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Umbilical artery pH and base excess at birth are poor predictors of neurodevelopmental morbidity in early childhood

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Short title: Acidosis and neurodevelopmental morbidity

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Abstract

Aim: We sought to evaluate the associations between umbilical artery pH and base excess and neurodevelopmental outcome at four years of age.

Methods: This study comprised 84,588 singleton children born alive at term in 2005-2011 in the hospital district of Helsinki and Uusimaa in Finland. Data from the maternity hospital information system were linked to the data from the Medical Birth Register and the Hospital Discharge Register. Neurodevelopmental morbidity included cerebral palsy, epilepsy, intellectual or sensorineural impairment.

Results: After adjustment for maternal and perinatal factors, a combination of pH <7.00 and base excess <-16.00 was associated with infant death (adjusted odds ratio 19.97; 95% confidence interval 5.38-74.17). Values of pH 7.00-7.10 was associated with cerebral palsy (adjusted odds ratio 2.40; 95% confidence interval 1.05-5.47). A combination of low five-minute Apgar score and umbilical artery base excess <-16.00 showed the highest positive predictive value (9.1%) for neurodevelopmental impairments. When umbilical artery pH <7.00 was included, a positive predictive value of 25.0% was observed for infant mortality.

Conclusion: Low umbilical artery pH and base excess at birth were poor predictors of long-term neurodevelopmental morbidity in an unselected population. However, these parameters might be useful in assessing the risk of infant mortality.

Key words: base excess, infant mortality, neurodevelopmental morbidity, pH, umbilical artery blood gas

Key Notes:

- Among unselected 84,588 term singleton children, no significant association was found between low umbilical pH and base excess and neurodevelopmental morbidity by four years of age.
- The combination of low umbilical artery pH <7.00 and base excess <-16.00 was associated with infant mortality.
- A low five-minute Apgar score (0-3) was strongly associated with any neurodevelopmental morbidity in early childhood and with infant mortality.

INTRODUCTION

Umbilical cord pH at birth is frequently used as an index to measure perinatal acidemia and assess birth asphyxia (1). Base excess is used as an indicator of metabolic acidosis in tissues and reflects the severity and duration of acidaemia (1,2).

Low umbilical artery pH has been associated with obstetric complications and adverse neonatal outcomes (3), hypoxic-ischaemic encephalopathy (1), neonatal encephalopathy with seizures (4) and neonatal mortality (1). However, less is known about the long-term effects when umbilical artery pH and base excess are low.

An extensive review from 2010 reported that low umbilical artery pH has associated with cerebral palsy (1). However, a meta-analysis for long-term outcomes other than cerebral palsy was not possible due to the wide variety of outcome measures and pH thresholds.

We sought to evaluate the association of umbilical artery pH and base excess with long-term neurodevelopmental morbidity by the age of four years in a Finnish regional cohort, which included all live-birth term singleton children born without anomalies from 2005-2011. Long-term neurodevelopmental morbidity included hospital-diagnosed cerebral palsy, epilepsy, intellectual disability and sensorineural defects consisting of visual and hearing impairments. The secondary outcome was infant mortality by the age of one year.

PATIENTS AND METHODS

This register-based retrospective study included all births from 2005-2011 in the hospital district of Helsinki and Uusimaa, which is the largest hospital district in Finland. A third of the children born in Finland are born in one of the six maternity hospitals in this district. A total of 103,689 children were identified from the maternity hospital information system of the hospital district of Helsinki and Uusimaa. The data from these children were linked to the Finnish Medical Birth Register (5). We excluded 3,315 (3.2%) multiple births, 4,651 (4.5%) preterm births <37 gestational weeks, 93 (0.1%) stillbirths and 4,312 (4.2%) children with major congenital anomalies according to the Register on Congenital Malformations. In addition, 6,730 (6.5%) children were excluded due to missing data on both pH and base excess values. Data of the 84,588 term children that met the inclusion criteria were linked to the Finnish Hospital Discharge Register (6).

All registers are maintained by the National Institute for Health and Welfare. The Finnish Medical Birth Register collects baseline data on care and interventions for mothers during pregnancy and delivery and on the newborn infant's outcome during the first days of life. All live births and stillbirths from gestational age 22+0 weeks onwards or with a birth weight of at least 500 grams are recorded in the Finnish Medical Birth Register. The Finnish Medical

Birth Register data are completed by obtaining basic information of every missing case from the Central Population Register, the Cause of Death Register and the birth hospital in cases of incomplete information. However, the Finnish Medical Birth Register does not contain information on newborn base excess levels; these data must be collected from the maternity hospital information system.

The Register on Congenital Malformations includes information on all births with at least one detected major structural anomaly, chromosomal defect or congenital hypothyroidism. These are coded according to the World Health Organisation International Classification of Diseases, Ninth Revision (ICD-9).

For all inpatient care and public hospital outpatient care, the Finnish Hospital Discharge Register records information on all diagnoses at discharge, including pregnancy-related and delivery-related diagnoses of mothers and diagnoses of children. Over 95% of discharges in Finland can be identified from the Finnish Hospital Discharge Register (6).

