Associations between metabolic acidosis at birth and reduced Apgar scores within the normal range (7-10): A Swedish cohort study of term non-malformed infants

Sven Cnattingius1 | Stefan Johansson1,2 | Neda Razaz1

Abstract

Background: Risks of neonatal and long-term neurological outcomes are influenced by metabolic acidosis at birth and by reduced Apgar scores, even within the normal range (7-10).

Objective: To analyse associations between metabolic acidosis at birth and risks of reduced Apgar scores within the normal range.

Methods: In a Swedish cohort of term non-malformed infants born between 2008 and 2013, we included 81 861 infants with information from cord blood gas analyses and Apgar score values of 7-10 at 1, 5, and 10 minutes. Poisson log-linear regression analyses were used to examine associations between metabolic acidosis at birth (defined as pH <7.05 or <7.10 and base deficit ≥12) and Apgar score values of 7-10 at 1, 5, and 10 minutes. Adjusted risk ratios (RRs) and risk differences (RDs) were calculated, using 95% confidence intervals (CI).

Results: Compared with infants without metabolic acidosis, the adjusted RR of an Apgar score of 9 at 5 minutes was 3.14 (95% CI 2.57, 3.84) in infants with metabolic acidosis (pH <7.05 as cut-off), and 10.13 (95% CI 7.63, 13.45) and 7.60 (95% CI 3.54, 16.33) for Apgar scores of 8 and 7, respectively. Corresponding RRs of Apgar scores at 10 minutes were also substantially increased. The magnitude of RDs varied, but was consistently increased. Both reduced Apgar scores and metabolic acidosis (pH <7.10) influenced neonatal morbidity.

Conclusions: Metabolic acidosis is associated with increased risks of reduced Apgar scores within the normal range. Due to international variations in the assessment of Apgar score, our findings need to be confirmed in other populations.

Keywords: Apgar score, metabolic acidosis, neonatal morbidity, risk
Apgar score is an imprecise, but universally used method to assess the newborn’s health. An Apgar score of <7 at 1 minute may indicate temporary depression, while markedly reduced Apgar scores (especially scores 0-3) at 5 or 10 minutes are associated with substantially increased risks of asphyxia-related neonatal morbidity, childhood epilepsy, and cerebral palsy (CP). However, Apgar score may also be influenced by gestational age, birthweight for gestational age, maternal drugs, fever during labour, congenital infections, and neurological diseases.

Within term (≥37 weeks) non-malformed infants with normal Apgar scores (7-10) at 1, 5, and 10 minutes, we recently found inverse associations between Apgar scores and risks of neonatal mortality and morbidity. Reduced Apgar scores of 7-9 at 10 minutes were generally associated with the highest risks. We and others have reported similar findings with respect to Apgar scores within the normal range and risks of long-term outcomes, including CP and epilepsy, autism, developmental physical or emotional vulnerability in childhood, and increasing needs of education in special schools.

Arterial umbilical cord blood analysis immediately after birth aims to assess intrapartal fetal stress, and metabolic acidosis may indicate birth asphyxia. Metabolic acidosis is associated with neonatal death, low (<7) Apgar score at 5 minutes, asphyxia-related morbidities, and long-term neurological outcomes, including CP. Whether metabolic acidosis influences Apgar score values within the normal range is not known.

In this Swedish cohort study, we included more than 80 000 term non-malformed infants with information from umbilical artery blood gas analyses. The primary objective of this study was to investigate associations between metabolic acidosis and risks of Apgar scores of 7, 8, and 9 at 5 and 10 minutes. We also estimated the joint impact of metabolic acidosis and Apgar score values within the normal range (7-10), with respect to risk of neonatal morbidity.

2 | METHODS

2.1 | Data sources and study population

This population-based cohort study was based on the Stockholm-Gotland Obstetrical Database, covering all antenatal, obstetric, and neonatal care within the counties of Stockholm and Gotland, Sweden. Data included information from standardised and computerised antenatal, obstetric, and neonatal records. Information was prospectively recorded from the first antenatal visit and until postpartum discharge.

Records from the Stockholm-Gotland Obstetrical Database were individually linked with nationwide on Swedish registries: the Medical Birth Register (including information about >98% of all births), the Patient Register (including dates and diagnoses of all inpatient and outpatient hospital care), and the Swedish Population Register. We also linked the database to the Swedish Neonatal Quality Register.

Synopsis

Study question

Does metabolic acidosis at birth increase risks of reduced Apgar scores within the normal range (7-10) in term non-malformed infants?

