

## CLINICAL ARTICLE

## Obstetrics

# Different antecedents and neonatal condition in neonatal arterial ischemic stroke and hypoxic-ischemic neonatal encephalopathy

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**Abstract**

**Objective:** To define similarities and differences between neonatal arterial ischemic stroke (NAIS) and hypoxic-ischemic neonatal encephalopathy (HINE).

**Methods:** A retrospective case-control study was conducted of neonates born at 35 weeks or more and weighing 1800 g or more at a tertiary care university hospital, between 2005 and 2016, with NAIS (group A), perinatal asphyxia (PA) with Stage II-III HINE (group B), and PA with or without Stage I HINE (group C). Ante- and intrapartum data, neonatal characteristics, and placental histopathology were compared.

**Results:** Eleven neonates were identified in group A, 10 in group B, and 227 in group C. Sentinel events occurred exclusively in groups B (80%) and C (41.4%). Umbilical cord blood gas values and Apgar score were worse in groups B and C compared to group A. No group A neonates required resuscitation at birth, whereas all group B and one-third of group C neonates did. Seizures developed only in neonates in groups A and B. One neonatal death occurred in group A. There were no significant differences in placental histopathology.

**Conclusion:** NAIS and PA/HINE cases have different intrapartum and neonatal features. PA does not seem necessary for the occurrence of NAIS. More research is needed regarding associated placental abnormalities.

**KEYWORDS**

encephalopathy, hypoxic-ischemic neonatal, neonatal arterial ischemic stroke, neonatal seizures, perinatal asphyxia, placental histology, sentinel events, umbilical artery pH

**1 | INTRODUCTION**

Ischemic perinatal stroke (IPS) is defined as "a group of heterogeneous conditions in which there is focal disruption of cerebral blood flow secondary to arterial or cerebral venous thrombosis, occurring between 20 weeks

of fetal life through the 28th postnatal day, and confirmed by neuroimaging or neuropathological studies".<sup>1</sup> In particular, neonatal arterial ischemic stroke (NAIS) refers to arterial events that manifest early in life.

The prevalence of NAIS is in the range of 6–17/100 000<sup>2–7</sup> and the mortality rate is in the range of 2%–5%. NAIS is the predominant

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cause of hemiplegic cerebral palsy in term/late preterm neonates.<sup>8-10</sup> Its complex pathogenesis has not been solved yet.

The role of hypoxia and perinatal asphyxia and hypoxic-ischemic neonatal encephalopathy (HINE) has been extensively investigated. Perinatal asphyxia concomitant to NAIS has been demonstrated in various studies.<sup>10-12</sup> In addition, similar intrapartum antecedents in infants with HINE and NAIS have been identified.<sup>13</sup> However, a recent report affirms that HINE and NAIS are two distinct entities, although possibly co-occurring.<sup>14</sup>

Alongside clinical factors, placental histological examination can provide additional insights.<sup>15-17</sup> Placental thrombosis, infection, and inflammation have been associated with neonatal neurologic injury.<sup>18-23</sup> A retrospective case-control study has reported a higher prevalence of placental pathology in IPS compared to controls without stroke<sup>24</sup> and placental abnormalities in infants with stroke were different from those previously described in hypoxic-ischemic injury.<sup>25</sup>

The aim of the present study was to investigate ante- and intrapartum characteristics, neonatal features, and placental histology of infants diagnosed with NAIS or HINE at a tertiary care center in order to define similarities and differences between these two conditions.

## 2 | MATERIALS AND METHODS

This is a retrospective case-control study including neonates born at 35 weeks or over with a birthweight of 1800 g or more and no lethal malformations at a tertiary care university hospital between 2005 and 2016 and diagnosed with (i) NAIS, defined as focal disruption of cerebral blood flow secondary to arterial thrombosis, diagnosed by magnetic resonance imaging during the neonatal period, (ii) perinatal asphyxia with the development of moderate or severe HINE (Stage II–III) according to modified Sarnat score,<sup>26,27</sup> and (iii) perinatal asphyxia with or without the development of mild HINE (Stage I).

