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Adverse motor outcome after paediatric ischaemic stroke: A nationwide cohort study

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Abstract

Background: Various frequencies of adverse motor outcomes (cerebral palsy and hemiplegia) after paediatric ischaemic stroke have been reported. Few reports on the risks of adverse motor outcomes in nationwide cohorts and contributing risk factors are available.

Objectives: To assess risk of adverse motor outcome and potential risk factors thereof after paediatric ischaemic stroke in a nationwide cohort.

Methods: This nationwide matched cohort study identified 877 children <18 years of age diagnosed with ischaemic stroke through the Swedish national health registers from 1997 to 2016. These children, exposed to ischaemic stroke, alive 1 week after stroke, were matched for age, sex and county of residence with 10 unexposed children. Using Cox regression, we estimated the risk of adverse motor outcomes in children with stroke compared to that in unexposed children. Logistic regression was applied to compare the characteristics of children with and without adverse motor outcomes after stroke.

Results: Out of the 877 children with ischaemic stroke, 280 (31.9%) suffered adverse motor outcomes compared with 21 (0.2%) of the 8770 unexposed: adjusted hazard ratio (aHR) 167.78 (95% confidence interval (CI) 107.58, 261.66). There were no differences between risk estimates of adverse motor outcome according to age at stroke: perinatal stroke (aHR 124.11, 95% CI 30.45, 505.84) and childhood stroke (aHR 182.37, 95% CI 113.65, 292.64). An association between adverse motor outcome and childhood stroke aOR 1.56 (95% CI 1.05, 2.31) was found when analysing only children with ischaemic stroke. No associations were found between adverse motor outcome and sex, gestational age or parental age at birth.

Conclusions: The risk of adverse motor outcome is substantial after paediatric ischaemic stroke, especially childhood stroke, confirming results of previous smaller studies. This study found no associations between sex, gestational age or parental age and adverse motor outcome after paediatric ischaemic stroke.

Katarina Svensson and Anna Walås equally contributed to this work.

KEYWORDS
adverse motor outcome, cerebral palsy, children, cohort studies, hemiplegia, ischaemic stroke

1 | BACKGROUND

Paediatric ischaemic stroke is a rare but severe disease affecting approximately 4.7–6 per 100,000 children.[1] When occurring from 20 weeks of gestation until 28 days after birth, it is called perinatal stroke, with an incidence of 10.2–13 per 100,000 live births.[2,3] After 28 days until 18 years of age, paediatric ischaemic stroke is marked as childhood stroke with an incidence rate of 1.2–1.6 per 100,000 per year.[4,5] Perinatal and childhood ischaemic stroke are different forms of paediatric ischaemic stroke, with somewhat other risk factors, initial symptoms, aetiology and recovery. However, the boundary between the two is not definitive; rather, it depends on brain maturation.

Paediatric stroke often leads to neurological sequelae, such as adverse motor outcomes, resulting in muscle weakness with or without spasticity, often affecting the afflicted child´s balance and coordination.

Adverse motor outcomes can be mild to severe, with changes in gross and fine motor function. Hemiplegia and unilateral CP are the most common adverse motor outcomes after stroke. The terms unilateral CP and hemiplegia are often used interchangeably in children up to 2 years of age. As CP is a result of an insult to the developing brain,[6] older children are diagnosed with hemiplegia and not unilateral CP.

CP has been estimated to affect approximately 30%–68%[7,8] of children with perinatal ischaemic stroke. In contrast, hemiplegia is reported in 56%–67%[9,10] of children with childhood ischaemic stroke. Adverse motor outcome seems to affect children with childhood stroke more often than perinatal stroke, indicating age at stroke as a risk factor. However, to our knowledge, no previous studies have reported the risk of adverse motor outcomes after paediatric ischaemic stroke in children with paediatric stroke compared to that in the general population.

Recent research on the development of adverse motor outcomes after different brain insults in children has focussed on genetic causes,[11,12] as well as potential risk factors such as male sex[8] and maternal age.[13] However, how these risk factors contribute to adverse motor outcome after paediatric stroke has not been evaluated in large cohorts.