What is already known

Fetal distress and birth asphyxia may precede metabolic acidosis, which influences neonatal and long-term morbidity risks. Apgar score is an imprecise tool to assess newborn’s health. Risks of neonatal mortality, morbidity, and long-term neurological morbidity increase with reduced Apgar scores at 5 and 10 minutes even within the normal range.

What this study adds

Metabolic acidosis at birth is associated with substantially increased risks of Apgar scores of 7, 8, and 9 at 5 and 10 minutes, respectively. An Apgar score between 7 and 9 at 5 or 10 minutes may not be an optimal Apgar score.
which includes detailed information of all infants subjected to neonatal intensive care. Maternal and offspring diseases were coded according to the International Classification of Diseases, tenth revision (ICD-10). The study was approved by the Regional Ethical Review Board in Stockholm, Sweden (No. 2009/275-31 and No. 2012/365-32).

Of 149,298 liveborn singleton infants delivered in the Stockholm-Gotland region between 2008 and 2013, we included infants from five delivery units performing routine cord sampling (n = 130,302). We excluded preterm born infants (<37 completed gestational weeks; n = 6,243) and infants with major congenital malformations (n = 7,323; see Table S1 for ICD-10 codes). Of 116,736 term non-malformed infants, we excluded 27% (n = 31,597) with either unrecorded umbilical cord arterial blood pH (n = 30,415), missing base deficit (n = 1156), or pH values likely to be erroneous (<6.4 or >7.7; n = 26). There were only minor differences in maternal and birth characteristics and Apgar scores between births with and without information on blood gas analysis (Table S2).

Of 85,139 infants with information on blood gas analysis, complete information on Apgar scores at 1, 5, and 10 minutes was available for 85,076 infants (99.9%). The main analyses were restricted to infants with Apgar scores of 7 to 10 at 1, 5, and 10 minutes (n = 81,861). The cohort selection is detailed in Figure 1.

2.2 | Main exposure

Blood gases were measured in umbilical arterial cord blood at birth. Metabolic acidosis was defined as a pH value <7.05 combined with a base deficit value ≥12 mmol/L and as a pH value <7.10 combined with a base deficit value ≥12 mmol/L. In analyses of neonatal morbidity, we used the broader definition of metabolic acidosis (ie pH value <7.10 combined with a base deficit value ≥12 mmol/L), due to power concerns.

2.3 | Covariates

Maternal age at delivery was computed from the mother’s birth date and the date of delivery. Parity, smoking habits, and maternal height were self-reported at the first antenatal visit. Maternal body mass index (BMI) in early pregnancy was calculated from measured weight at the first antenatal visit divided by squared height (kg/m²). Information on mother’s country of birth was obtained from the Swedish Population Register. Infant sex, birthweight, and date of delivery were recorded by the midwife immediately after delivery. Gestational age was determined using the following hierarchy: (a) date of embryo transfer (3.9%), (b) early second trimester ultrasound (94.3%), and (c) date of last menstrual period (1.8%). Birthweight for gestational age was estimated using the sex-specific Swedish reference curve for normal fetal growth. Mode of delivery was recorded in standardised checkboxes as non-instrumental or instrumental vaginal delivery, or as emergency or elective caesarean section (CS). Variables were categorised as presented in Table 1.

2.4 | Outcomes

Our main outcomes were Apgar scores at 1, 5, and 10 minutes after birth. In addition, we also studied the combined impact of metabolic acidosis and Apgar scores at 5 and 10 minutes on risks of neonatal morbidity, including respiratory distress, neonatal infections, and neonatal hypoglycaemia. Because of power concerns, we could not investigate risks of neonatal convulsions/seizures, hypoxic-ischaemic encephalopathy, and related conditions (see Table S1 for specific ICD-10 codes).

