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Associations Of Blood Gas And Acid-Base Values With Motor And Language Outcomes In Preterm-Born Preschoolers

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ASSOCIATIONS OF BLOOD GAS AND ACID-BASE VALUES WITH MOTOR AND LANGUAGE OUTCOMES IN PRETERM-BORN PRESCHOOLERS

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CHAPTER 1: INTRODUCTION

Introduction to Hypoxia-Ischemia

Early hypoxic-ischemic brain damage may occur in utero, during birth, or during the first weeks of life in the preterm infant (Brown et al., 2018; Graziani et al., 1992; Goswami et al., 2021; H. Huang et al., 2017; Leviton et al., 2010; Malin et al., 2010; Randolph et al., 2014; Victory et al., 2003). Hypoxia refers to low levels of oxygen in cell tissues (Samuel & Franklin, 2008) and ischemia refers to a disruption in tissue blood flow (Laptook, 2016), though the two frequently give rise to each other and co-occur in fetuses and preterm infants to cause brain damage (Laptook, 2016). Compared to term infants, preterm infants are at increased risk of hypoxic-ischemic injury, with infants of lower gestational age at an even greater risk (B. Y. Huang & Castillo, 2008). In the perinatal period of preterm infants, hypoxia-ischemia may be due to a multitude of complications, including maternal preeclampsia, congenital fetal infections, fetal anemia, umbilical cord compression, intrauterine restriction, placental insufficiency, and fetal or infant lung or heart disease (Laptook, 2016; Logitharajah et al., 2009). In this high-risk population, hypoxic ischemic brain damage may alter brain structure (Barkovich & Truit, 1990; Goplerud & Delivoria-Papadopoulos, 1993) or brain function (Hellström-Westas & Rosén; Hüppi & Amato), and may lead to cerebral palsy (CP; Leviton et al., 2010; Malin et al., 2010; Wang et al., 2014), a neuromotor disorder.

Not surprisingly, numerous studies reveal lower functioning in a variety of neuropsychological domains in the preterm population, including cognition (Brydges et al., 2018; Twilhaar et al., 2018), language (Barre et al., 2011; van Noort-van der Spek et al., 2012), executive functions (Brydges et al., 2018; Sandoval et al., 2021; van Houdt et al., 2019), and motor functioning (Davis et al., 2007; Feder et al., 2005; Foulder-Hughes & Cooke, 2003; Larson et al.,

2011; Goyen & Lui, 2009). Though there is a large body of studies on the neuropsychological outcome of preterm birth, there is a dearth of studies connecting early biochemical indices of hypoxic-ischemic risk, particularly blood gas and acid-base balance measures, to neuropsychological deficits. In this study, I focused on the link between measures obtained either at birth, immediately after birth, or within the first week of life and language and motor functioning at preschool age. In the following sections, I briefly review the mechanisms and functions of blood-gas exchange and acid-base status in the preterm infant (see page 2, *Overview of Blood Gas Exchange and Acid-Base Balance*). I then discuss brain regions and neuropsychological functions vulnerable to hypoxic-ischemic injury in preterm infants. Finally, I systematically review the literature on blood-gas and acid-base levels in the fetus and preterm infant and their associations with neuropsychological outcome.

Overview of Blood Gas Exchange and Acid-Base Balance in the Fetus and Term and Preterm Neonate

The normal function of nearly all physiological processes in the body depends on optimal tissue oxygenation, and relatedly, adequate gas exchange and maintenance of an appropriate acid-base balance. In this section, I discuss the mechanisms of gas exchange in the fetus and term and preterm newborn, how gas exchange affects acid-base status, and the consequences of abnormal blood gas or acid-base levels.

Gas Exchange in the Fetus

In the fetus, gas exchange between the fetus and mother primarily takes place in the placenta, an organ that attaches the fetus to the uterine wall and is responsible for providing it with nutrients (Goplerud & Delivoria-Papdopoulos, 1985). The umbilical cord connects the fetus and placenta and is tasked with providing unimpeded blood flow to the developing organism. The

umbilical cord has two arteries and one vein. The umbilical artery is responsible for carrying blood away from the fetus to the mother while the umbilical vein transports oxygenated blood from the mother to the fetus (Goplerud & Delivoria-Papdopoulos, 1985).