A diagnosis of adverse motor outcome should be established promptly to provide interventions after an ischaemic stroke. This is less of a challenge in childhood and adulthood than in younger infants, and studies have shown that CP is diagnosed after 1 year of age in most children.[14–16]

Because paediatric stroke is a rare disease, the disorder is challenging to study prospectively. National health registers can provide prospectively collected data from large population-based cohorts and enable the use of matched unexposed individuals to estimate the risk of adverse motor outcome in children with paediatric ischaemic stroke compared to that in the general population. The registers can also deliver data on potential confounding factors.

This nationwide population-based cohort study aimed to assess the risk of adverse motor outcomes in children with paediatric ischaemic stroke. A secondary aim was to evaluate the influence of age at stroke, male sex, gestational age and parental age on this risk.

Synopsis

Study question

What is the risk of adverse motor outcome after paediatric ischaemic stroke and is this risk influenced by sex, age at stroke, gestational age or parental age?

What's already known

Varying frequencies of adverse motor outcomes have been previously reported: 30%–68% after perinatal stroke and 56%–67% after childhood ischaemic stroke. However, few studies have reported risks of adverse motor outcomes after paediatric stroke in large nationwide cohorts.

What this study adds

This large nationwide cohort study shows that sex, gestational age or parental age do not influence the risk of adverse motor outcomes after paediatric ischaemic stroke. Further, it confirms that risk of adverse motor outcome is substantial after paediatric ischaemic stroke, especially childhood stroke, as previously reported in smaller studies.

2 | METHODS

2.1 | Cohort

The PedStroke cohort[17] includes individuals diagnosed with paediatric ischaemic stroke registered between 1969 and 2016 in the Swedish National Patient Register (NPR), the Medical Birth Register or the Cause of Death Register. For the present study, individuals exposed to paediatric ischaemic stroke from 1997 and alive 1 week after the insult were included (due to a high early mortality rate of paediatric ischaemic stroke) (Figure 1). Each exposed individual was matched for sex, age and county of residence with 10 unexposed from the Swedish Total Population Register at the time of stroke diagnosis.

2.2 | Data sources

The NPR was established in 1964, and since 1987, the registration has been nationwide, containing diagnoses from inpatient care since 1969, and specialised outpatient care since 2001.[18] The Medical Birth Register, introduced in 1973, contains data on more than 98% of all pregnancies and deliveries in Sweden.[19] The Cause of Death Register includes causes of death in all Swedish residents since 1961. The unique personal identification number that all Swedish residents receive at birth or through immigration was used to link all registers at the individual level. The paediatric ischaemic stroke diagnosis in the registers has been validated in a sample (n = 273) of the PedStroke cohort showing a positive predictive value of 89%.[17]

2.3 | Exposure

The primary exposure is ischaemic stroke in children before 18 years of age as defined by the Swedish version of the International Classification of Diseases (ICD) (ICD 10: I63, I64). In the analyses of risk factors for adverse motor outcome after ischaemic stroke, we only included children with stroke from 1997 to 2014.

2.4 | Outcome

The primary outcome is adverse motor outcome, defined as a diagnosis of CP or hemiplegia (ICD 10: G80 or G81) in the NPR. CP is as an insult to the developing brain and the expected adverse motor outcome of an insult below 2 years of age, regardless of subtype.[6] We define hemiplegia as the result of an insult above 2 years of age, a movement disorder distinct from CP. An individual with these ICD codes was considered to have an adverse motor outcome due to an interchangeable use of the different diagnoses, leading to an overlap between diagnoses (Figure 2). Hence, we choose not to estimate the risk of the different outcome diagnoses separately.

2.5 | Potential confounders and other covariates

Gestational age (full-term ≥37 weeks, preterm ≤36 weeks) were retrieved from the Medical Birth Register and parental age (mother's and father's age at birth), sex (female and male) and age at stroke diagnosis (≤28 days, >28 days, >28 days-2 years, 3–6 years, 7–12 years, 13–<18 years) from the NPR and Medical Birth Register.