In Finland, midwives take an umbilical artery blood sample routinely from every newborn immediately after birth. The sample is analysed for pH and base excess values by an automatic blood gas analyser. The pH and base excess values were classified into the following three categories: pH <7.00, pH 7.00 to 7.10 and pH >7.10 and base excess <-16.00, base excess -16.00 to -12.00 and base excess >-12.00. Only births with at least one value available were included in the study. To examine the combined impact of pH and base excess, we classified values into the following four categories: low (pH <7.00 and base excess <-16.00), intermediate (pH <7.10 and base excess <-12.00, excluding those in category pH <7.00 and base excess <-16.00), normal (pH >7.10 and base excess >-12.00) and

other (other combination or one of the two values is unknown). We chose commonly used pH limits 7.10 and 7.00 (1,4,7) and base excess limits -12.00 and -16.00 (8) which have been suggested to predict adverse neurodevelopmental outcome.

Apgar scores were provided by midwives or paediatricians according to standardised procedures. The one and five-minute Apgar scores were classified into the following three groups: low (0-3), intermediate (4-6) and normal (7-10) (9). In 46,277 (54.7%) births, data were available for the one-minute, but not the five-minute Apgar score. A common practice in some hospitals of the Helsinki and Uusimaa hospital district is that the five-minute score is not recorded if the one-minute score is high (>7) and the child remains in good condition. If the one-minute Apgar score was normal and the child was discharged within the first week, the five-minute Apgar score was substituted by the score at one minute. Newborns were divided into the following subgroups by gestational weeks: early term (37+0 to 38+6), full term (39+0 to 40+6) and late or post term (≥41+0). Gestational age was determined by the first trimester ultrasound.

A neurodevelopmental impairment was recorded if by the age of four years the child was recorded in the Finnish Hospital Discharge Register with ICD-10 codes for neurodevelopmental diagnoses. We collected data on cerebral palsy (G80.0-G80.9), epilepsy (G40.0-G40.9), intellectual disability (F70.0-F73.9 and F78.0-F79.9) and sensorineural defects consisting of visual impairment (H53.0-H53.4 and H54.0-H54.7) and hearing impairment (H90.0-H90.8) from the Finnish Hospital Discharge Register. These diagnoses were based on medical history, clinical evaluation, brain imaging and clinical neurophysiological investigations when appropriate. A specialist always sets these diagnoses according to national guidelines in either secondary or tertiary care public hospitals. In

Finland, all preschool children are invited to an annual medical and developmental check-up free of charge. Practically all children attend these check-ups. Accordingly, cerebral palsy, severe intellectual disability and sensorineural defects are diagnosed by four years of age and epilepsy is diagnosed at the time of first symptoms. Data on deaths were available in the Finnish Medical Birth Register only for the first year of life.

For this study, the National Institute for Health and Welfare and the hospital district of Helsinki and Uusimaa gave the necessary authorization (THL/1200/5.05.00/2012; THL/1699/5.05.00/2014; HUS/42/2017) required by the data protection legislation in Finland. All register and hospital data were linked by using unique personal identification numbers anonymised by the authorities.

Statistical methods

Characteristics of newborn infants and their mothers are shown as percentages for categorical variables and as means with standard deviations for normally distributed continuous variables. Correlation analysis was performed by Pearson Correlation Coefficients. Umbilical artery pH and base excess groups were compared with each other by Cochran-Mantel-Haenszel statistics when appropriate.

Confounders of neurodevelopmental morbidity were analysed by logistic regression using multivariate enter models. The variables were selected on the basis of availability, clinical importance and previous literature of risk factors for neurodevelopmental morbidity (10). The following variables were collected from the Finnish Medical Birth Register: in vitro fertilisation, maternal age, maternal smoking, socio-economic position based on mother's occupation, maternal body mass index, mode of delivery (vaginal delivery, planned

Caesarean section, emergency Caesarean section), the newborn infant's sex, birth weight adjusted for gestational age according to the sex-specific national standard, umbilical artery pH and base excess. Missing values were set in a separate category.

Statistical analyses were performed with SAS version 9.3 (SAS Institute Inc., Cary, North Carolina, USA). The results are shown as odds ratios (OR) with 95% confidence intervals (CI). P values lower than 0.05 were considered statistically significant.

RESULTS

Of 84,588 term singleton children, 1,340 (1.6%) children had both umbilical artery pH ≤ 7.10 and base excess <-12.00. The incidence of umbilical artery pH <7.00 was 0.5% (n=404) and 3.7% (n=3,099) for pH 7.00 to 7.10. The incidence of umbilical artery base excess <-16.00 was 0.3% (n=277) and 2.0% (n=1,675) for base excess -16.00 to -12.00. Characteristics of mothers and newborns are shown in Table 1.

The correlation between umbilical cord pH and base excess was strong (r=0.688, p<0.001). There was a statistically significant but weak correlation between five-minute Apgar score and pH (r=0.103, p<0.001) and between five-minute Apgar score and base excess (r=0.152, p<0.001).