Perinatal asphyxia was defined as pH of 7.0 or less or base excess (BE) –12 mMol/L or less in the umbilical artery within 1 h after birth, 10-minute Apgar score less than 5, or need for resuscitation more than 10 min.<sup>28</sup>

Since groups A and B were composed of fewer cases than group C, unmatched group C cases were randomly selected in a ratio of approximately 1:3.<sup>29</sup>

Data regarding maternal history, pregnancy complications, labor, and delivery were collected. Sentinel events defined as acute intrapartum events (uterine rupture, placental abruptio, shoulder dystocia, cord prolapse, amniotic fluid embolism, sustained bradycardia in the presence of a previously normal fetal heart rate).

In addition, neonatal characteristics were registered, as well as neuropsychiatric follow-up at 12 and 24 months.

Placentas were reviewed by a single pathologist specializing in placental pathology and were classified as (i) maternal vascular malperfusion (MVM), (ii) fetal stromal vascular malperfusion (FVM), (iii) inflammatory processes, and (iv) normal.<sup>30,31</sup>

R software version 3.6.0 and SPSS version 25 (IBM Corp., Armonk, NY, USA) were used to run the analyses. All tests were two-tailed and the level of significance was set at 0.05.

The study was approved on April 13, 2006, by the institutional review board (protocol No. 236) of the University of Milan-Bicocca, Italy.

## 3 | RESULTS

During the study period, 11 neonates were identified with NAIS (group A), 10 with moderate to severe HINE (group B), and 227 with perinatal asphyxia with or without mild HINE (group C), with an incidence per neonates born of 0.32‰ (11/34 772), 0.29‰, and 6.53‰, respectively.

A total of 29 unmatched neonates in group C were randomly selected to undergo statistical analyses.

Table 1 shows maternal and antenatal characteristics. No significant differences were identified in any of the variables examined. A lower rate of present pregnancy complications were noted in group A than in groups B and C (27.3% vs 70.0% vs 58.6%, respectively;  $P = 0.122$ ).

Intrapartum characteristics are listed in Table 2. The study groups were similar in terms of type of onset of labor, mode of delivery, use of oxytocin, analgesia, or labor complications, such as clinical chorioamnionitis, meconium, and tachysystole. No sentinel events occurred in group A whereas there were 8 (80.0%) and 12 (41.4%) in groups B and C, respectively ( $P = 0.001$ ). Sentinel events in group B were bradycardia ( $n = 4$ ), cord prolapse ( $n = 2$ ), shoulder dystocia ( $n = 1$ ), and massive hemorrhage from placenta previa ( $n = 1$ ); 8 cases of bradycardia, two cases of cord prolapse, and two cases of placental abruptio occurred in group C.

Table 3 displays neonatal characteristics.

Most neonates were male. Umbilical cord blood gas values (pH, BE) at birth and at 6 h after birth were substantially worse in groups B and C compared to group A. In addition, neonates in group B showed lower pH and BE values than neonates in group C. No cases of abnormal pH at birth (i.e.  $\leq 7$ ) were identified in group A, whereas there were 8 (80%) and 11 (38%) in groups B and C, respectively ( $P < 0.001$ ). Neonates in group B also displayed substantially lower Apgar score at 1, 5, and 10 minutes compared to the other two groups, with all neonates in group A showing normal scores. In addition, no neonates in group A required neonatal resuscitation at birth, which was performed in 10 (100%) and 8 (27.6%) neonates in groups B and C, respectively.

Seizures developed in 81.8% neonates in group A and 80% in group B, but in none in group C. The median time for the onset of seizures was 24 h (range 6–72 h) in group A and 12 h (range 3–48 h) in group B. Hyponatremia did not occur in any of the neonates in group C, whereas it was diagnosed in 54.5% and 60% of group A and B neonates, respectively.

In group A, there were no neonates with co-morbidities possibly correlated with NAIS (e.g. congenital heart defect) or with thrombophilia. In addition, coagulation parameters and platelet count were within normal range in this group.