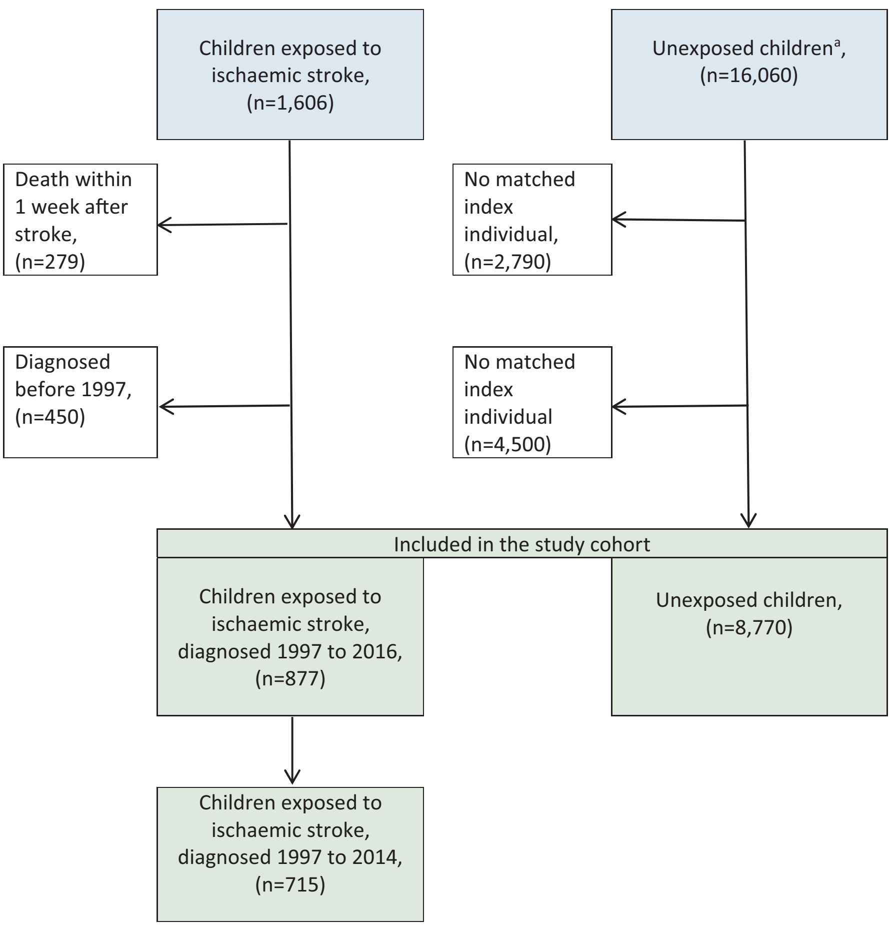
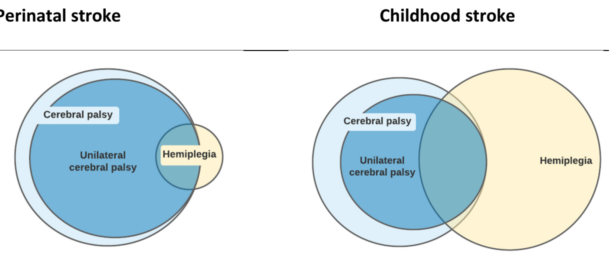


FIGURE 1 Study cohort of children exposed to ischaemic stroke and matched unexposed children. [a]Unexposed individuals were matched for sex, age and county of residence of the exposed

FIGURE 2 Diagnoses of adverse motor outcome in paediatric ischaemic stroke cases registered in the Swedish National Patient Register, 1997–2016. CP, cerebral palsy; ICD, International classification of diseases. Adverse motor outcome was defined as a diagnosis of CP (ICD 10: G80) or hemiplegia (ICD 10: G81) [a]Unilateral CP is presented separately, although also included in all cerebral palsy cases



		Perinatal stroke: *Only one diagnosis, n*	Perinatal stroke: *Total with diagnosis, n*	Childhood stroke: *Only one diagnosis, n*	Childhood stroke: *Total with diagnosis, n*
CP	All	64	71	60	122
	Unilateral[a]	*19*	*60*	*13*	*78*
Hemiplegia		2	9	80	139
Hemiplegia or unilateral CP			62		174
All adverse motor outcome		66	73	140	207

2.6 | Follow-up

To calculate the risk of adverse motor outcome, follow-up started at birth and ended with a diagnosis of adverse motor outcome, death or 31 December 2016, whichever came first. The unexposed individuals were censored at the time of stroke diagnosis. For the analyses of risk factors for adverse motor outcome after ischaemic stroke, the follow-up time was from birth until 31 December 2014.