2.5 | Statistical analysis

Descriptive statistics of maternal and infant characteristics and metabolic acidosis are presented as numbers and rates (Table 1). Poisson log-linear models were used to examine associations between metabolic acidosis and Apgar scores of 7 and 8 at 1, 5, and 10 minutes, and Apgar scores of 7, 8, and 9 at 5 and 10 minutes as the dependent variables. Risk ratios (RRs) were calculated, with 95% confidence intervals (CI). We further quantified associations between metabolic acidosis and the magnitude of absolute effects by calculating risk differences for each Apgar score value. The risk difference (RD) represents the number of excess cases of low Apgar score per 100 births among infants with metabolic acidosis compared with infants without metabolic acidosis. In the multivariable analyses, RR and RD estimates were adjusted for maternal characteristics (age, parity, height, BMI, country of birth, and smoking), infant sex, gestational age, birthweight for gestational age, and year of birth. We used a casual diagram to guide the selection of confounders in our multivariable model (Figure S1). We considered both gestational age and birthweight for gestational age as confounders, given that both influence umbilical artery blood gases at birth and Apgar score values in term infants. Mode of delivery is also associated with metabolic acidosis and reduced Apgar scores. However, an emergency caesarean section or vaginal instrumental delivery may be caused by (confirmed or suspected) fetal asphyxia. Since mode of delivery may also act as a mediator, it was not included in the analysis. Poisson log-linear regression analysis was also used when studying the combined impact of metabolic acidosis (pH cut-off value <7.10) and Apgar scores and risks of neonatal morbidity. We categorised our exposure into four groups: infants with or without metabolic acidosis, and infants with Apgar scores of 7-8 vs 9-10 at 5 or 10 minutes. Due to limited statistical power, we only adjusted for gestational age in multivariable analyses. The SAS software package version 9.4 (SAS Institute Inc) was used for statistical analyses.

3 | RESULTS

3.1 | Metabolic acidosis and Apgar scores

Of 81,861 term non-malformed infants with normal Apgar scores (7-10) at 1, 5, and 10 minutes, 450 (0.5%) had severe metabolic acidosis,
defined as pH < 7.05 and base deficit ≥ 12 mmol/L, and 997 (1.2%) had metabolic acidosis defined as pH < 7.10 and base deficit ≥ 12 mmol/L (Table 1). Rates of metabolic acidosis were increased in infants of primiparous mothers, overweight, or obese mothers (BMI ≥ 25), and increased with decreasing maternal height. Rate of acidosis was also increased in later birth years (2012-2013), in infants with low birthweight for gestational age (<10th percentile), and increased with gestational age. Infants born through vaginal instrumental deliveries or emergency caesarean sections had higher rates of metabolic acidosis than infants with elective caesarean or non-instrumental vaginal deliveries.

Most (81%) infants had an Apgar score of 9 at 1 minute, while at 5 and 10 minutes, 92% and 98% had an Apgar score of 10 (Table 2). At one minute, 29.8% of infants with metabolic acidosis (pH < 7.05) had

| TABLE 1 | Metabolic acidosis by maternal and infant characteristics. Non-malformed singleton term (≥37 wk) births with normal Apgar scores (7-10) in Sweden 2008-2013 |
| Maternal and infant characteristics | Metabolic acidosis |
|-----------------------------------|------------------|
| | No acidosis<sup>a</sup> | pH < 7.05 and base deficit ≥ 12 mmol/L | pH < 7.10 and base deficit ≥ 12 mmol/L |
| No. (%)<sup>b</sup> | No. (%)<sup>b</sup> | No. (%)<sup>b</sup> |
| Total | 80 864 (98.8) | 450 (0.5) | 997 (1.2) |
| Maternal age (years) | | | |
| ≤19 | 870 (99.1) | 2 (0.2) | 8 (0.9) |
| 20-24 | 7862 (98.7) | 46 (0.6) | 102 (1.3) |
| 25-29 | 20 422 (98.8) | 99 (0.5) | 239 (1.2) |
| 30-34 | 29 791 (98.8) | 182 (0.6) | 377 (1.2) |
| ≥35 | 21 919 (98.8) | 121 (0.5) | 271 (1.2) |
| Parity | | | |
| 1 | 38 149 (98.3) | 275 (0.7) | 652 (1.7) |
| 2 | 29 153 (99.1) | 133 (0.5) | 251 (0.9) |
| 3 | 9838 (99.4) | 27 (0.3) | 64 (0.6) |
| 4+ | 3724 (99.2) | 15 (0.4) | 30 (0.8) |
| Maternal height (cm) | | | |
| ≤159 | 11 244 (98.7) | 77 (0.7) | 152 (1.3) |
| 160-164 | 20 103 (98.6) | 131 (0.6) | 286 (1.4) |
| 165-169 | 22 803 (98.8) | 125 (0.5) | 284 (1.2) |
| ≥170 | 25 974 (99.0) | 111 (0.4) | 265 (1.0) |
| Missing | 740 (98.7) | 6 (0.8) | 10 (1.3) |
| Maternal BMI | | | |
| <18.5 | 2157 (99.1) | 10 (0.5) | 20 (0.9) |
| 18.5-24.9 | 50 557 (98.9) | 257 (0.5) | 575 (1.1) |
| 25.0-29.9 | 17 592 (98.5) | 117 (0.7) | 266 (1.5) |
| 30.0-34.9 | 5468 (98.8) | 32 (0.6) | 68 (1.2) |
| ≥35.0 | 1937 (98.4) | 20 (1.0) | 32 (1.6) |
| Missing | 3153 (98.9) | 14 (0.4) | 36 (1.1) |
| Country of birth | | | |
| Sweden | 55 260 (98.7) | 315 (0.6) | 710 (1.3) |
| Nordic | 1348 (98.4) | 9 (0.7) | 22 (1.6) |
| Non-nordic | 23 043 (99.0) | 118 (0.5) | 244 (1.0) |
| Missing | 1213 (98.3) | 8 (0.6) | 21 (1.7) |
| Smoking | | | |
| No | 76 425 (98.8) | 432 (0.6) | 949 (1.2) |
| Yes | 4345 (98.9) | 17 (0.4) | 47 (1.1) |
| Missing | 94 (98.9) | 1 (1.1) | 1 (1.1) |
| Year of delivery | | | |
| 2008-2009 | 21 301 (99.1) | 81 (0.4) | 199 (0.9) |
| 2010-2011 | 30 852 (98.8) | 169 (0.5) | 360 (1.2) |
| 2012-2013 | 28 711 (98.5) | 200 (0.7) | 438 (1.5) |
| Infant sex (Continues) |