The incidence of cord blood gas groups was compared with perinatal factors. Children with umbilical artery pH <7.00 were more likely to be born late term or post term (35.1% versus 28.1%; p=0.002), by an emergency Caesarean section (25.2% versus 10.1%; p<0.001) and to have a five-minute Apgar score of 0-3 (7.4% versus 0.1%; p<0.001) than children with umbilical artery pH >7.10. Similarly, children with umbilical artery base excess <-16.00 were

more often born late or post term (39.4% versus 28.5%; p<0.001) or by an emergency Caesarean section (21.7% versus 9.8%; p<0.001) and more often had a five-minute Apgar score of 0-3 (7.9% versus 0.1%; p<0.001) than children with normal umbilical artery base excess >-12.00. Of all 166 children with umbilical artery pH <7.00 and base excess <-16.00, 60 (36.1%) were born late term or post term, 50 (30.1%) by an emergency Caesarean section and 20 (12.0%) had a five-minute Apgar score of 0-3 (Table 2).

Neurodevelopmental impairment was diagnosed in 667 (0.8%) children. Of these children, 94 (14.1%) had both umbilical artery pH ≤7.10 and base excess ≤-12.00. Umbilical artery pH ≤7.10 and base excess ≤-12.00 were associated with increased rates of cerebral palsy, epilepsy, intellectual disability and sensorineural defects by the age of four years. Infant mortality incidence rates were the highest in children with umbilical artery pH <7.00 or base excess <-16.00 and especially when both values were low (Table 3). Among the 6,730 children who were excluded from the study due to missing data on both pH and base excess values, the incidence rates of neurodevelopmental impairments did not differ and the percentage infant mortality (n=4, 0.06%) was similar.

Of the 667 children with any neurodevelopmental impairment, 70 (10.5%) had two diagnoses, 12 (1.8%) had three and three (0.4%) children had four endpoint diagnoses. Among the 347 children with sensorineural defects, 175 (50.4%) had visual impairment, 168 (48.4%) had hearing impairment and four (1.2%) had both.

In separate multivariable logistic regression analysis for pH and base excess, the only statistically significant association was between pH 7.00 to 7.10 and cerebral palsy (adjusted OR 2.40; 95% CI 1.05-5.47). Multivariable logistic regression analysis did not show a

significant association between pH <7.00, base excess <-16.00, or base excess -16.00 to -12.00 and any neurodevelopmental impairment, even in the model with combined pH and base excess. However, a combination of pH <7.00 and base excess <-16.00 was associated with infant death (adjusted OR 19.97; 95% CI 5.38-74.17). A low five-minute Apgar score was the strongest independent risk factor for cerebral palsy, epilepsy, intellectual disability, sensorineural defects, any impairment and infant death in multivariable logistic regression analyses (Table 4).

The highest positive predictive value for neurodevelopmental impairments was observed for a combination of low five-minute Apgar score and umbilical artery base excess <-16.00 (9.1%). The positive predictive value for infant mortality was 25.0% for a combination of low five-minute Apgar score, low umbilical artery pH (<7.00) and base excess (<-16.00) (Table 5).

DISCUSSION

In this study, we sought to identify an asphyxia marker that would predict later neurodevelopmental morbidity. We found that isolated low or intermediate umbilical artery pH is not a risk factor for epilepsy, intellectual disability or sensorineural defects. A low or intermediate umbilical base excess was not associated with any of neurodevelopmental impairments, neither alone nor when combined with pH. However, we found an association between umbilical cord pH and cerebral palsy (OR 2.40) but only when pH was 7.00 to 7.10; no association was observed when umbilical pH was <7.00. In addition, a combination of pH <7.00 and base excess <-16.00 was significantly associated with infant mortality. A low five-minute Apgar score (0-3) showed the strongest association with any neurodevelopmental morbidity and infant mortality.

Both pH and base excess are measured at the time of delivery by umbilical cord blood gas analysis. As pH and base excess are not independent (2), both low umbilical artery base excess and low umbilical artery pH have been associated with neonatal morbidity such as meconium aspiration syndrome (3), neonatal sepsis (3), neonatal intensive care unit admission (3) and moderate and severe newborn encephalopathy and respiratory complications (8). Low Apgar scores have been related to a higher risk of long-term neurodevelopmental impairments, especially when Apgar scores remain low at five (11) and ten minutes (12). One study reported that a low umbilical artery base excess and a low five-minute Apgar score can predict neonatal morbidity in neonates with an umbilical artery pH <7.00 (13). Another study showed no added predictive value of low base excess for adverse outcomes once pH was considered (14).

Malin et al reported an OR of 2.3 for the overall association between low umbilical pH and cerebral palsy in a meta-analysis of seven studies including 1,117 infants (1). However, six of the studies had been performed in high-risk populations in the 1990s. Furthermore, a Japanese study reported that more than 10% of infants with severe cerebral palsy did not have acidaemic status at birth (15). Kelly et al presented a dose-dependent relationship between low pH or base excess at birth and likelihood of death or cerebral palsy (16). However, we found an association between pH and cerebral palsy only when pH was 7.00 to 7.10 (OR 2.40). We did not observe a significant association with umbilical pH <7.00, which may be due to the fact that only one child with cerebral palsy had umbilical artery pH <7.00.