2.7 | Statistical analyses

The risk of adverse motor outcome in children with ischaemic stroke was estimated by calculating crude hazard ratios (HRs) and adjusted hazard ratios (aHRs) with 95% confidence intervals (CIs) using Cox proportional hazards regression. Analyses were adjusted for gestational age and parental age at birth. When using a variable for stratification, it was omitted from the adjusted model. The cohort was stratified by sex, gestational age and age at diagnosis of the exposed individual.

2.8 | Missing data

There are no missing data for the exposure or outcome in the data set, although there are missing data on the following covariates: mother´s (0.7%) and father´s (2.3%) age at childbirth and gestational age of the child (6.4%) resulting in 7.2% incomplete cases. Therefore, we conducted multiple imputation by fully conditional specification, resulting in 50 randomly generated values for each missing value. Pooled values of these were used when conducting Cox regression.

Among children with ischaemic stroke between 1997 and 2014, we excluded all (6.4%) incomplete cases for sensitivity analysis.

2.9 | Sensitivity and subanalyses

As sensitivity analyses, we evaluated risk factors for adverse motor outcome after paediatric ischaemic stroke performing logistic regression to estimate odds ratios (ORs) and adjusted odds ratios (aORs) for sex, preterm birth, parental age at birth and age at diagnosis of stroke. We also stratified for perinatal and childhood stroke and adjusted for sex, gestational age, age at stroke diagnosis and parental age at birth, excluding the adjustment variable used as an outcome measure in each calculation.

Analyses on age at adverse motor outcome diagnosis were performed on the group of children with perinatal ischaemic stroke, as an insult in this group should lead to a diagnosis of CP.

We investigated the interchangeable use of different ICD diagnoses defined as an adverse motor outcome for all individuals with paediatric ischaemic stroke.

All analyses were performed using IBM SPSS Statistics software for Windows, Version 27.0 (IBM Corp., Armonk, NY).

2.10 | Ethical approval

The study was approved by the Regional Ethics Committee, Linköping (2017/31-10), on 23 January 2017. Due to the register-based nature of the study and that we only had access to pseudonymised data, the ethics committee did not require individual informed consent.[20]

3 | RESULTS

3.1 | Characteristics of the study participants

A total of 877 children with paediatric ischaemic stroke and alive 1 week after the stroke event were identified: 30.1% with perinatal stroke and 69.9% with childhood stroke (Table 1). There were slightly

TABLE 1 Characteristics of the study cohort by children exposed and unexposed to ischaemic stroke

	Exposed *n* (%)	Unexposed[a] *n* (%)
All	877 (100)	8770 (100)
Sex		
Male	459 (52.3)	4590 (52.3)
Female	418 (47.7)	4180 (47.7)
Age at diagnosis of stroke		
Perinatal	264 (30.1)	n/a
Childhood	613 (69.9)	n/a
>28 days–<2 years	181 (20.6)	n/a
2–6 years	148 (16.9)	n/a
7–12 years	107 (12.2)	n/a
13–<18 years	177 (20.2)	n/a
Gestational age (weeks)		
Full-term	726 (82.8)	7761 (88.5)
32–36	71 (8.1)	393 (4.5)
28–31	10 (1.1)	45 (0.5)
<28	8 (0.9)	18 (2.1)
Missing	62 (7.1)	553 (6.3)
Mother's age at birth (years)		
<26	61 (7.0)	611 (7.0)
26–35	392 (44.7)	3838 (43.8)
>35	420 (47.9)	4257 (48.5)
Missing	4 (0.4)	64 (0.7)
Father's age at birth (years)		
<26	26 (3.0)	284 (3.2)
26–35	305 (34.8)	2953 (33.7)
>35	527 (60.1)	5332 (60.8)
Missing	19 (2.2)	201 (2.3)

[a]Unexposed individuals were matched for sex, age and county of residence of the exposed.

more males (52.3%) in our cohort. Most children with ischaemic stroke were born full-term (82.8%), which was somewhat less than in the unexposed children (88.5%). Other participant characteristics are summarised in Table 1 and Figure 1.