Oxygen delivery to the fetus is a function of the umbilical venous cord blood oxygen concentration and blood flow, though oxygenation can be impacted by numerous maternal or fetal factors (e.g., maternal hypertension, placenta previa, cord compression; Goplerud & Delivoria-Papdopoulos, 1985). Fetal hemoglobin, which has a high affinity for oxygen, binds with oxygen to aid in transport of oxygen from maternal to fetal circulation (Murray, 2012). Once transported to fetal cells and tissue, oxygen is converted to energy in the form of adenosine triphosphate (ATP), which is crucial for numerous intracellular biochemical mechanisms and essential for cell survival and function (McNamara & El-Khuffash, 2017). Carbon dioxide is produced as a waste product of the fetal metabolism and eliminated back to the mother via the umbilical arteries. As the blood contains a mixture of gases, each constituent gas exerts a pressure. The unique pressure that any single gas exerts is called a partial pressure. The partial pressure of oxygen, pO_2, and carbon dioxide, pCO_2, are measurements of oxygen and carbon dioxide pressures in the blood, respectively. See Table 2 for the accepted ranges for umbilical cord partial pressures of blood gases of infants born at different gestational ages.

Gas Exchange in the Term and Preterm Neonate

In general, when a newborn transitions into the extra-uterine environment, gas exchange quickly becomes the responsibility of the lungs, rather than the placenta and umbilical cord. When an unventilated newborn inhales, oxygen enters the lungs, diffuses into the blood stream, and binds with hemoglobin to be transported to peripheral tissues (McNamara & El-Khuffash, 2017). Again, carbon dioxide is produced as a byproduct of this reaction, and is expired and eliminated via the

lungs (McNamara & El-Khuffash, 2017). See Table 2 for the accepted ranges for newborn blood-gas measurements in the preterm infant.

Acid-Base Balance in the Fetus and Term and Preterm Neonate

Acid-base balance is essential for the maintenance of homeostasis, respiratory and cardiovascular circulation, and functioning (Hamm et al., 2015). An acid-base balance refers to the balance between input (intake and production) and output (elimination) of hydrogen ions (H^+). An acid is a substance that produces H^+ ions when it is added to water, while a base neutralizes acids. Blood pH is a representation of the logarithmic H^+ concentration ($pH = -\log[H^+]$) in blood and base deficit (BD)/base excess (BE) represents the amount of base required to titrate a whole arterial blood to a normal pH. Of note, BD refers to an excess amount of acid or a lack of base in the blood and is expressed as a negative number. BE refers an excess of base or a lack of acid in the blood and is expressed as a positive number (Berend, 2018). Blood pH is used to determine blood acidity ($pH < 7.35$) or alkalinity ($pH > 7.45$). A system of buffers in blood and other tissue permits the body to maintain pH at a relatively constant level despite the continuous production of acid by cellular metabolism (Carter et al., 1993). A higher concentration of H^+ ions (carbonic and lactic acids) in the blood or tissues refers to acidemia and acidosis, respectively. A lower concentration of H^+ ions in the blood or tissues refers to alkalemia and alkalosis, respectively. Acidemia is not uncommonly observed in the fetus and is often due to impairment of uteroplacental circulation (Bobrow & Soothill, 1999). Likewise, acidemia in the preterm infant is often due to poor lung or kidney function or general physiological instability (Paul et al., 2020). Alkalemia is uncommon in the fetus, as it is often the result of maternal hyperemesis (Schimert et al., 2007). Alkalemia is also rare in the newborn (preterm or term), as it is often due to infant hyperemesis or

dehydration (Kakita et al., 2007). Nonetheless, the acid-base status of the blood is heavily dependent on fetal or infant gas exchange (i.e., oxygen, carbon dioxide).

Abnormal Oxygen Levels in the Fetus and Term and Preterm Neonate

Oxygen deprivation (or hypoxia) is one of the most common challenges in fetal and newborn life (Giussani, 2016), and is often the result of uterine contractions, compression of the umbilical cord, and newly acquired cardiorespiratory responsibilities upon birth. When oxygen is deficient, the body resorts to anaerobic metabolism, breaking down glucose to use for ATP, and eventually producing lactic acid (McNamara & El-Khuffash, 2017). Lactic acid is normally metabolized via the liver and kidney and separates into lactate and H^+ ions. However, with increased production, lactic acid concentrations exceed the capacity of these organs. Thus, oxygen deprivation can lead to high levels of H^+ in the body, decreasing pH and increasing the acidity of the blood (McNamara & El-Khuffash, 2017). A low concentration of oxygen in the blood or tissues is referred to hypoxemia or hypoxia, respectively.