Conflicting results exist for the long-term neurocognitive outcome in acidaemic newborn infants. A Finnish study revealed that low umbilical artery pH is associated with intellectual disability (10). However, other studies did not reveal an association between acidosis and

neurodevelopmental impairments at the age of four years (17,18). In infants with metabolic acidosis at birth who appeared well in the neonatal period, Hafström et al did not observe an increased risk for neurologic or behavioural problems that required special education at the age of 6.5 years (19). Previously, pH was significantly negatively correlated with literacy and non-verbal intelligence (20). We did not find an association between low umbilical artery pH or base excess and severe intellectual disability as determined by ICD-10 codes.

To our knowledge, only a few studies have assessed the association between metabolic acidosis at birth and epilepsy diagnosed later in childhood. Garcias Da Silva et al reported that perinatal asphyxia is more frequently associated with neonatal seizures, but not with postnatal epilepsy (21). We did not find an association between low umbilical artery pH or base excess and epilepsy diagnosed by four years of age.

Durmus et al did not find a difference in pH values of those who passed a transient otoacoustic emission test compared with those who had no response to a stimulus (22). In contrast, a previous study found an association between adverse acid-base status and major sensorineural impairment in infants weighing less than 1,000 grams (23). An association between acidosis and retinopathy of prematurity in infants with birth weight less than 1,000 grams has also been reported (24). In our term study population, low umbilical artery pH or base excess was not associated with impairments of vision or hearing.

According to our study, perinatal asphyxia as measured by pH and base excess was associated primarily with infant mortality; no significant association was found with neurodevelopmental impairments in early childhood. The relatively large incidence of infant mortality among children with low umbilical artery pH and base excess may explain the

absence of a statistically significant association with neurodevelopmental impairments. Another possible mechanism is that delivery, in particular together with asphyxia, triggers the release of catecholamines. The catecholamine surge at birth sustains homeostasis and helps newborns to adapt to the extra uterine environment (25). The Apgar score increase, but catecholamines also cause metabolic acidosis (25), which may explain our findings to some extent.

Additional attention should be considered for children with low umbilical artery pH and base excess values. This is of particular importance if there are clinical signs of perinatal asphyxia or newborn encephalopathy. In these cases, other clinical assessments such as neuroimaging and neurophysiologic methods should be considered to better evaluate any possible brain injury (26). A low five-minute Apgar score (0-3) was strongly associated with any neurodevelopmental morbidity by the age of four years and with infant mortality. As such, the Apgar score may be the one of the newborn signs to consider for estimating the neurodevelopmental outcome in term children.

The strength of our study was the population-based regional cohort, which included nearly 85,000 births. The study population was quite homogeneous and obstetric and paediatric practices remained the same during the study period. Diagnoses were specifically defined and always made by a specialist in neurodevelopmental disorders. The majority of the data were collected from high-quality and comprehensive registers (5,6), which allowed us to adjust for important confounders.

However, we had no data on obstetric and neonatal interventions, such as labour medication or induced hypothermia in newborns with hypoxic-ischaemic encephalopathy. This may influence acid-base values or reduce the risk of death and adverse neurodevelopmental outcomes. We also used supplemental data from the maternity hospital information system, which tended to be less comprehensive than national registers. However, only 6.5% of children were excluded due to missing data on both pH and base excess values; 6.4% of the remaining children did not have an available umbilical base excess value. We used arterial umbilical cord samples, which have been recommended rather than venous samples (7). One of the limitations of this study was unavailable paired cord gas samples (arterial and venous) in the hospital district of Helsinki and Uusimaa hospitals at the time this study was performed. It is possible that at the age of four year some neurodevelopmental impairments may not have been found. In particular, the milder developmental disabilities may not have emerged at this age. It might be worthwhile to follow the correlation of less severe impairments with measured parameters in the future.

CONCLUSION

We did not find a significant association between low umbilical pH and base excess and neurodevelopmental morbidity by the age of four years in an unselected term population. However, the combination of low umbilical artery pH <7.00 and base excess <-16.00 was associated with infant mortality. A low five-minute Apgar score was strongly associated with any neurodevelopmental morbidity and with infant mortality. A combination of Apgar score with the results of umbilical artery blood gas analyses provided further support for estimating the risk of infant mortality and adverse neurodevelopmental outcome.

FINANCE

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

ABBREVIATIONS

CI, confidence interval; OR, odds ratio; SD, standard deviation.