3.2 | Risk of adverse motor outcome after paediatric ischaemic stroke

In all, 280 children (31.9%) exposed to stroke had an adverse motor outcome, rendering a highly increased risk of this outcome compared with unexposed: aHR 167.78 (95% CI 107.58, 261.66) (Table 2). No major differences were observed in risk estimates between males and females. Some 27.7% of children exposed to perinatal stroke and 33.8% of children with childhood stroke had an adverse motor outcome, resulting in HRs of 124.11 (95% CI 30.45, 505.84) and 182.37 (95% CI 113.65, 292.64), respectively, in comparison with unexposed. Risk of adverse motor outcome was higher in children with ischaemic stroke born full-term (aHR 269.10, 95% CI 150.54, 481.03) than children born preterm (aHR 34.78, 95% CI 14.47, 83.61) (Table 2).

3.3 | Association between adverse motor outcome and potential risk factors

Childhood stroke was associated with adverse motor outcome, aOR 1.56 (95% CI 1.05, 2.31), when comparing children with ischaemic stroke with and without adverse motor outcome. There were no associations between adverse motor outcome after ischaemic stroke and male sex (aOR 1.04, 95% CI 0.75, 1.45), preterm birth (aOR 1.06, 95% CI 0.60, 1.84), full-term birth (aOR 0.95, 95% CI 0.54, 1.65), maternal age at birth (aOR 0.81, 95% CI 0.48, 1.36) or paternal age at birth (aOR 1.16, 95% CI 0.72, 1.87), nor after stratifying for perinatal and childhood stroke (Table 3).

3.4 | Age at CP diagnosis

The children (n = 73) with perinatal ischaemic stroke received their first diagnosis of an adverse motor outcome at a median age of 14.2 months. No differences were noted according to sex or gestational age at birth (Table 4).

3.5 | Adverse motor outcome diagnoses in paediatric ischaemic stroke cases

Of the 73 children with perinatal ischaemic stroke and adverse motor outcome, 66 (90.4%) had only one diagnosis of adverse motor outcome registered in the NPR. For 62 (84.9%) of these 73 children, unilateral CP or hemiplegia was diagnosed as adverse outcome.

Among children with childhood ischaemic stroke, 140 (67.6%) had only one diagnosis of an adverse motor outcome and 174 (84%) had a diagnosis of unilateral CP and/or hemiplegia (Figure 2).

4 | COMMENT

4.1 | Principal findings

In this nationwide population-based cohort study of 877 children surviving the first week after paediatric ischaemic stroke, 280 (31.9%) suffered an adverse motor outcome corresponding to a 168-fold increased risk compared to that of the general population. The risk was similar in children with perinatal or childhood stroke; although when comparing only children with ischaemic stroke with and without adverse motor outcome, childhood stroke was associated with adverse motor outcome. We found no associations

TABLE 2 Risk of adverse motor outcome in children with paediatric ischaemic stroke compared with children unexposed to stroke, 1997–2016

	Adverse motor outcome, n/total (%)			
	Paediatric ischaemic stroke	Unexposed	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
All	280/877 (31.9)	21/8,770 (0.2)	162.59 (104.34, 253.37)	167.78 (107.58, 261.66)
Sex				
Male	146/459 (31.8)	12/4,590 (0.3)	149.70 (83.08, 269.75)	153.62 (85.14, 277.15)
Female	134/418 (32.1)	9/4,180 (0.2)	179.53 (91.40, 352.64)	186.97 (95.10, 367.60)
Gestational age[a]				
Full-term[b]	233/726 (32.1)	12/7,761 (0.2)	252.61 (141.39, 451.32)	269.10 (150.54, 481.03)
Preterm	31/89 (34.8)	6/456 (1.3)	33.88 (14.12, 81.32)	34.78 (14.47, 83.61)
Age at stroke				
Perinatal	73/264 (27.7)	2/ 741 (0.3)	188.47 (25.81, 1376.32)	124.11 (30.45, 505.84)
Childhood	207/613 (33.8)	19/8,029 (0.2)	158.31 (98.96, 253.26)	182.37 (113.65, 292.64)

Note: Adjusted for gestational age, mother's age at birth and father's age at birth. Stratification variables were omitted from adjustment. Unexposed individuals were matched for sex, age and county of residence of the exposed.

Abbreviations: CI, confidence interval; HR, Hazard ratio.