Excess oxygen levels (or hyperoxia) are less commonly observed in the fetus or newborn at birth. Fetal hyperoxia is often due to maternal hyperoxygenation (Khazin et al., 1971), while preterm infant hyperoxia is often due to infant mechanical ventilation (Mohamed et al., 2020). Reactive oxygen species (ROS) are byproducts of normal oxidative metabolism, functioning in cell signaling and homeostasis (Gore et al., 2010). As ROS is produced in higher quantities due to increased oxygen levels, increased ROS levels react with other molecules, and can directly damage cellular components and lead to cell death (Shields et al., 2021). Though preterm-born infants frequently require mechanical ventilation for inadequate oxygen saturation levels, medical care advances and practice changes have reduced the frequency of hyperoxia in preterm newborns (Deuber & Terhaar, 2011).

Abnormal Carbon Dioxide Levels in the Fetus and Term and Preterm Neonate

Carbon dioxide is a regulator of blood pH and respiration (Messina & Patrick, 2021). In both the fetal and newborn (term or preterm) metabolism, when carbon dioxide enters the blood stream, it is converted into carbonic acid (Messina & Patrick, 2021) which, in turn, rapidly converts to HCO_{3-} and H^+. As a result, when the H^+ concentration increases, pH, which is a measurement of H^+ ions in the blood, decreases and the blood becomes more acidic. Central and peripheral chemoreceptors function to detect changes in the pH of blood. In the fetus, chemoreceptors mediate the redistribution of the cardiac output to preferentially perfuse organs, such as the heart and brain (Giussani, 2016). In the unventilated term or preterm newborn, chemoreceptors communicate with the respiratory centers of the brain (i.e., medulla, pons) to increase or decrease ventilation rate (Messina & Patrick, 2021). Thus, high levels of pCO_2 in the blood trigger hyperventilation, which functions to decrease pCO_2 levels (Patel & Sharma, 2021). Low levels of pCO_2 in the blood lead to hypoventilation, which functions to increase pCO_2 levels in the blood (Patel & Sharma, 2021). An excess of pCO_2 in the blood is known as hypercapnia while a shortage of pCO_2 in the blood is known as hypocarbia. Of importance, pCO_2 and H^+ ions have allosteric effects on hemoglobin, binding to different sites on the hemoglobin molecule and consequently, lowering its affinity to bind to oxygen (Benner et al., 2018). As a result, higher pCO_2 levels are associated with oxygen deprivation and lower pH levels, while lower pCO_2 levels are associated with an excess of oxygen and higher pH levels. Again, medical care advances and practice changes have reduced the frequency of hypocarbia in preterm newborns, with a shift towards permissive hypercapnia guiding ventilation (discussed below; Chenault et al., 2020).

Source and Time Period of Blood Gas and Acid-Base Measurement in Preterm Neonates

As discussed (see page 2, *Overview of Blood Gas Exchange and Acid-Base Balance*), blood-gas and acid-base disturbances can occur in-utero, during the birth and delivery process, or during the preterm infant's immediate or initial neonatal adjustment period. Blood gas and acid-base measurements can be collected from the umbilical cord (i.e., vein or artery) and directly from the infant (i.e., artery, vein, capillary) to assess fetal and infant well-being at different adjustment periods. In this section, I discuss sources of blood gas and acid-base measurements (e.g., umbilical cord versus newborn) as well as the information gained from postnatal blood gas sampling in the neonatal intensive care unit (NICU).