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TABLE 1 Characteristics of the Study Population

	n (%)
Total	84,588 (100.0)
Maternal age (year), mean (± SD)	31.0 (±5.2)
Socioeconomic status	
Blue collar	17,723 (21.0)
Lower white collar	20,722 (24.5)
Higher white collar	6,313 (7.5)
Other or unknown	39,830 (47.1)
Maternal BMI (kg/m^2)	
Overweight: BMI 25.0-29.9	15,910 (18.8)
Obese: BMI ≥ 30.0	7,323 (8.7)
Smoking	
No smoking during pregnancy	71,663 (84.7)
Quit smoking at 1st trimester	4,080 (4.8)
Current smokers	7,250 (8.6)
No information	1,595 (1.9)
In vitro fertilization	2,838 (3.4)
Parity	
0	38,765 (45.8)
1	29,412 (34.8)
2 or more	16,153 (19.1)
Unknown	258 (0.3)
Maternal diabetes	
GDM	3,439 (4.1)
Insulin-treated GDM	643 (0.8)
Diabetes type I	373 (0.4)
Pre-eclampsia	1,586 (1.9)
Induced delivery	15,263 (18.0)
Mode of delivery	
Vaginal delivery	70,754 (83.6)
Normal	61,726 (73.0)
Breech vaginal delivery	451 (0.5)
Vacuum extraction/Forceps	8,577 (10.1)
Section	13,548 (16.0)
Emergency Caesarean section	8,614 (10.2)
Planned Caesarean section	4,934 (5.8)
Unknown	286 (0.3)
Male	43,349 (51.2)
Gestational age (wk)	
37+0 - 38+6	12,617 (14.9)
39+0 - 40+6	47,509 (56.2)
41+0 - 41+6	18,077 (21.4)
≥42+0	5,889 (7.0)
Unknown	496 (0.6)
Birth weight (g)	

<2500	743 (0.9)
≥4500	2,394 (2.8)
Birth weight (g); mean (± SD)	3578 (± 466)
SGA	2,413 (2.9)
LGA	1,908 (2.3)
Mortality	
0-27 days	16 (0.02)
28-364 days	34 (0.04)

BMI, body mass index; GDM, gestational diabetes; LGA, large for gestational age; SD, standard deviation; SGA, small for gestational age.

TABLE 2 Incidence of and risk for low umbilical artery pH and base excess according to gestational age, mode of delivery, and five-minute Apgar score

A)		Umbilical artery pH									
		<7.00				7.00 – 7.10				>7.10	Unknown
	Total *N*	*n* (%)	OR	95% CI		*n* (%)	OR	95% CI		*n* (%)	*n* (%)
Gestational age											
37+0 - 38+6	12,617	53 (0.4)	0.95	0.71	1.29	327 (2.6)	0.75	0.67	0.85	12,230 (96.9)	7 (0.1)
39+0 - 40+6	47,509	209 (0.4)	Reference			1,623 (3.4)	Reference			45,652 (96.1)	25 (0.1)
41+0 - 41+6	18,077	99 (0.5)	1.25	0.98	1.58	802 (4.4)	1.31	1.20	1.43	17,170 (95.0)	6 (0.0)
≥42+0	5,889	43 (0.7)	1.66	1.20	2.31	347 (5.9)	1.77	1.57	1.99	5,499 (93.4)	0 (0.0)
Unknown	496	0 (0.0)	N/A			0 (0.0)	N/A			3 (0.6)	493 (99.4)
Mode of delivery											
Vaginal delivery*	70,754	299 (0.4)	Reference			2,751 (3.9)	Reference			67,518 (95.4)	186 (0.3)
Emergency Caesarean section	8,614	102 (1.2)	2.82	2.25	3.54	318 (3.7)	0.95	0.84	1.07	8,145 (94.6)	49 (0.6)
Planned Caesarean section	4,934	3 (0.1)	0.14	0.05	0.45	30 (0.6)	0.15	0.11	0.22	4,891 (99.1)	10 (0.2)
Unknown	286	0 (0.0)	N/A			0 (0.0)	N/A			0 (0.0)	286 (100.0)
Five-minute Apgar score											
Low (0-3)	126	30 (23.8)	96.96	63.25	148.64	25 (19.8)	7.03	4.53	10.91	69 (54.8)	2 (1.6)
Intermediate (4-6)	918	95 (10.3)	35.82	28.06	45.71	224 (24.4)	9.17	7.85	10.71	594 (64.7)	5 (0.5)
Normal (7-10)	83,110	267 (0.3)	Reference			2,827 (3.4)	Reference			79,783 (96.0)	233 (0.3)
Unknown	434	12 (2.8)	8.82	4.91	15.86	23 (5.3)	1.59	1.04	2.42	108 (24.9)	291 (67.1)
Total	84 588	404 (0.5)				3,099 (3.7)				80,554 (95.2)	531 (0.6)
B)		Umbilical artery base excess									