<sup>a</sup>Numbers in the no acidosis group exclude births without metabolic acidosis, defined as pH < 7.10 and base deficit ≥ 12 mmol/L. Births in the middle column (pH < 7.05) are also included in the right column (pH < 7.10).

<sup>b</sup>Rates refer to row percentages.

defined as Ph < 7.05 and base deficit ≥ 12 mmol/L, and 997 (1.2%) had metabolic acidosis defined as pH < 7.10 and base deficit ≥ 12 mmol/L (Table 1). Rates of metabolic acidosis were increased in infants of primiparous mothers, overweight, or obese mothers (BMI ≥ 25), and increased with decreasing maternal height. Rate of acidosis was also increased in later birth years (2012-2013), in infants with low birthweight for gestational age (<10th percentile), and increased with gestational age. Infants born through vaginal instrumental deliveries or emergency caesarean sections had higher rates of metabolic acidosis than infants with elective caesarean or non-instrumental vaginal deliveries.

Most (81%) infants had an Apgar score of 9 at 1 minute, while at 5 and 10 minutes, 92% and 98% had an Apgar score of 10 (Table 2). At one minute, 29.8% of infants with metabolic acidosis (pH < 7.05) had
an Apgar score of 7, while corresponding rates at 5 and 10 minutes were 1.6% and 0.4%, respectively.

Compared with infants without acidosis, the adjusted RRs of Apgar scores of 8 and 7 at 1 minute were approximately 4- and 8-fold higher among infants with severe metabolic acidosis. Slightly less pronounced RRs were obtained when we used a higher pH cut-off to define metabolic acidosis (pH <7.10). The adjusted RDs between metabolic acidosis (yes vs no) and a 1 minute Apgar score of 7 or 8 were substantial, ranging between 20% and 26% (Table 3, upper panel). Similar results were obtained when we did not adjust for birthweight for gestational age (data not shown).

Compared with infants without severe metabolic acidosis, the adjusted RRs of an Apgar score of 9 at 5 minutes were more than 3-fold higher in infants with severe metabolic acidosis, and corresponding RRs for Apgar scores of 8 and 7 were more than 10- and 7-fold higher, respectively. When we used a higher pH cut-off (<7.10) for defining metabolic acidosis, corresponding RRs were also increased. The adjusted RDs ranged from 1.2% to 16% (Table 3, middle panel).

At 10 minutes, infants with metabolic acidosis had also, regardless of definition, substantially increased RRs of Apgar scores of 9, 8, and 7, compared with infants without metabolic acidosis. Metabolic acidosis was also associated with increased RDs in Apgar score at 10 minutes, although the estimates were lower than at 1 and 5 minutes (Table 3, lower panel).

3.2 | Metabolic acidosis, Apgar scores, and neonatal morbidity

Rates of neonatal morbidities were lowest in infants with no metabolic acidosis (pH cut-off value <7.10) and Apgar scores of 9-10 at 5 or 10 minutes, and generally highest among infants with the combination of metabolic acidosis and Apgar scores of 7-8 (Table 4). Both in infants with and without metabolic acidosis, infants with Apgar scores of 7-8 had generally higher morbidity rates compared with infants with Apgar scores of 9-10.