Umbilical Cord Blood Gas and Acid-Base Measurement in the Preterm Newborn

Evaluation of the metabolic state of the newborn is essential to understand hypoxic risk associated with *birth and delivery* (Westgate et al., 1994). Umbilical cord blood gas analysis is recommended for all high-risk deliveries (e.g., preterm birth) and provides important information about an infant's in utero condition, as well as current status, that may inform future clinical care (Westgate et al., 1994). As the umbilical artery is responsible for carrying deoxygenated blood from the fetus to the mother (Thorp et al., 1996), blood gas values obtained from the arterial umbilical cord primarily resemble fetal blood gas and acid-base status. Conversely, umbilical vein blood gas values represent a combination of maternal blood gas and acid-base status as well as placental function (Thorp et al., 1996). In general, arterial cord pH, BD, and pO_2 are reported to be lower than venous cord pH, BD, and pO_2 in both term (Thorp et al., 1989) and preterm (Dickinson et al., 1992) newborns. Conversely, arterial cord pCO_2 is reported to be higher than venous cord pCO_2 in both term (Thorp et al., 1989) and preterm (Dickinson e al., 1992) newborns, though arterial and venous blood gas and acid base values vary depending on gestational age

(Dickinson et al., 1992; Victory et al., 2003). Thus, arterial cord blood gas and acid base values more accurately reflect the status of the fetus during the later stages of birth and delivery for both term and preterm newborns (Thorp et al., 1996; Westgate et al., 1994). See Table 2 for a comparison of umbilical vein and artery blood gas and acid-base values in preterm infants.

Blood Gas and Acid-Base Measurement from the Preterm Neonate

The first hours of an infant's life come with critical cardiorespiratory changes, as nutritional, excretory, and respiratory systems must rapidly assume new responsibilities as the infant changes from a dependent to a free-living organism (Brouillette & Waxman, 1997). Initial newborn blood gas measurements are critical to providing essential information about the *immediate* functioning of these newly assumed, independent cardiorespiratory responsibilities and aid in newborn assessment and clinical care. The first week of life represents the preterm infant's *initial* extra-uterine adjustment period and is a period of the highest frequency of respiratory, cardiovascular, and metabolic pathology in preterm infants (Greisen, 1986). Therefore, blood gas and acid-base status conveys important information to providers about longer-term physiological functioning and stability. Arterial blood gas and acid-base analyses are the gold standard for evaluation of acid-base balance, ventilation, and oxygenation in preterm newborns (Brodkorb et al., 2022). However, arterial lines can be difficult to obtain (Goldsmith et al., 2016), are often invasive and painful (e.g., umbilical artery catheter, radial, tibial, or temporal artery), and come with some risk. Repeated arterial punctures, especially in infants with small arteries, can lead to arterial injury, hemorrhage, aneurysm formation, and thrombosis with distal ischemia (Barker, 1998). Capillary values are widely accepted as accurate alternatives to arterial pH, BD, and pCO_2 (but not pO_2) measurements in preterm infants and are easier to obtain, less invasive (e.g., heel stick), and avoid the risks of arterial punctures (Brodkorb et al., 2022; McLain et al., 1988; Yang

et al., 2018). In fact, over half of all procedures in the neonatal unit are performed using capillary blood samples, making it the most frequent blood sampling source in the neonate (Barker & Rutter, 1995; Johnston et al., 1997). Venous blood measurements are often less accurate than either capillary or arterial samples, are associated with more pain compared to capillary measurements, and thus are infrequently used in the assessment of preterm newborns (Yapicioğlu et al., 2014).

Frequency of Blood Gas Analysis in the Preterm Neonate

The frequency of blood gas and acid-base balance analysis often depends on the stability and adjustment status of the infant. As cord blood analysis is routine for all high-risk births, the results of the analysis inform future clinical decision-making for the preterm infant, with abnormal cord values rendering the infant more likely to be monitored with follow-up blood gas and acid-base measurements (Madsen et al., 2009; McKee et al., 2009). Indeed, blood samples from critically ill preterm infants are often obtained more frequently than non-critically ill infants in order to monitor their on-going metabolic status (Madsen et al., 2009).

Hypoxia and Neonatal Outcome in the Preterm Infant: An Overview

As mentioned above, hypoxia refers to a low level of pO_2 in cell *tissues* (Samuel & Franklin, 2008). In this section, I discuss fetal and neonatal hypoxia and its relationship to neonatal outcome in preterm infants.