TABLE 1 Antenatal characteristics of the study groups<sup>a</sup>

Variables	Brain damage category			P <sup>b</sup>
	Group A (n = 11)	Group B (n = 10)	Group C (n = 29)	
<b>Maternal characteristics</b>				
Age (years)	35.2 ± 5.3	36.2 ± 3.2	34.8 ± 5.0	0.713
Caucasian	11 (100.0)	7 (70.0)	26 (89.7)	0.082
Pre-gestational BMI (kg/m <sup>2</sup> )	21.8 ± 4.0	24.4 ± 4.1	21.7 ± 3.7	0.152
ART	2 (18.2)	1 (10.0)	0	0.068
Cigarette smoking/alcohol/substance abuse	2 (18.2)	0	4 (13.8)	0.595
Primiparous	7 (63.6)	4 (40.0)	20 (69.0)	0.273
Previous cesarean delivery	1 (9.1)	1 (10.0)	7 (24.1)	0.536
<b>Antepartum characteristics</b>				
Family history of neurologic events (thrombosis/seizures)	0	0	1 (3.7)	1
Family history of thrombophilia	1 (9.1)	0	1 (3.7)	0.689
Autoimmune disease	2 (18.2)	0	0	0.082
Gynecological disease	3 (27.3)	1 (10.0)	3 (10.7)	0.531
Previous pregnancy adverse outcome <sup>c</sup>	1 (9.1)	1 (10.0)	7 (24.1)	0.536
Present pregnancy complications <sup>d</sup>	3 (27.3)	7 (70.0)	17 (58.6)	0.122

Abbreviations: ART, assisted reproductive technology; BMI, body mass index.

<sup>a</sup>Values are given as number (percentage) or mean ± SD.

<sup>b</sup>P values are for overall tests (Fisher or Kruskal-Wallis) comparing the three groups.

<sup>c</sup>Including gestational diabetes, thyroid diseases, polyhydramnios, oligohydramnios, hypertensive disorders, fetal growth restriction, intrauterine fetal death, placental abruption, preterm premature rupture of membranes.

<sup>d</sup>Including gestational diabetes, thyroid diseases, polyhydramnios, oligohydramnios, hypertensive disorders, cholestasis, antepartum hemorrhage, reduced fetal movements, fetal growth restriction, placenta abruption, preterm premature rupture of membranes, chicken-pox infection, thrombocytopenia.

Postnatal complications, including meconium aspiration syndrome, respiratory distress syndrome, and sepsis, were rarely diagnosed and did not differ among study groups.

There was only one case of neonatal death in the study population, which occurred in a 3-day-old neonate with NAIS.

Magnetic resonance imaging was performed in all cases in groups A and B: in group A, after the onset of symptoms with the middle cerebral artery being affected in the majority of cases (10/11, five cases on the left side, three cases on the right side, and two cases bilaterally); and in group B, on postnatal days 7-10 with all reports compatible with previous hypoxic-ischemic injury (bilateral lesions with involvement of thalami and basal ganglia, and, rarely, cerebral cortex).

Neurological follow-up was assessed at 12 and 24 months. One neonate in group A was lost at the 12-month follow-up and one additional neonate in each group at the 24-month follow-up. Among the cases in group C, neurological follow-up was performed in all neonates diagnosed with HINE Stage I.

At 12 months, three cases of hemiplegia and three cases of cerebral palsy were identified in groups A and B, respectively. A regular normal motor outcome was recognized in the remaining infants. Cognitive status was assessed at the 24-month visit by means of the Griffith test, which diagnosed one case of cognitive delay in group A. No cases of cognitive delay were diagnosed in group B after

excluding children with cerebral palsy. All infants in group C with HINE Stage I showed normal outcomes at both 12 and 24 months.

Placentas were available for histological examination in 8 of 11 cases in group A, 8 of 12 cases in group B, and in all cases in group C.

No statistically significant differences were identified among the study groups for any of the subcategories assessed (Table 4). However, abnormal placental pathology, including MVM, FVM, and inflammatory processes, was identified in 87.5% (n = 7) and 79.3% (n = 23) of the cases in groups A and C, respectively, compared to 50.0% (n = 4) of the cases in group B. MVM was the most common pathology report for groups A and C, whereas placentas in group B were more frequently classified as normal. In addition, FVM was identified in less than 15% of the placentas in each group.

Umbilical cord abnormalities, such as abnormal placental cord insertion (marginal or velamentous) or hypercoiling, were identified in 50% of the neonates in group A compared to 16.7% and 13.8% of the neonates in groups B and C, respectively (P = 0.111).

## 4 | DISCUSSION

The present retrospective study focused on the clinical and placental features of cases with NAIS, HINE, or perinatal asphyxia at a single tertiary care institution over a period of 10 years.