In the multivariable analysis of neonatal morbidity, we only adjusted for gestational age because of power concerns. Compared with infants without metabolic acidosis and 5 minutes Apgar score of 9-10, infants with metabolic acidosis and similar Apgar scores had more than threefold increased RR of respiratory distress, non-acidotic infants with Apgar score of 7-8 had a 17-fold increase in RR, and acidotic infants with Apgar score of 7-8 had a 19-fold increase in RR. For Apgar score at 10 minutes and respiratory distress, the RRs...
were generally higher. Apgar score and metabolic acidosis were also similarly associated with RRs of neonatal infections and hypoglycaemia, although RR estimates were lower.

4 | COMMENT

4.1 | Principal findings

In this population-based Swedish cohort study of term non-malformed infants with normal Apgar scores (7-10), we found that metabolic acidosis was associated with substantially increased risks of reduced Apgar scores within the normal range (ie <9 at 1 minute or <10 at 5 and 10 minutes, respectively). We also found that the combination of metabolic acidosis (yes vs. no) and Apgar scores at 5 minutes (7-8 vs 9-10) influenced risks of neonatal morbidity.

4.2 | Strengths of the study

Study strengths include using original and prospectively collected information from standardised antenatal, obstetric, and neonatal records. Information on Apgar scores was virtually complete, and follow-up was complete.

4.3 | Limitations of the data

We excluded a large proportion (27%) of eligible births due to missing information on blood gases. However, there were only minor differences in maternal and birth characteristics and Apgar scores between births with and without information from blood gas analysis (Table S2). The low absolute risk differences of an Apgar score of 7 at 5 and 10 minutes may be an effect of overall low rate of an Apgar score of 7. Still, the low number of infants with metabolic acidosis and an Apgar score of 7 indicate that these analyses may be hampered by limited statistical power. Our study was conducted within two counties of Sweden, and Apgar scores are in low-risk deliveries generally assessed by the midwife assisting the mother at delivery. The interobserver variability of assessing the Apgar score is considered substantial, and we do not know whether the interobserver variability differs with respect to results from blood gas analyses. However, our experience is that results of the umbilical cord gas are usually not readily available within the first

### Table 3

| pH <7.05 and base deficit ≥12 mmol/L | Apgar score 1 min | Apgar score 5 min | Apgar score 10 min |
|-------------------------------------|------------------|-------------------|-------------------|
| **Apgar 7**                         | **Apgar 8**      | **Apgar 9**       |
| RR (95% CI)                         | RR (95% CI)      | RR (95% CI)       |
| pH <7.05                            |                  |                   |
| Yes                                 | 7.97 (6.65, 9.55)| 3.97 (3.35, 4.71)| 3.14 (2.57, 3.84)|
| No                                  | 1.00 (Reference) | 1.00 (Reference)  | 1.00 (Reference) |
| pH <7.10                            |                  |                   |
| Yes                                 | 6.63 (5.76, 7.62)| 3.55 (3.14, 4.02)| 2.71 (2.33, 3.14)|
| No                                  | 1.00 (Reference) | 1.00 (Reference)  | 1.00 (Reference) |
| **Apgar score 5 min**               |                  |                   |
| pH <7.05                            |                  |                   |
| Yes                                 | 7.60 (3.54, 16.33)| 10.13 (7.63, 13.45)| 3.14 (2.57, 3.84)|
| No                                  | 1.00 (Reference) | 1.00 (Reference)  | 1.00 (Reference) |
| pH <7.10                            |                  |                   |
| Yes                                 | 6.36 (3.58, 11.31)| 8.49 (6.82, 10.57)| 2.71 (2.33, 3.14)|
| No                                  | 1.00 (Reference) | 1.00 (Reference)  | 1.00 (Reference) |
| **Apgar score 10 min**              |                  |                   |
| pH <7.05                            |                  |                   |
| Yes                                 | 7.43 (1.78, 31.06)| 15.04 (9.21, 24.56)| 6.34 (4.68, 8.58)|
| No                                  | 1.00 (Reference) | 1.00 (Reference)  | 1.00 (Reference) |
| pH <7.10                            |                  |                   |
| Yes                                 | 4.94 (1.51, 16.14)| 13.22 (8.98, 19.46)| 4.55 (3.56, 5.82)|
| No                                  | 1.00 (Reference) | 1.00 (Reference)  | 1.00 (Reference) |

*Adjusted for maternal smoking, age at childbirth, country of birth, height, pre-pregnancy BMI, parity, infant sex, gestational age, birthweight for gestational age, and year of birth.
ten minutes after delivery. There are also substantial international variations in Apgar score values at 5 minutes, especially within the normal range (7-10). Thus, our results need to be confirmed in other populations.