		<-16.00				-16.00 – -12.00				>-12.00	Unknown
	Total *N*	*n* (%)	OR	95% CI		*n* (%)	OR	95% CI		*n* (%)	*n* (%)
Gestational age											
37+0 - 38+6	12,617	29 (0.2)	0.80	0.54	1.20	144 (1.1)	0.62	0.52	0.74	11,424 (90.5)	1,020 (8.1)
39+0 - 40+6	47,509	136 (0.3)	Reference			868 (1.8)	Reference			43,295 (91.1)	3,210 (6.8)
41+0 - 41+6	18,077	66 (0.4)	1.28	0.95	1.71	463 (2.6)	1.41	1.26	1.58	16,651 (92.1)	897 (5.0)
≥42+0	5,889	43 (0.7)	2.56	1.82	3.61	189 (3.2)	1.78	1.52	2.09	5,400 (91.7)	257 (4.4)
Unknown	496	3 (0.6)	2.12	0.67	6.68	11 (2.2)	1.22	0.67	2.22	482 (97.2)	0 (0.0)
Mode of delivery											
Vaginal delivery*	70,754	211 (0.3)	Reference			1,464 (2.1)	Reference			65,411 (92.4)	3,668 (5.2)
Emergency Caesarean section	8,614	60 (0.7)	2.35	1.76	3.13	187 (2.2)	1.05	0.90	1.22	7,596 (88.2)	771 (9.0)
Planned Caesarean section	4,934	4 (0.1)	0.27	0.10	0.73	16 (0.3)	0.15	0.09	0.25	3,969 (80.4)	945 (19.2)
Unknown	286	2 (0.7)	2.35	0.58	9.52	8 (2.8)	1.36	0.67	2.76	276 (96.5)	0 (0.0)
Five-minute Apgar score											
Low (0-3)	126	22 (17.5)	85.13	52.69	137.56	19 (15.1)	9.71	5.95	15.87	81 (64.3)	4 (3.2)
Intermediate (4-6)	918	44 (4.8)	20.26	14.53	28.25	140 (15.3)	9.84	8.16	11.87	713 (77.7)	21 (2.3)
Normal (7-10)	83,110	206 (0.2)	Reference			1,492 (1.8)	Reference			76,060 (91.5)	5,352 (6.4)
Unknown	434	5 (1.2)	4.69	1.92	11.45	24 (5.5)	3.20	2.11	4.85	398 (91.7)	7 (1.6)
Total	84,588	277 (0.3)				1,675 (2.0)				77,252 (91.3)	5,384 (6.4)

C)		Combined pH and base excess[†]									
		Low				Intermediate				Normal	Other combination or unknown
	Total *N*	*n* (%)	OR	95% CI		*n* (%)	OR	95% CI		*n* (%)	*n* (%)
Gestational age											
37+0 - 38+6	12,617	18 (0.1)	0.77	0.46	1.28	103 (0.8)	0.65	0.53	0.81	11,158 (88.4)	1,338 (10.6)

39+0 - 40+6	47,509	88 (0.2)	Reference			591 (1.2)	Reference			42,122 (88.7)	4,708 (9.9)
41+0 - 41+6	18,077	35 (0.2)	1.05	0.71	1.55	336 (1.9)	1.50	1.31	1.72	16,115 (89.1)	1,591 (8.8)
≥42+0	5,889	25 (0.4)	2.30	1.47	3.59	144 (2.4)	1.99	1.66	2.39	5,179 (87.9)	541 (9.2)
Unknown	496	0 (0.0)	N/A			0 (0.0)	N/A			3 (0.6)	493 (99.4)
Mode of delivery											
Vaginal delivery*	70,754	114 (0.2)	Reference			1,020 (1.4)	Reference			63,317 (89.5)	6,303 (8.9)
Emergency Caesarean section	8,614	50 (0.6)	3.62	2.59	5.05	141 (1.6)	1.14	0.95	1.36	7,319 (85.0)	1,104 (12.8)
Planned Caesarean section	4,934	2 (0.0)	0.25	0.06	1.02	13 (0.3)	0.18	0.10	0.31	3,941 (79.9)	978 (19.8)
Unknown	286	0 (0.0)	N/A			0 (0.0)	N/A			0 (0.0)	286 (100.0)
Five-minute Apgar score											
Low (0-3)	126	20 (15.9)	145.01	86.75	242.39	20 (15.9)	15.20	9.39	24.61	64 (50.8)	22 (17.5)
Intermediate (4-6)	918	35 (3.8)	30.46	20.69	44.86	122 (13.3)	12.35	10.11	15.09	549 (59.8)	212 (23.1)
Normal (7-10)	83,110	108 (0.1)	Reference			1,019 (1.2)	Reference			73,866 (88.9)	8,117 (9.8)
Unknown	434	3 (0.7)	5.35	1.69	16.91	13 (3.0)	2.49	1.43	4.33	98 (22.6)	320 (73.7)
Total	84,588	166 (0.2)				1,174 (1.4)				74,577 (88.2)	8,671 (10.3)

CI, confidence interval; N/A, not applicable; OR, odds ratio.

* Vaginal delivery: normal delivery, breech vaginal delivery, vacuum extraction/forceps.

† Combined pH and base excess: Low=pH <7.00 and base excess <-16.00; intermediate=pH ≤7.10 and base excess ≤-12.00 (excluding those in category low); normal= pH >7.10 and base excess >-12.00.