Fetal Hypoxia in the Preterm Infant

Fetal hypoxia is one of the most common challenges of fetal life (Giussani, 2016), as transient episodes of acute hypoxia, lasting seconds to minutes, are frequently associated with labor and delivery as the uterine contracts and the umbilical cord is compressed (Huch et al., 1977). However, oxygen deprivation lasting for weeks to months, known as chronic fetal hypoxia, is often the consequence of common antenatal complications, such as intrauterine growth restriction,

preeclampsia, or gestational diabetes, which impair utero-placental functioning leading to reduced oxygenation (Giussani et al., 2016). The fetal brain undergoes rapid growth beginning in the second trimester, with a 20-fold increase in brain volume occurring between 20 weeks of gestation and term (Andescavage et al., 2016), and is thus, highly susceptible to adverse uterine experiences. Compared to normoxic fetuses, fetal hypoxia increases the risk of intrauterine death by 7-fold and 30-day mortality by 10-fold (McIntire et al., 1999). Even more so, fetuses that do survive hypoxic conditions are at increased risk for postnatal morbidity due to associated abnormal development of organs. In general, fetal hypoxia is most commonly measured by umbilical cord pH (Nordstrom & Sabaratnam, 1998), which is a measure of acidosis and is related to hypoxia, as will be discussed (see page 13, *Acid-Base Status (pH and BD) and Neonatal Outcome)* (Carter et al., 1993). However, fetal hypoxia is often accompanied by fetal hypercapnia (Zhou & Liu, 2008), and thus cord pCO_2 levels can provide important physiological information about infant status as well.

Neonatal Hypoxia in the Preterm Infant

When an infant transitions into its extrauterine environment, critical cardiorespiratory changes quickly occur, as nutritional, excretory, and respiratory systems must rapidly assume new responsibilities as the infant changes from a dependent to a free-living organism (Brouillette & Waxman, 1997). Compared to term infants, the respiratory system of preterm infants is structurally and biochemically immature, frequently resulting in respiratory distress and perinatal hypoxia (Wiswell, 2011). Though most preterm infants breathe spontaneously at birth, respiratory support is often needed to ensure adequate gas exchange (O'Donnell et al., 2010). Nonetheless, perinatal hypoxia in preterm infants has also been associated with injury to neurons, glia, and white matter (Barkovich & Truit, 1990; Goplerud & Delivoria-Papadopoulos, 1993). Intermittent episodes of mild and transient hypoxia have also been linked to other morbidities, such as retinopathy of

prematurity (Di Fiore et al., 2010) and BPD (Fairchild et al., 2019), and mortality (Di Fiore et al., 2017) in this high-risk group.

Hypoxic-Ischemic Brain Injury in the Preterm Infant

As mentioned above (see page 1, *Introduction to Hypoxia-Ischemia*), early hypoxic-ischemic brain damage may occur in utero, during birth, or during the first weeks of life in the preterm infant (Brown et al., 2018; Graziani et al., 1992; Goswami et al., 2021; J. Huang et al., 2017; Leviton et al., 2010; Malin et al., 2010; Randolph et al., 2014; Victory et al., 2003) and may be attributed to a multitude of complications (Laptook, 2016; Logitharajah et al., 2009). Even without exacerbating factors, preterm birth is associated with subtle brain pathology (Rees & Inder, 2005). Very premature infants (≤ 32 weeks gestation) show high rates of white matter (31.6%) and grey matter (21.1%) abnormalities on MRI (Iwata et al., 2012), with degree of injury related to cumulative perinatal risk (Barnett et al., 2017). Nonetheless, hypoxia and ischemia are of the most common causes of acquired brain injury in term and preterm infants (Ravarino et al., 2014). While term infants appear to be at increased risk for cortical as well as subcortical hypoxic damage, preterm infants appear to be at increased risk for primarily *subcortical damage* (Barkovich & Truit, 1990; Goplerud & Delivoria-Papadopoulos, 1993) with relative cortical sparing (Barkovich & Truit, 1990; Goplerud & Delivoria-Papadopoulos, 1993). This pattern of injury is thought to be due poor cerebral autoregulation, coupled with immaturity in the neural vascular system in preterm fetuses or infants (Hill & Fitch, 2012). Furthermore, white matter is dominated by pre-myelinating oligodendrocytes (preOLs) during approximately 23-32 weeks gestation, which is highly susceptible to oxidative stress compared to other later OLs (Back, 2017; Back et al., 2002).