### 4.4 Interpretation

Initially, the Apgar score was developed to assess the infant’s viability and need of resuscitation at 1 minute of age. Later on, information of Apgar score at 5 minutes was used as a tool to assess the infant’s response to resuscitation. Apgar scores of 0-3 has, since the early 1960s, been defined as a low score, and an Apgar score of 4-6 as a moderately low score. Low and moderately low Apgar scores at 5 or 10 minutes are associated with substantially increased risks of asphyxia-related neonatal and long-term morbidities. A large Scottish study found that low and moderately low Apgar scores were primarily associated with risks of infant deaths attributed to anoxia.

An Apgar score of 7-10 at 5 minutes has been considered as reassuring, and in some countries Apgar score at 10 minutes is only measured if the 5 minutes Apgar score is less than 7. Still, we and others have recently found associations between progressively reduced normal Apgar scores (ie with scores of 7, 8, and 9) at 1, 5, or 10 minutes and increasing risks of neonatal mortality and morbidity, and long-term morbidity in term infants. For example, compared with infants with Apgar score of 10 at 5 minutes, infants with Apgar score of 7 had more than 5-fold increased risk of neonatal mortality and a 7-fold increased risk of cerebral palsy. The lowest risks were consistently obtained for infants with Apgar scores of 10 at both 5 and 10 minutes.

Fetal distress and intrapartal asphyxia may, if prolonged, lead to metabolic acidosis. The neonatal risks are reported to increase with a lower pH threshold, and associations between umbilical cord pH and neonatal morbidity are reported to be present in both high- and low-risk populations. In a study of term non-malformed infants with normal Apgar scores (7-10) at 5 minutes, metabolic acidosis was associated with a substantially increased risk of respiratory distress syndrome. Apgar score is influenced by many factors and should not be used to define birth asphyxia. Within this population of term non-anomalous infants with normal Apgar scores (7-10) at 1, 5, and 10 minutes, we found that metabolic acidosis was associated with substantially increased risks of reduced Apgar scores within the normal range. Our results also suggest that the combination of metabolic acidosis (yes vs no) and Apgar score at 5 minutes (7-8 vs 9-10) was associated with increased risks of neonatal morbidity. These morbidity risks were, if anything, more influenced by Apgar score than metabolic acidosis, although the results may be hampered by statistical power. Nevertheless, another study found that both low Apgar score (0-3) at 5 minutes and umbilical artery pH ≤7.0 increased risks of neonatal mortality in term infants, but low Apgar score was associated with an eightfold higher risk than low pH.

We found that metabolic acidosis is associated with increased risks of reduced Apgar score values within the normal range. This may in turn explain that term infants with reduced Apgar scores within the normal range are reported to be at increased risks of neonatal mortality and morbidity, and long-term outcomes related to neurodevelopment. Our results further support that a “normal” Apgar score (ie 7-9) is not an optimal Apgar score and that the highest risks of neonatal morbidity are reported for infants with reduced Apgar score at

### TABLE 4 Combination of metabolic acidosis (pH <7.10 and base deficit ≥12 mmol/L) and Apgar scores and risks of neonatal morbidities

| Neonatal morbidity | Metabolic acidosis | Apgar score | No. (%) | Adjusted risk ratio (95% CI)* | No. (%) | Adjusted risk ratio (95% CI)* |
|--------------------|--------------------|-------------|---------|------------------------------|---------|------------------------------|
| Respiratory distress | Yes | 7-8 | 32 (28.8) | 19.38 (13.62, 27.58) | 17 (48.6) | 30.35 (18.79, 49.04) |
| No | 7-8 | 250 (25.3) | 16.96 (14.79, 19.45) | 107 (48.0) | 29.28 (24.04, 35.67) |
| Yes | 9-10 | 45 (5.1) | 3.50 (2.59, 4.71) | 60 (6.2) | 3.83 (2.96, 4.97) |
| No | 9-10 | 1152 (1.4) | 1.00 (Reference) | 1295 (1.6) | 1.00 (Reference) |
| Infections | Yes | 7-8 | 5 (4.5) | 9.30 (3.84, 22.53) | 3 (8.6) | 17.47 (5.60, 54.49) |
| No | 7-8 | 18 (1.8) | 3.96 (2.47, 6.36) | 6 (2.7) | 5.77 (2.58, 12.93) |
| Yes | 9-10 | 7 (0.8) | 1.67 (0.79, 3.53) | 9 (0.9) | 1.93 (0.99, 3.74) |
| No | 9-10 | 366 (0.5) | 1.00 (Reference) | 378 (0.5) | 1.00 (Reference) |
| Hypoglycaemia | Yes | 7-8 | 11 (9.9) | 4.97 (2.74, 8.99) | 2 (5.7) | 2.97 (0.74, 11.89) |
| No | 7-8 | 79 (8.0) | 3.19 (2.55, 4.00) | 29 (13.0) | 5.19 (3.60, 7.49) |
| Yes | 9-10 | 53 (6.0) | 2.80 (2.13, 3.68) | 62 (6.4) | 2.98 (2.31, 3.84) |
| No | 9-10 | 1891 (2.4) | 1.00 (Reference) | 1941 (2.4) | 1.00 (Reference) |