[a]Due to missing data on gestational age (6.4%), mothers' age (0.7%) and fathers' age (2.3%) at birth, multiple imputations were made for these variables and pooled values were used.

[b]Gestational age ≥37 weeks.

between male sex, low gestational age or high parental age and adverse motor outcome after paediatric stroke.

4.2 | Strengths of the study

The major strength of our study is the nationwide cohort study design with a relatively large study population consisting of 877 children with paediatric ischaemic stroke. We used matched children without ischaemic stroke from the general population with data on potential risk factors, enabling risk calculations for adverse motor outcomes. Studies on adverse motor outcomes after paediatric ischaemic stroke often had smaller cohorts and lacked controls,[7–10] preventing the possibility of studying different subgroups and potential risk factors. Other strengths include the prospective collection of data, a high follow-up rate and a low number of missing data.

4.3 | Limitations of the data

Because onset symptoms of perinatal stroke can be subtle, the diagnosis is sometimes delayed into childhood. Perinatal strokes not discovered before the 28th day after birth are diagnosed if and when symptoms of adverse motor symptoms are apparent, contributing to an overrepresentation of stroke cases resulting in adverse motor outcomes. However, to retrospectively register a paediatric stroke diagnosis in Sweden is rare, shown by our validation of the PedStroke cohort where only 3.6% of cases registered after 28 days of age has perinatal ischaemic stroke.[17]

Moreover, the difference in onset symptoms complicates the interpretation of our data, with hemiplegia much more common in childhood stroke.[2,17] Even though 86%–93% of the children with childhood stroke has hemiplegia as an onset symptom, only 56%–67% was persistent at follow-up.[9,10] In contrast, the reverse pattern is seen in younger ages, with an increased frequency of hemiplegia at follow-up in children <1 year of age.[21] From our register data, the onset of symptoms of adverse motor outcome cannot be distinguished from the long-term outcome. This is because diagnoses in registers are not corrected even after symptom recovery. Accordingly, we expected our frequency of adverse motor outcomes to be high. Yet, our results are slightly lower than those reported in other studies.[7–10] This discrepancy may be partly due to the population-based approach of our study, including less severe stroke cases. The register-based data do not distinguish between mild or severe adverse motor outcomes, nor do the data contain information on other functional deficits such as balance or dyscoordination. The synoptic view of the study can be seen as a limitation given that the functional ability of fine and gross motor function would be of great interest.

The initial analysis of our data revealed an overlap of the diagnoses of adverse motor outcomes. Our register data make it impossible to discern subcategories of adverse motor outcomes, so subtype analysis is not possible. Diagnoses are used interchangeably, with approximately 26% of our cohort having two or more diagnoses of an adverse motor outcome. Inconsistent coding can be due to unclear definitions, arbitrary administrative errors made by certified health care staff, or that doctors establishing the ICD codes lack expertise in the neurological field. Of the children with adverse motor outcomes after perinatal stroke, 97.3%

TABLE 3 Association of possible risk factors and adverse motor outcome in children exposed to paediatric ischaemic stroke, 1997–2014[a]