The neuropathological correlates of brain damage due to hypoxia and ischemia in preterm infants include various brain lesions, most notably periventricular leukomalacia (PVL; Folkerth,

2006) and intraventricular hemorrhage (IVH; Ment et al., 2013). PVL refers to focal necrosis in the periventricular region and diffuse gliosis in the surrounding cerebral white and grey matter (Folkerth, 2006). IVH refers to bleeding into the fluid-filled ventricles of the brain, and is most commonly observed in the germinal matrix in the preterm infant (B. Y. Huang & Castillo, 2008).

Most periventricular injury occurs in the region of the white matter that is traversed by descending fibers of the corticospinal tract in preterm infants (Volpe, 2001). Studies utilizing diffusion tensor imaging (DTI) have noted decreased connectivity in the cerebral peduncle, posterior limb of the internal capsule, corona radiata, and posterior corpus callosum (Gao et al., 2012; Lvov et al., 2019; Varghese et al., 2016) in mild hypoxic-ischemic preterm neonates. Importantly, many of these regions house the corticospinal tract, the major neuronal pathway that functions in voluntary motor function. The corpus callosum connects the bilateral hemispheres and its splenium connects the primary motor, premotor, and supplementary motor cortices (Wahl et al., 2007). Relatedly, hypoxic-ischemic brain injury in preterm infants, such as PVL and IVH, has been linked to early motor impairment (Bolisetty et al., 2014; Imamura et al., 2013; O'Shea et al., 2012; van Haastert et al., 2008), as well as cerebral palsy (CP; Bolisetty et al., 2014; O'Shea et al., 2012; van Haastert et al.. 2008), a primarily neuromotor disorder that affects the development of movement, muscle tone, and posture. In addition to early motor impairment, PVL (Choi et al., 2016; Luu et al.. 2009; Panceri et al., 2020) and IVH (Bayram et al., 2012; Hollebrandse et al., 2021; Luu et al., 2009) have consistently been linked to cognitive (Choi et al., 2016; Hollebrandse et al.. 2021; Luu et al., 2009) or language (Bayram et al., 2012; Panceri et al., 2020) functioning in preterm infants. It has been established that connectivity in the internal capsule as well as corpus callosum are associated with language processing in preterm infants, with increased radial diffusivity and decreased size associated with lower scores (Mürner-Lavanchy et al., 2018; Nosarti

et al., 2004; Stipdonk et al., 2018; Young et al., 2017). As previously discussed, these regions are at heightened risk of white matter injury from hypoxic-ischemic episodes in preterm infants (Lvov et al., 2019; Varghese et al., 2016).

Nonetheless, even in preterm infants without such lesions (i.e., PVL, IVH) or neurodevelopmental disorders (i.e., CP), there is evidence to suggest a dose-response relationship between hypoxic *risk* and motor, cognitive, and language functioning (Piercy, 2019). As I will review, there is clear paucity of literature that has investigated the dose-response relationship between early physiological indicators of hypoxic risk and later motor or language functioning, skills that are highly vulnerable to hypoxic-ischemic damage in the preterm child. In the next sections, I review early fetal and neonatal physiological markers (e.g., pH, BD, pCO_2, pO_2) of hypoxic risk and their relationship with neuropsychological functioning in preterm children.

Acid-Base Status (pH and BD) and Neonatal Outcome in the Preterm Infant

As mentioned above (see page 4, *Acid-Base Balance in the Fetus and Term and Preterm Neonate)*, acidemia refers to a high concentration of H^+ ions (carbonic and lactic acids) in the *blood* while acidosis refers to a high H^+ ion concentration in the tissues. In general, pH and BD are used to measure acidosis and acidemia (Brodkorb et al., 2022; Leuthner, 2004), which are both indicators of hypoxia in the fetus and preterm (or term) infant (American College of Obstetricians & Gynecologists, 2014). Acidosis is typically classified as either respiratory or metabolic (Ouellet et al., 2021). Respiratory acidosis typically occurs due to a failure of ventilation and an overabundance of pCO_2 (Patel & Sharma, 2022), causing a decrease in pH. In the fetus, isolated respiratory acidosis is usually the result of short-lived impairment of uteroplacental or fetoplacental circulation. In the neonate, respiratory acidosis is often the result of poor lung function or depressed breathing (Armstrong et al., 2007). Conversely, metabolic acidosis is caused

by an overproduction of acid that builds up in the blood or an excess loss of bicarbonate from the blood (Ouellet et al., 2021). Metabolic acidosis is often the result of an underlying physiological issue (i.e., immature kidneys in preterm infants) and strongly linked to hypoxic-ischemic brain damage (Baalbaki et al., 2021; Malin et al. 2010; Ouellet et al., 2021; Randolph et al., 2014). While both respiratory and metabolic acidosis are characterized by a low pH, BD is used to quantify the metabolic or non-respiratory component of acidosis, with lower BD levels related to metabolic issues and higher BD levels related to respiratory causes (Berend, 2018; Carter et al., 1993; Ouellet et al., 2021).