*Adjusted for gestational age.
10 minutes. Taken together with previous findings,2,9 we would advise that that Apgar score should be routinely measured on all infants at 10 minutes, regardless of their scores at 1 and 5 minutes. Infants with a 10-minute Apgar score of <10 should be continuously assessed until their status corresponds to a 10-point Apgar score. Infants that continue to exhibit symptoms or signs covered by the Apgar scoring, such as decreased muscle tone, should be considered for observation in the neonatal intensive care unit (NICU).

Current knowledge of long-term consequences of metabolic acidosis is primarily based on results from meta-analyses or consecutively collected large samples of umbilical cord arterial blood gas analyses.14,15 If umbilical artery blood gas analyses were routinely analysed and added to large databases with prospective follow-up, this would render excellent future possibilities to perform high-quality studies of long-term consequences of metabolic acidosis at birth.

4.5 Conclusions

To summarise, metabolic acidosis was associated with markedly increased risks of reduced Apgar scores in term non-malformed infants with normal (7-10) Apgar scores at 1, 5, and 10 minutes. Apgar scores of 7-9 at 5 and 10 minutes have previously been reported to be associated with increased risks of neonatal mortality and morbidity and long-term neurological morbidity. Fetal distress and birth asphyxia may be the preceding events leading to metabolic acidosis, resulting in a reduced Apgar score within the normal range, with neonatal and long-term consequences. Thus, a “normal” Apgar score of 7-9 may not be an optimal Apgar score. Due to international variations in the assessment of Apgar score within the normal range,27 these risks may vary between populations. Needless to say, Apgar score continues to be an important measure in the 21st century.

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CONFLICTS OF INTEREST

The authors report no conflicts of interest.