TABLE 3 Incidence of neurodevelopmental impairments and infant mortality per 1,000 children according to umbilical artery pH and base excess

		Cerebral palsy			Epilepsy			Intellectual disability			Sensorineural defects*			Any			Infant mortality†		
	Total *n*	*n*	Incidence per 1,000	*P* value‡	*n*	Incidence per 1,000	*P* value‡	*n*	Incidence per 1,000	*P* value‡	*n*	Incidence per 1,000	*P* value‡	*n*	Incidence per 1,000	*P* value‡	*n*	Incidence per 1,000	*P* value‡
Umbilical artery pH																			
<7.00	404	1	2.5		3	7.4		2	5		3	7.4		5	12.4		7	17.3	
7.00 – 7.10	3,099	8	2.6	<0.001	12	3.9	0.31	5	1.6	<0.001	16	5.2	0.5	32	10.3	0.22	2	0.6	<0.001
>7.10	80,554	50	0.6		257	3.2		54	0.7		325	4		624	7.7		41	0.5	
Unknown	531	0	0		3	5.6		2	3.8		3	5.6		6	11.3		0	0	
Umbilical artery base excess																			
<-16.00	277	2	7.2		3	10.8		2	7.2		4	14.4		5	18.1		6	21.7	
-16.00 – -12.00	1,675	2	1.2	<0.001	8	4.8	0.007	3	1.8	<0.001	4	2.4	0.04	15	9	0.16	2	1.2	0.06
>-12.00	77,252	54	0.7		237	3.1		54	0.7		317	4.1		598	7.7		40	0.5	
Unknown	5,384	1	0.2		27	5		4	0.7		22	4.1		49	9.1		2	0.4	
Combined pH and base excess																			
Low (pH <7.00 and base excess <-16.00)	166	1	6		2	12		2	12		2	12		3	18.1		6	36.1	
Intermediate (pH ≤7.10 and base excess ≤-12.00) §	1,174	3	2.6	0.07	7	6	0.04	3	2.6	0.65	6	5.1	0.9	15	12.8	0.4	2	1.7	0.05
Normal (pH >7.10 and base excess >-12.00)	74,577	49	0.7		228	3.1		50	0.7		303	4.1		573	7.7		39	0.5	
Other combination or unknown	8,671	6	0.7		38	4.4		8	0.9		36	4.2		76	8.8		3	0.3	
Total	84,588	59	0.7		275	3.3		63	0.7		347	4.1		667	7.9		50	0.6	

* Sensorineural defects include impairments of vision and hearing.

† Mortality by the first year.

‡ *P* value: Cochran-Mantel-Haenszel statistics.

§ Excluding those in category low (pH <7.00 and base excess <-16.00).

TABLE 4 Results of multivariable logistic regression for the association of selected variables with neurodevelopmental impairments by the age of four years and infant mortality by the first year.

	Cerebral palsy			Epilepsy			Intellectual disability			Sensorineural defects*			Any			Infant mortality†		
Variable	**OR**	**95% CI**		**OR**	**95% CI**		**OR**	**95% CI**		**OR**	**95% CI**		**OR**	**95% CI**		**OR**	**95% CI**	
Maternal age, y																		
<20	1.12	0.48	2.62	1.14	0.81	1.62	1.77	0.90	3.48	1.01	0.73	1.39	1.12	0.89	1.41	**2.32**	**1.18**	**4.56**
20-34	1.00	Reference		1.00	Reference		1.00	Reference		1.00	Reference		1.00	Reference		1.00	Reference	
≥35	**1.90**	**1.08**	**3.33**	1.03	0.77	1.39	0.90	0.47	1.70	0.89	0.68	1.17	1.02	0.84	1.23	0.96	0.44	2.11
Low socioeconomic position	0.43	0.10	1.77	1.23	0.82	1.84	1.35	0.58	3.17	1.31	0.92	1.88	1.24	0.95	1.61	**2.47**	**1.20**	**5.09**
Maternal BMI (kg/m^2)																		
Normal weight (BMI <25.0)	1.00	Reference		1.00	Reference		1.00	Reference		1.00	Reference		1.00	Reference		1.00	Reference	
Overweight (BMI 25.0-29.9)	0.84	0.42	1.68	1.16	0.86	1.56	1.30	0.72	2.34	0.98	0.75	1.30	1.02	0.83	1.24	0.60	0.26	1.40
Obese (BMI ≥30.0)	1.09	0.46	2.60	**1.62**	**1.13**	**2.31**	0.60	0.19	1.94	1.11	0.77	1.59	**1.29**	**1.01**	**1.66**	1.28	0.53	3.10
Smoking	1.17	0.54	2.55	**1.40**	**1.02**	**1.93**	0.69	0.30	1.56	1.17	0.86	1.58	1.21	0.97	1.50	**2.07**	**1.07**	**4.01**
In vitro fertilization	2.07	0.81	5.29	1.20	0.65	2.21	**2.92**	**1.22**	**6.96**	1.36	0.81	2.30	1.37	0.94	1.98	2.09	0.61	7.15
Mode of delivery																		
Vaginal delivery	1.00	Reference		1.00	Reference		1.00	Reference		1.00	Reference		1.00	Reference		1.00	Reference	
Emergency Caesarean section	0.63	0.15	2.63	**1.83**	**1.22**	**2.74**	1.71	0.67	4.33	1.20	0.79	1.83	**1.49**	**1.12**	**1.98**	0.44	0.06	3.27