	Children exposed to paediatric ischaemic stroke, n (%)			
	With adverse motor outcome	Without adverse motor outcome	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
All	***n* = 215**	***n* = 454**		
Sex				
Male	113 (52.6)	235 (51.8)	1.03 (0.75, 1.43)	1.04 (0.75, 1.45)
Female	102 (47.4)	219 (48.2)	0.97 (0.70, 1.34)	0.96 (0.69, 1.34)
Gestational age				
Full-term	194 (90.2)	412 (90.7)	0.94 (0.54, 1.63)	0.95 (0.54, 1.65)
Preterm, all	21 (9.8)	42 (9.3)	1.06 (0.61, 1.84)	1.06 (0.60, 1.84)
Parental age at birth				
Mother >35 years	82 (38.1)	226 (49.8)	0.62 (0.45, 0.87)	0.81 (0.48, 1.36)
Father >35 years	120 (55.8)	286 (63.0)	0.74 (0.53, 1.03)	1.16 (0.72, 1.87)
Age at stroke				
Perinatal	66 (30.7)	155 (34.1)	0.85 (0.60, 1.21)	0.64 (0.43, 0.95)
Childhood	149 (69.3)	299 (65.9)	1.17 (0.83, 1.66)	1.56 (1.05, 2.31)
29 days–<2 years	61 (28.4)	76 (16.7)	1.97 (1.34, 2.90)	1.67 (1.16, 2.50)
2–6 years	36 (16.7)	67 (14.8)	1.16 (0.75, 1.81)	1.20 (0.77, 1.89)
7–12 years	28 (13.0)	53 (11.7)	1.13 (0.69, 1.85)	1.36 (0.81, 2.26)
13–18 years	24 (11.2)	103 (22.7)	0.43 (0.27, 0.69)	0.61 (0.33, 1.14)
Perinatal stroke	***n* = 66**	***n* = 155**		
Sex				
Male	34 (51.5)	75 (48.4)	1.13 (0.64, 2.02)	1.13 (0.63, 2.02)
Female	32 (48.5)	80 (51.6)	0.88 (0.50, 1.57)	0.88 (0.49, 1.59)
Gestational age				
Full-term	60 (90.9)	142 (91.6)	0.91 (0.33, 2.52)	0.90 (0.32, 2.51)
Preterm, all	6 (9.1)	13 (8.4)	1.09 (0.40, 3.00)	1.12 (0.40, 3.14)
Parental age at birth				
Mother >35 years	13 (19.7)	30 (19.4)	1.02 (0.49, 2.11)	0.87 (0.36, 2.12)
Father >35 years	27 (40.6)	55 (35.5)	1.26 (0.70, 2.27)	1.43 (0.68, 2.99)
Childhood stroke	***n* = 149**	***n* = 299**		
Sex				
Male	79 (53.0)	160 (53.5)	0.98 (0.66, 1.45)	1.00 (0.66, 1.50)
Female	70 (47.0)	139 (46.5)	1.02 (0.69, 1.51)	1.00 (0.66, 1.50)
Gestational age				
Full-term	134 (89.9)	270 (90.3)	0.96 (0.49, 1.85)	1.01 (0.51, 1.98)
Preterm, all	15 (10.1)	29 (10.1)	1.04 (0.54, 2.01)	1.00 (0.51, 1.96)
Parental age at birth				
Mother >35 years	69 (46.3)	196 (65.6)	0.45 (0.30, 0.68)	0.83 (0.43, 1.60)
Father >35 years	93 (62.4)	231 (77.3)	0.49 (0.32, 0.75)	0.96 (0.50, 1.83)

Note: Adjusted for sex, gestational age, age at stroke, mother's age at birth and father's age at birth. Stratification variables were omitted from adjustment.

Abbreviations: CI, confidence interval; OR, odds ratio.

[a]Incomplete cases are excluded from this analyses.

were diagnosed with CP and 12.3% had an additional diagnosis of hemiplegia. CP has not been validated in the NPR; however, CP in the Norwegian National Patient Registry is only correct in 59.5% of cases.[22] We therefore consider reporting adverse motor outcomes without discriminating between different diagnoses as an advantage of our study.

TABLE 4 Age at first diagnosis of adverse motor outcome in children with perinatal stroke, 1997–2016

		Median (95% CI)	Mean (95% CI)
	n (%)	Months	
All	73 (100)	14.2 (10.3, 18.0)	23.6 (17.1, 30.1)
Sex			
Male	36 (49.3)	12.5 (7.5, 16.3)	17.9 (12.2, 23.6)
Female	37 (50.7)	15.8 (12.0, 25.3)	29.1 (17.5, 40.7)
Gestational age[a]			
<37 weeks	6 (8.2)	11.3 (7.6, 20.4)	14.9 (4.3, 25.5)
≥37 weeks	64 (91.7)	14.2 (10.0, 16.9)	23.1 (16.3, 30.0)

[a]Due to missing data: $n = 70$.