TABLE 2 Intrapartum characteristics of the study groups<sup>a</sup>

Variables	Brain damage category			P <sup>b</sup>
	Group A (n = 11)	Group B (n = 10)	Group C (n = 29)	
Gestational age at delivery (weeks)	39.4 (38.8–39.6)	38.6 (37.7–39.8)	40.0 (38.3–41.0)	0.269
Labor				0.811
No labor	3 (27.3)	3 (30.0)	5 (17.2)	
Spontaneous	3 (27.3)	4 (40.0)	12 (41.4)	
Induced	5 (45.5)	3 (30.0)	12 (41.4)	
Delivery				0.169
Spontaneous VD	8 (72.7)	3 (30.0)	14 (48.3)	
Operative VD	0	1 (10.0)	3 (10.3)	
Elective CD	1 (9.1)	0	0	
Urgent CD	2 (18.2)	6 (60.0)	12 (41.4)	
Tachysystole <sup>c</sup>	3 (27.3)	5 (50.0)	16 (55.2)	0.316
Oxytocin use	5 (45.5)	4 (40.0)	6 (20.7)	0.213
Epidural analgesia in labor	4 (36.4)	1 (10.0)	3 (10.3)	0.123
Sentinel events	0	8 (80.0)	12 (41.4)	0.001 <sup>s,d,e</sup>

Abbreviations: CD, cesarean delivery; VD, vaginal delivery.

<sup>a</sup>Values are given as number (percentage) or median (interquartile range).

<sup>b</sup>P values are for overall tests (Fisher or Kruskal–Wallis) comparing the three groups.

<sup>c</sup>≥5 contractions in 10 min for 30 min or more.

<sup>d</sup>Pairwise comparisons are performed using Fisher or Mann–Whitney tests with Holm correction (Table S1): A vs B is statistically significant.

<sup>e</sup>Pairwise comparisons are performed using Fisher or Mann–Whitney tests with Holm correction (Table S1): A vs C is statistically significant.

Neonates with perinatal asphyxia were divided into two groups according to the severity of the resulting HINE (group B: perinatal asphyxia +Stage II–III HINE, group C: perinatal asphyxia/perinatal asphyxia +Stage I HINE) since it is known that neonates with only perinatal asphyxia or with perinatal asphyxia +Stage I HINE have few, if any, adverse outcome.<sup>32</sup>

Here it is demonstrated that cases of NAIS and perinatal asphyxia/HINE have different intrapartum and neonatal features.

In the present series, sentinel events were present only in cases of perinatal asphyxia/HINE, especially Stage II–III HINE, but in none of the neonates diagnosed with NAIS. In addition, neonates with perinatal asphyxia/HINE displayed an abnormal condition at birth, represented by altered umbilical cord blood gas values, low Apgar scores, and need for neonatal resuscitation, which was not identified in neonates with NAIS.

Sentinel events are known to be asphyxial birth events with a pivotal role in the pathogenesis of perinatal asphyxia and HINE.<sup>33–35</sup> The data in the present study confirm this: the rate of sentinel events was 80% in group B and 41.4% in group C, whereas no events occurred in group A ( $P = 0.001$ ).

In previous studies, birth asphyxia, need for neonatal resuscitation, and 5-minute Apgar score less than 7 have been associated with NAIS.<sup>7,12,13,16</sup> Conversely, in the present study, all neonates in group A had normal neonatal adaptation.

Together, these data support the hypothesis that NAIS and perinatal asphyxia/HINE may have different etiological mechanisms. The high frequency of sentinel events and the abnormal

conditions at birth in neonates with perinatal asphyxia/HINE highlight the importance of the intrapartum period in birth asphyxia. The fact that neonates with NAIS do not usually experience sentinel events and are frequently healthy at birth suggests that multiple factors, in addition to intrapartum ones, must become involved for NAIS to occur.

