah Sj, Newman TB, Najjar DV. Cerebral palsy in a term population: risk factors and neuroimaging findings. Pediatrics 2006; 118: 690–7.
4. Kirton A, deVeber G. Cerebral palsy secondary to perinatal ischemic stroke. Clio Perinatul 2006; 33: 367–86.
5. Harteman JC, Groenendaal F, Kwee A, Weling PM, Benders MJ, de Vries LS. Risk factors for perinatal arterial ischaemic stroke in full-term infants: a case-control study. Arch Dis Child Fetal Neonatal Ed 2012; 97: F411–6.
6. Tuckuviene R, Christensen AL, Helgested J, Hundborg HH, Kristensen SR, Johnsen SP. Infant, obstetrical and maternal characteristics associated with thromboembolism in infancy: a nationwide population-based case-control study. Arch Dis Child Fetal Neonatal Ed 2012; 97: F417–22.
7. Martinez-Biarge M, Cheong JLY, Diez-Sebastian J, Mercuri E, Dubowitz LMS, Cowan FM. Risk factors...
for neonatal arterial ischemic stroke: the importance of the intrapartum period. *J Pediatr* 2016; 173: 82–8.e1.
8. Li C, Miao JK, Xu Y, et al. Prenatal, perinatal and neonatal risk factors for perinatal arterial ischemic stroke: a systematic review and meta-analysis. *Eur J Neurol* 2017; 24: 1006–15.
9. Luo L, Chen D, Qiu Y, Wu J, Li X, Mu D. Association between hypoxia and perinatal arterial ischemic stroke: a meta-analysis. *PLoS One* 2014; 9: e90106.
10. Darmency-Stamboul V, Chantegret C, Ferdynus C, et al. Antenatal factors associated with perinatal arterial ischemic stroke. *Stroke* 2012; 43: 2107–12.
11. Wu YW, March WM, Croen LA, Grether JK, Delhuneau C, Hurton JL, Dolk H. Multiple birth and cerebral palsy in Europe: a multicenter study. *Acta Obstet Gynecol Scand* 2008; 87: 548–53.
12. Petterson B, Nelson KB, Watson L, Stanley F, Twins, triplets, and cerebral palsy in births in Western Australia in the 1980s. *BMJ* 1993; 307: 1239–43.
13. Pharaoh PO, Cooke T. Cerebral palsy and multiple births. *Arch Dis Child Fetal Neonatal Ed* 1996; 75: F174–7.
14. Hart AR, Connolly DJA, Singh R. Perinatal arterial ischemic stroke in term babies. *Pediatrics* 2004; 114: 612–9.
15. Lee J, Croen LA, Backstrand KH, et al. Maternal and infant characteristics associated with perinatal arterial stroke in the preterm infant. *Stroke* 2007; 38: 1759–65.
16. Hernán MA, Hernández-Díaz S, Werler MM, Mitchell AA. Causal knowledge as a prerequisite for confounding evaluation: an application to birth defects epidemiology. *Am J Epidemiol* 2002; 155: 176–84.
17. Topp M, Huusom LD, Langhoff-Roos J, Delhuneau C, Hurton JL, Dolk H. Multiple birth and cerebral palsy in Europe: a multicenter study. *Acta Obstet Gynecol Scand* 2008; 87: 548–53.
18. Petterson B, Nelson KB, Watson L, Stanley F, Twins, triplets, and cerebral palsy in births in Western Australia in the 1980s. *BMJ* 1993; 307: 1239–43.
19. Pharaoh PO, Cooke T. Cerebral palsy and multiple births. *Arch Dis Child Fetal Neonatal Ed* 1996; 75: F174–7.
20. van der Maar NE, Benders MJ, Nikkels PG, Groenendaal F, de Vries LS. Cortical sparing in preterm ischemic stroke in children. *Eur J Neurol* 2004; 11: 417–24.
21. Benders MJ, Groenendaal F, Uiterwaal CS, et al. Maternal and infant characteristics associated with perinatal arterial stroke in the preterm infant. *Stroke* 2007; 38: 1759–65.
22. Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. *Epidemiology* 1999; 10: 37–48.
23. Fullerton HJ, Wu YW, Zhao S, Johnston SC. Risk of stroke in children: ethnic and gender disparities. *Neurology* 2003; 61: 189–94.
24. Govaert PM, Ramenghi L, Taal R, de Vries L, Deveber G. Diagnosis of perinatal stroke: definitions, differential diagnosis and registration. *Acta Paediatr* 2009; 98: 1556–67.
25. Dunn L, Prior T, Greer R, Kumar S. Gender specific intrapartum and neonatal outcomes for term babies. *Eur J Obstet Gynecol Reprod Biol* 2015; 185: 19–22.
26. Huang E, Levy A, Katz M, Herschkowitz R, Leron E, Mazor M. Gender does matter in perinatal medicine. *Fetal Diagn Ther* 2004; 19: 366–9.
27. Krebs C, Macara LM, Leiser R, Bowman AW, Greer IA, Kingdom JC. Intrauterine growth restriction with absent end-diastolic flow velocity in the umbilical artery is associated with maldevelopment of the placental terminal villous tree. *Am J Obstet Gynecol* 1996; 175: 1534–42.
28. Mann JR, McDermott S, Pan C, Hardin JW. Maternal hypertension and intrapartum fever are associated with increased risk of ischemic stroke during infancy. *Dev Med Child Neurol* 2013; 55: 58–64.
29. Statistisches Bundesamt Destatis. Krankenhausstatistik Grunddaten der Krankenhäuser und Vorsorge- oder Rehabilitationseinrichtungen [Internet]. Wiesbaden: Statistisches Bundesamt. https://www.destatis.de/DE/Presse/Pressematerial/2018/09/PD18_149_231.html (accessed 18th July 2019).
30. Ezurum-Gossen GM, van der Haar M, Snijt L,S, et al. Neurodevelopmental outcome after neonatal perforator stroke. *Dev Med Child Neurol* 2016; 58: 49–56.