4.4 | Interpretation

The extremely high HRs in our study show that there is an increased risk of an adverse motor outcome after paediatric ischaemic stroke. This finding confirms previous results.[7–10]

Although we did not find any association between male sex and the risk of adverse motor outcomes after paediatric stroke, several studies have reported that male sex is a risk factor for paediatric stroke[23,24] and adverse motor outcome after perinatal stroke.[8]

In our study, children born full-term and preterm had similar proportions of adverse motor outcomes after paediatric stroke (full-term, 31.8% vs. preterm, 34.8%). However, children born at full-term seem to be at a much higher risk than children born preterm, perhaps reflecting increased risk of adverse motor outcome due to prematurity rather than stroke. Our analysis of risk factors for adverse motor outcomes using only children with ischaemic stroke supports this claim, contradicting a link between gestational age and adverse motor outcomes after paediatric ischaemic stroke. Because most studies on perinatal ischaemic stroke have focussed on children born full-term, there are, to our knowledge, no previous reliable data for comparison.

In contrast to Schneider et al.,[13] we found no association between maternal age at birth and adverse motor outcomes after ischaemic stroke and when adjusting for sex, gestational age, age at stroke and father's age at birth. Stroke characteristics seem to be stronger and more consistent determinants of outcome.[25,26]

Of the children with perinatal stroke, 27.7% had an adverse motor outcome, a slightly lower prevalence than in childhood stroke (33.8%). However, no difference was found in the risk estimates for adverse motor outcomes between children with perinatal and childhood stroke.

There was an association between adverse motor outcome and childhood stroke when analysing only children with ischaemic stroke. This finding is in line with previous results indicating that brain maturation and the neurodevelopmental stage of the child at the time of stroke are two crucial factors determining the risk of adverse motor outcome.[27] Our study cohort probably does not include all cases of presumed perinatal stroke, which could have contributed to the association between adverse motor outcome and childhood stroke. However, the developing immature brain has been assumed to have a larger capacity for neuroplasticity and motor recovery than the brain of a child who has already developed motor trajectories and skills. This view is illustrated by a report that an insult affecting the same cerebral territory more often causes motor impairments in individuals with childhood stroke compared with perinatal stroke.[28] Infants with perinatal isolated perforator stroke seem to have a lower risk of adverse motor outcome.[29] However, the epidemiological approach of the study does not allow for an analysis of different types of stroke.

CP is defined as loss or impairment of motor function due to an insult to the developing brain and is diagnosed when a child is constantly developing new motor skills.[6,30] CP can sometimes be challenging to determine and classify. This challenge is reflected in the interchangeable use of the different adverse motor outcome diagnoses and a reason for not discriminating between types of adverse motor outcomes in our study. Irrespective of the type of adverse motor outcome diagnosis, we believe that CP is the consequence of perinatal ischaemic stroke and all insults <2 years of age.

Our study shows that children with perinatal stroke were diagnosed with adverse motor outcomes at a median age of 14.2 months, slightly later than reported in other studies. An American study reported a mean age of 18 months, which improved to 13 months by early screening.[15] In a Danish study, a median age of 11 months was reported for all types of CP and 13.5 months for unilateral CP.[14] Stroke most often causes unilateral CP, which could be a reason for a later diagnosis of CP in our study. An early diagnosis is important for interventions seeking to maximise the child's future motor development.[31]

5 | CONCLUSIONS

This study confirms the results from previous smaller studies that the risk of adverse motor outcomes is substantial after paediatric ischaemic stroke, both after perinatal and especially childhood stroke. We could not confirm sex, gestational or parental age as risk factors for adverse motor outcomes after paediatric stroke. The children in our study are older at diagnosis of CP than those in other studies, possibly hindering early intervention.

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CONFLICT OF INTEREST

None of the authors have anything to declare.

AUTHOR CONTRIBUTIONS

Katarina Svensson involved in study concept and design, acquisition and interpretation of data, drafting and revising the manuscript. Anna Walås involved in study concept and design, acquisition of data, analysis and interpretation of data, critical revision of the manuscript for intellectual content. Jenny Bolk involved in analysis and interpretation of data, critical revision of the manuscript for intellectual content. Peter Bang involved in study concept and design, interpretation of data, critical revision of the manuscript for intellectual content. Heléne EK Sundelin involved in study concept and design, data acquisition, analysis and interpretation of data, critical revision of the manuscript for intellectual content. All authors approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

DATA AVAILABILITY STATEMENT

Because of legal frameworks for Swedish health registers, we are not allowed to share raw data sets. The Swedish National Board of Health and Welfare and Statistics Sweden have access to all the data in this study. They can be contacted to request the data after ethical approval from the Swedish Ethical Review Authority.

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