Neonates with NAIS and Stage II–III HINE shared a similar incidence of severe neurological symptoms, such as hyponatremia and seizures, whereas no neonate with perinatal asphyxia/Stage I HINE had postnatal neurological complications. Seizures were the leading neurological presenting symptom in infants with NAIS, as previously described.<sup>36</sup>

Brain imaging revealed two typical patterns of brain injury, in line with the available literature.<sup>37,38</sup>

Hyponatremia and seizures are the result of anatomical brain damage. Evidence of similar neurological symptoms between neonates with NAIS and Stage II–III HINE suggests that these two conditions may share a similar final outcome of brain injury and its clinical characteristics in the neonatal period, even though localization of lesions is different, thus leading to a dissimilar long-term neurological outcome (i.e. hemiplegia in group A and cerebral palsy in group B).

Regarding placental pathology, no significant differences were identified among the study groups for any of the sub-categories of placental abnormalities analyzed. The small sample size of the study population may have affected this result. Notwithstanding this, some considerations can be done. First,

TABLE 3 Neonatal characteristics of the study groups<sup>a</sup>

Variables	Brain damage category			p <sup>b</sup>
	Group A (n = 11)	Group B (n = 10)	Group C (n = 29)	
Birth weight (g)	3060.0 (2840.0–3265.0)	3450.0 (2677.5–3855.0)	3180.0 (2610.0–3400.0)	0.560
Birth weight percentile	27.0 (18.0–59.0)	57.5 (19.0–94.25)	31.0 (13.0–50.0)	0.409
SGA	2 (18.2)	2 (20.0)	7 (24.1)	1
Male	6 (54.5)	8 (80.0)	17 (58.6)	0.446
UA pH	7.24 (7.19–7.27)	6.81 (6.77–6.98)	7.02 (6.97–7.13)	0.001 <sup>c,d,e</sup>
UA pH $\leq$ 7	0	8 (80.0)	11 (37.9)	<0.001 <sup>c,d,e</sup>
UA BE	–5.9 (–7.5 to –4.5)	–17.7 (–23.3 to –13.6)	–13.6 (–15.3 to –12.3)	0.001 <sup>c,d</sup>
UA BE $\geq$ –12	1 (10.0)	8 (80.0)	24 (82.8)	<0.001 <sup>c,d</sup>
UA lactates (mmol/L)	6.5 (6.3–9.0)	14.5 (13.1–16.6)	11.9 (8.8–13.8)	0.052
1 min Apgar	9.00 (7.00–9.00)	1.00 (0.00–3.00)	6.00 (5.00–8.00)	<0.001 <sup>c,d,e</sup>
5 min Apgar	10.0 (9.0–10.0)	2.0 (1.0–4.0)	8.0 (8.0–9.0)	<0.001 <sup>c,d,e</sup>
10 Min Apgar	–	6.0 (5.0–7.0)	8.50 (7.75–9.25)	0.037
Neonatal resuscitation	0	10 (100.0)	8 (27.6)	<0.001 <sup>c,e</sup>
Hyponatremia <sup>f</sup>	6 (54.5)	6 (60.0)	0	0.001 <sup>d,e</sup>
Meconium aspiration syndrome	0	1 (8.3)	0	0.442
Respiratory distress syndrome	1 (9.1)	3 (25.0)	4 (13.8)	0.147
Infection/sepsis	1 (9.1)	1 (8.3)	0	0.191
Seizures	9 (81.8)	8 (80.0)	0	<0.001 <sup>d,e</sup>
Length of hospital stay (days)	21.0 (13.0–22.5)	21.0 (17.0–30.0)	4.0 (3.0–7.0)	<0.001 <sup>d,e</sup>
Neonatal death	1 (9.1)	0	0	0.420

Abbreviations: BE, base excess; SGA, small for gestational age; UA, umbilical artery.

<sup>a</sup>Values are given as number (percentage) or median (interquartile range).

<sup>b</sup>P values are for overall tests (Fisher or Kruskal–Wallis) comparing the three groups.

<sup>c</sup>Pairwise comparisons are performed using Fisher or Mann–Whitney tests with Holm correction (Table S1): A vs B is statistically significant.

<sup>d</sup>Pairwise comparisons are performed using Fisher or Mann–Whitney tests with Holm correction (Table S1): A vs C is statistically significant.

<sup>e</sup>Pairwise comparisons are performed using Fisher or Mann–Whitney tests with Holm correction (Table S1): B vs C is statistically significant.