Fetal Acid-Base Status (pH and BD) and Neonatal Outcome in the Preterm Infant

Umbilical cord pH and BD are commonly used as a measure of fetal acidemia and acidosis present at the time of birth (Leuthner, 2004). Severe cord blood acidemia is indicated by a cord pH < 7.0 and BD ≤ -12 mEq/L (Jonsson et al., 2009), while mild cord acidemia is indicated by a cord pH < 7.2 with unclear BD cutoff (Leuthner, 2004; see Table 3 for a review of the pH and BD cutoffs for acidosis severities). Fetal acidemia, as indexed by arterial cord pH, has been consistently associated with brain lesions, including IVH (Lavrijsen et al., 2005; Malin et al. 2010; Randolph et al., 2014; Victory et al., 2003) and PVL (J. Huang et al., 2017; Malin et al. 2010; Victory et al., 2003), as well as subsequent neuromotor impairment (i.e., CP; Baalbaki et al., 2021; Malin et al. 2010; Randolph et al., 2014). Severity of cord BD levels have also been linked to PVL (J. Huang et al., 2017; Victory et al., 2003) and IVH (Randolph et al., 2014; Victory et al. 2003). One study (Victory et al., 2003) documented an increased risk for IVH or PVL with worsening acidosis in preterm infants. However, based on a comprehensive meta-analysis, Malin and colleagues (2010) concluded that arterial cord pH was inversely and more strongly associated with increased frequency of neonatal mortality (seven studies; preterm only sample; approximated large

effect size, $d = 0.69$), CP (seven studies; mixed term and preterm sample; approximated medium effect size, $d = 0.59$), and IVH/PVL (seven studies; preterm only sample; approximated medium effect size, $d = 0.59$) compared to arterial BD.

Neonatal Acid-Base Status (pH and BD) in the Preterm Newborn and Neonatal Outcome

Newborn arterial blood analysis is the gold standard for acquiring blood gases and acid-base measures (Brodkorb et al., 2022). Mild neonatal acidosis is determined by arterial pH < 7.3 while severe neonatal acidosis is defined as arterial pH < 7.1, with unclear cutoffs for BD (Korones, 1981; see Table 3). Unsurprisingly, both abnormal arterial and capillary blood pH (Brown et al., 2018; Goswami et al., 2021; Graziani et al., 1992; Lee et al., 2018; Levition et al., 2010; Ma et al., 2015; Van De Bor et al., 1986; Vela Huerta et al., 2009; Zayek et al., 2014) or BD (Goswami et al., 2010; Lee et al., 2018; Ma et al., 2015; Mires et al., 1991; Van De Bor et al., 1986; Vela Huerta et al., 2009; Zayek et al., 2014) levels observed immediately after birth (Lee et al., 2018; Ma et al., 2015; Mires et al., 1991) and within the first week of life (Brown et al., 2018; Goswami et al., 2021; Graziani et al., 1992; Leviton et al., 2010; Mantoo et al., 2021; Van De Bor et al., 1986; Vela-Huerta et al., 2009; Zayek et al., 2014) in preterm infants, have been associated with brain lesions, including IVH (Brown et al., 2018; Goswami et al., 2021; Graziani et al., 1992; Lee et al., 2018; Mires et al., 1991; Van De Bor et al., 1986; Vela Huerta et al., 2009; Zayek et al., 2014), ventriculomegaly (Leviton et al., 2010), and PVL (Mires et al., 1991), as well as neuromotor impairment (e.g., CP; Leviton et al., 2010),

Acid-Base Measurements and Neuropsychological Outcome in Preterm-Born Children: Systematic Review

The methodological characteristics and results of 13 studies using acid-base measurements are described in Tables 1a through 1c. Table 1a includes studies using cord blood acid-base

analysis, thus reflecting risk for hypoxia ischemia *during the birth and delivery period*. Table 1b includes studies using acid-base analysis based on blood obtained from the newborn *immediately after birth*. Table 1c includes studies *during the infant's first week of life*.