Planned Caesarean section	1.77	0.92	3.37	1.13	0.78	1.65	1.29	0.63	2.65	0.90	0.63	1.29	1.06	0.83	1.35	1.71	0.82	3.56
Male	**2.28**	**1.30**	**4.01**	1.00	0.79	1.26	1.12	0.68	1.83	**1.48**	**1.19**	**1.83**	**1.29**	**1.11**	**1.51**	1.12	0.63	1.97
Birth weight																		
SGA	0.48	0.07	3.47	1.23	0.65	2.32	**3.33**	**1.42**	**7.80**	1.51	0.90	2.55	**1.61**	**1.12**	**2.32**	N/A		
Normal birth weight	1.00	Reference		1.00	Reference		1.00	Reference		1.00	Reference		1.00	Reference		1.00	Reference	
LGA	N/A			0.68	0.28	1.66	N/A			1.41	0.77	2.60	0.99	0.60	1.63	1.84	0.43	7.90
Five-minute Apgar score																		
0-3	**28.98**	**7.74**	**108.56**	**8.66**	**2.93**	**25.61**	**39.14**	**12.47**	**122.87**	**7.53**	**2.61**	**21.75**	**8.10**	**3.80**	**17.28**	**29.52**	**8.60**	**101.31**
4-6	**8.10**	**3.26**	**20.13**	2.10	0.97	4.55	2.46	0.57	10.56	**2.37**	**1.20**	**4.68**	**2.49**	**1.55**	**4.00**	N/A		
7-10	1.00	Reference		1.00	Reference		1.00	Reference		1.00	Reference		1.00	Reference		1.00	Reference	
Combined pH and base excess																		
Low (pH <7.00 and base excess <-16.00)	1.52	0.18	13.18	1.82	0.40	8.24	2.64	0.47	14.72	1.56	0.35	6.89	1.13	0.34	3.79	**19.97**	**5.38**	**74.17**
Intermediate (pH ≤7.10 and base excess ≤-12.00)‡	1.65	0.47	5.77	1.57	0.72	3.40	2.04	0.58	7.12	1.02	0.45	2.33	1.33	0.78	2.25	2.23	0.50	9.93
Normal (pH >7.10 and base excess >-12.00)	1.00	Reference		1.00	Reference		1.00	Reference		1.00	Reference		1.00	Reference		1.00	Reference	

All variables in the table were included to logistic regression analysis, other variables were not included.

Statistically significant values are in bold.

BMI, body mass index; CI, confidence interval; LGA, large for the gestational age; N/A, not applicable; OR, odds ratio; SD, standard deviation; SGA, small for the gestational age.

* Sensorineural defects include impairments of vision and hearing.

† Mortality by the first year.

‡ Excluding those in category low (pH <7.00 and base excess <-16.00).

TABLE 5 Predictive models of neurodevelopmental impaiments by the age of four years and infant mortality by the first year

Model variables	Total *n*	Cerebral palsy			Epilepsy			Intellectual disability			Sensorineural defects*			Any			Infant mortality†		
		n	Predictive value		*n*	Predictive value		*n*	Predictive value		*n*	Predictive value		*n*	Predictive value		*n*	Predictive value	
			Positive	Negative		Positive	Negative		Positive	Negative		Positive	Negative		Positive	Negative		Positive	Negative
Umbilical artery pH <7.00	404	1	0.2 %	99.9 %	3	0.7 %	99.7 %	2	0.5 %	99.9 %	3	0.7 %	99.6 %	5	1.2 %	99.2 %	7	1.7 %	99.9 %
Umbilical artery base excess <-16.00	277	2	0.7 %	99.9 %	3	1.1 %	99.7 %	2	0.7 %	99.9 %	4	1.4 %	99.6 %	5	1.8 %	99.2 %	6	2.2 %	99.9 %
Five-minute Apgar score 0-3	126	3	2.4 %	99.9 %	4	3.2 %	99.7 %	5	4.0 %	99.9 %	4	3.2 %	99.6 %	8	6.3 %	99.2 %	7	5.6 %	99.9 %
Umbilical artery pH <7.00 and base excess <-16.00	166	1	0.6 %	99.9 %	2	1.2 %	99.7 %	2	1.2 %	99.9 %	2	1.2 %	99.6 %	3	1.8 %	99.2 %	6	3.6 %	99.9 %
Umbilical artery pH <7.00 and five-minute Apgar score 0-3	30	1	3.3 %	99.9 %	1	3.3 %	99.7 %	1	3.3 %	99.9 %	1	3.3 %	99.6 %	1	3.3 %	99.2 %	5	16.7 %	99.9 %
Umbilical artery base excess <-16.00 and five-minute Apgar score 0-3	22	2	9.1 %	99.9 %	2	9.1 %	99.7 %	1	4.5 %	99.9 %	2	9.1 %	99.6 %	2	9.1 %	99.2 %	5	22.7 %	99.9 %
Umbilical artery pH <7.00, base excess <-16.00, and five-minute Apgar score 0-3	20	1	5.0 %	99.9 %	1	5.0 %	99.7 %	1	5.0 %	99.9 %	1	5.0 %	99.6 %	1	5.0 %	99.2 %	5	25.0 %	99.9 %

* Sensorineural defects include impairments of vision and hearing.

† Mortality by the first year.