<sup>f</sup>Defined as plasmatic sodium concentration <130 mmol/L.

the probability of having a normal placenta was relatively high among cases of Stage II–III HINE, further highlighting the importance of acute intrapartum events in the etiology of this condition. Sentinel events are catastrophic occurrences that do not have time to alter placental histology but influence neonatal prognosis. Second, there was a higher prevalence of abnormal histology in cases of NAIS, including MVM, FVM, and inflammation, compared to neonates with Stage II–III HINE. These results are in line with previous studies reporting a lower rate of placental abnormalities in neonates meeting the criteria for therapeutic hypothermia after hypoxic injury than in cases of stroke<sup>28</sup> and may point to a more predominant role of antepartum, chronic events in causing stroke. Third, MVM was identified in more than 60% of placentas with NAIS; this differs from the available data showing FVM as the most prevalent pattern in NAIS. This could be related to the more selective inclusion criteria of the present study<sup>28</sup>: only cases of arterial ischemic stroke in term/late preterm neonates

( $\geq$ 35 weeks) with early preterm neonates and venous infarction or presumed IPS being excluded. Last, histological examination of placentas with perinatal asphyxia/Stage I HINE showed unexpected results: more similar to cases of NAIS than to cases of Stage II–III HINE. This could be partly explained by the wide heterogeneity of this group, but the interpretation of this finding is limited by the lack of studies on perinatal asphyxia/Stage I HINE placentas. Larger studies assessing placental histology and its association with different types of neurological neonatal injury are warranted.

The strengths of the present study are as follows: the addition of placental histological examination to clinical data; the accurate characterization of NAIS, since only neonates with arterial ischemic stroke diagnosed in the first days of life were included in the analyses; the evaluation of only term/late preterm neonates; and the differentiation of cases of perinatal asphyxia/Stage I HINE from cases of Stage II–III HINE, which allowed for the comparison of neonates with anatomical brain damage (NAIS and Stage II–III HINE).

TABLE 4 Placental histological examination data<sup>a</sup>

	Brain damage category			<i>p</i> <sup>b</sup>
	Group A ( <i>n</i> = 8)	Group B ( <i>n</i> = 8)	Group C ( <i>n</i> = 29)	
MVM	5 (62.5)	3 (37.5)	15 (51.7)	0.732
FVM	1 (12.5)	1 (12.5)	4 (13.8)	0.811
IP	1 (12.5)	0	4 (13.8)	
N	1 (12.5)	4 (50.0)	6 (20.7)	

Abbreviations: FVM, fetal vascular malperfusion; IP, inflammatory processes; MVM, maternal vascular malperfusion; N, normal (according to Redline and Amsterdam nomenclature).<sup>33,34</sup>

<sup>a</sup>Values are given as number (percentage).

<sup>b</sup>*P* value is for overall test (Fisher) comparing the three groups.

The present study also has some limitations: a retrospective design; single-center setting; small number of cases, and unavailability of placenta for histological examination in a few cases.

## 5 | CONCLUSION

The data from the present study show that cases of NAIS and perinatal asphyxia/HINE have different intrapartum and neonatal features. Neonates with NAIS do not usually experience sentinel events and are frequently healthy at birth. Conversely, sentinel events demonstrated once again their role in determining perinatal asphyxia/HINE with affected neonates displaying abnormal conditions at birth.

Thus, the present results suggest that birth asphyxia does not need to be present for the occurrence of NAIS and the two conditions do not necessarily share common antecedents. However, infants with NAIS and Stage II–III HINE both suffer from brain injury, and its related clinical manifestation in the neonatal period can be similar (i.e. seizures).

The histology data in the present study highlight the need for further research on this topic to better define the typical pattern of placental abnormalities associated with NAIS and perinatal asphyxia/HINE. Such studies could generate new insights into the pathophysiology of these conditions, thus possibly providing new avenues of treatment or prevention.

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## CONFLICTS OF INTEREST

The authors have no conflicts of interest.

## AUTHOR CONTRIBUTIONS

LL: study design, data collection and analysis, manuscript preparation, and final review of the manuscript. SO: study design, data

analysis, manuscript preparation, and final review of the manuscript. GDM: study design and data collection. GP: study design, data analysis, and neonatal follow-up. DPB: study design and data analysis. FM: study design and histological placenta examination. PV: study design, manuscript preparation, and final review of the manuscript.

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#### SUPPORTING INFORMATION

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

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