ORCID

Sven Cnattingius https://orcid.org/0000-0002-0805-8093

REFERENCES

1. American Academy of Pediatrics Committee on Fetus and Newborn; American College of Obstetricians and Gynecologists Committee on Obstetric Practice. The Apgar score. Pediatrics. 2015;136:819-822.
2. Persson M, Razaz N, Tedroff K, Joseph KS, Cnattingius S. Five and 10 minute Apgar scores and risks of cerebral palsy and epilepsy: population based cohort study in Sweden. Br Med J. 2018;360:k207.
3. Casey BM, McEntire DD, Leveno KJ. The continuing value of the Apgar score for the assessment of newborn infants. N Engl J Med. 2001;344:467-471.
4. Ilodromiti S, Mackay DF, Smith GC, Pell JP, Nelson SM. Apgar score and the risk of cause-specific infant mortality: a population-based cohort study. Lancet. 2014;384:1749-1755.
5. Nelson KB, Ellenberg JH. Apgar scores as predictors of chronic neurologic disability. Pediatrics. 1981;68:36-44.
6. Villamor E, Tedroff K, Peterson M, et al. Association between maternal body mass index in early pregnancy and incidence of cerebral palsy. JAMA. 2017;317:925-936.
7. Razaz N, Tedroff K, Villamor E, Cnattingius S. Maternal body mass index in early pregnancy and risk of epilepsy in offspring. JAMA Neurol. 2017;74:668-676.
8. Razaz N, Cnattingius S, Persson M, Tedroff K, Lisonkova S, Joseph KS. One-minute and five-minute Apgar scores and child development mental health at 5 years of age: a population-based cohort study in British Columbia, Canada. Br Med J Open. 2019;9:e027655.
9. Razaz N, Cnattingius S, Joseph K. Association between Apgar scores of 7 to 9 and neonatal mortality and morbidity: population based cohort study of term infants in Sweden. Br Med J. 2019;365:l1656.
10. Modabbernia A, Sandin S, Gross R, et al. Apgar score and risk of autism. Eur J Epidemiol. 2019;34:105-114.
11. Razaz N, Boyce WT, Brownell M, et al. Five-minute Apgar score as a marker for developmental vulnerability at 5 years of age. Arch Dis Child Fetal Neonatal Ed. 2016;101:F114-120.
12. Stuart A, Otterblad Olausson P, Kallen K. Apgar scores at 5 minutes after birth in relation to school performance at 16 years of age. Obstet Gynecol. 2011;118:201-208.
13. Armstrong L, Stenson BJ. Use of umbilical cord blood gas analysis in the assessment of the newborn. Arch Dis Child Fetal Neonat Ed. 2007;92:430-434.
14. Malin GL, Morris RK, Khan KS. Strength of association between umbilical cord pH and perinatal and long term outcomes: systematic review and meta-analysis. Br Med J. 2010;340:c1471.
15. Yeh P, Emary K, Impey L. The relationship between umbilical cord arterial pH and serious adverse neonatal outcome: analysis of 51,519 consecutive validated samples. Br J Obstet Gynaecol. 2012;119:824-831.
16. Stephansson O, Sandstrom A, Petersson G, Wikstrom AK, Cnattingius S. Prolonged second stage of labour, maternal infectious disease, urinary retention and other complications in the early postpartum period. Br J Obstet Gynaecol. 2016;123:608-616.
17. Swedish National Board of Health and Welfare. The Swedish Medical Birth Register. A summary of content and quality. 2003. Available from: http://www.socialstyrelsen.se/Lists/Artikelkatalog/Attachment s/10655/2003-112-3_20031123.pdf.
18. Ludvigsson JF, Andersson E, Ekbom A, et al. External review and validation of the Swedish national inpatient register. BMC Public Health. 2011;11:450.
19. Ludvigsson JF, Almqvist C, Bonamy AK, et al. Registers of the Swedish total population and their use in medical research. Eur J Epidemiol. 2016;31:125-136.
20. Refsum E, Hakansson S, Mortberg A, Wikman A, Westgren M. Intracranial hemorrhages in neonates born from 32 weeks of gestation-low frequency of associated fetal and neonatal alloimmune thrombocytopenia: a register-based study. Transfusion. 2018;58:223-231.
21. Sabol BA, Caughey AB. Acidemia in neonates with a 5-minute Apgar score of 7 or greater - What are the outcomes? Am J Obstet Gynecol. 2016;215(486):e481-486.
22. Skio1d B, Petersson G, Ahlberg M, Stephansson O, Johansson S. Population-based reference curve for umbilical cord arterial pH in infants born at 28 to 42 weeks. *J Perinatol*. 2017;37:254-259.
23. Marsal K, Persson PH, Larsen T, Lilja H, Selbing A, Sultan B. Intrauterine growth curves based on ultrasonically estimated foetal weights. *Acta Paediatr*. 1996;85:843-848.
24. Pallotto EK, Kilbride HW. Perinatal outcome and later implications of intrauterine growth restriction. *Clin Obstet Gynecol*. 2006;49:257-269.
25. Prior T, Kumar S. Mode of delivery has an independent impact on neonatal condition at birth. *Eur J Obstet Gynecol Reprod Biol*. 2014;181:135-139.
26. O’Donnell CPF, Kamlin COF, Davis PG, Carlin JB, Morley CJ. Interobserver variability of the 5-minute Apgar score. *J Pediatr*. 2006;149:486-489.
27. Siddiqui A, Cuttini M, Wood R, et al. Can the Apgar score be used for international comparisons of newborn health? *Paediatr Perinat Epidemiol*. 2017;31:338-345.
28. Apgar V. A proposal for a new method of evaluation of the newborn infant. *Curr Res Anesth Analg*. 1953;32:260-267.
29. James LS. Acidosis of the newborn and its relation to birth asphyxia. *Acta Paediatr Suppl*. 1960;49(Suppl 122):17-28.
30. Freeman JM, Nelson KB. Intrapartum asphyxia and cerebral palsy. *Pediatrics*. 1988;82:240-249.
31. Lie KK, Groholt EK, Eskild A. Association of cerebral palsy with Apgar score in low and normal birthweight infants: population based cohort study. *Br Med J*. 2010;341:c4990.
32. Salutiano EMA, Campos JADB, Ibidi SM, Ruano R, Zugaib M. Low Apgar scores at 5 minutes in a low risk population: maternal and obstetrical factors and postnatal outcome. *Rev Assoc Med Bras*. 2012;58:587-593.
33. Sun Y, Vestergaard M, Pedersen CB, Christensen J, Olsen J. Apgar scores and long-term risk of epilepsy. *Epidemiology*. 2006;17:296-301.

**SUPPORTING INFORMATION**
Additional supporting information may be found online in the Supporting Information section.

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