Cord Blood Acid-Base Measurements in Preterm-Born Children and Neuropsychological Outcome

As presented in Table 1a**,** eight studies (Baalbaki et al., 2021; Beeby et al., 1994; Hüseman et al., 2011; Kato et al., 1996; Lavrijsen et al., 2003; Mittendorf et al., 2008; Piercy, 2019; Randolph et al., 2014) investigated the relationship between arterial cord pH and neuropsychological outcome of preterm-born children. Two of the eight studies (Baalbaki et al., 2021; Randolph et al., 2014) also examined BD. Six of the eight studies focused on infancy (12 to 20 months) (Beeby et al., 1994; Hüseman et al., 2011; Kato et al., 1996; Lavrijsen et al., 2003; Mittendorf et al., 2008; Randolph et al., 2014) and used infancy development measures to assess infant cognitive or motor outcomes. As outlined in Table 1a, two of the eight studies (Baalbaki et al., 2021; Piercy, 2019) examined outcomes beyond infancy, one of which focused on preschool-age (Piercy, 2019) and the other on school-age (Baalbaki et al., 2021). Of these studies, one included a developmental measure (Baalbaki et al., 2021) and one (Piercy, 2019) included a broad range of neuropsychological measures.

Five of the eight abovementioned research groups (Baalbaki et al., 2021; Kato et al., 1996; Lavrijsen et al., 2003; Piercy, 2019; Randolph et al., 2014) reported that lower arterial cord pH values are linked to lower scores on developmental (Baalbaki et al., 2021; Kato et al., 1996; Lavrijsen et al., 2005; Randolph et al., 2014), motor (Piercy, 2019), or cognitive (Kato et al., 1996; Piercy, 2019) measures in preterm children. Two studies (Baalbaki et al., 2021; Randolph et al.,

2014) that included arterial cord BD as the variable of interest documented a significant association between severity of BD and neuropsychological outcome in preterm children.

The eight studies varied in the degree of prematurity of the target group or sample. Four of the eight studies included extremely and very preterm (< 32 weeks) or extremely and very low birth weight (< 1500 g) infants (Lavrijsen et al, 2004; Beeby et al,. 1994; Kato et al., 1996; Baalbaki et al., 2021). One focused on the extremely low birthweight category only (Randolph et al., 2014) and three included a broader gestational age range (< 35 weeks) (Hüseman et al., 2011; Mittendorf et al., 2008; Piercy, 2019; see Table 1a).

Of the eight studies, six excluded children with congenital/chromosomal anomalies or severe malformations (Baalbaki et al., 2021; Beeby et al., 1994; Kato et al., 1996; Lavrijsen et al., 2004; Piercy, 2019; Randolph et al., 2014), while the remaining two (Mittendorf et al., 2008; Hüseman et al., 2011) did not mention exclusion of participants with congenital/chromosomal anomalies or severe malformations. Two studies excluded multiples (Baalbaki et al., 2021; Kato et al., 1996). Six studies (Randolph et al., 2014; Beeby et al., 1994; Lavrijsen et al., 2003; Hüseman et al., 2011; Mittendorf et al., 2008; Kato et al., 1996) did not mention adjustment for SES. One study (Kato et al., 1996) statistically adjusted for malpresentation and tocolytics, but no other medical risk factors.

Seven of eight available studies (Baalbaki et al., 2021; Beeby et al., 1994; Hüseman et al., 2011; Kato et al., 1996; Lavrijsen et al., 2004; Mittendorf et al., 2008; Randolph et al., 2014) compared groups above and/or below specified pH (Baalbaki et al., 2021; Beeby et al., 1994; Hüseman et al., 2011; Kato et al., 1996; Lavrijsen et al., 2004; Mittendorf et al., 2008; Randolph et al., 2014) or BD (Baalbaki et al., 2021; Randolph et al., 2014) threshold values. Three of the seven studies also included statistical analyses treating pH (Hüseman et al., 2011; Mittendorf et

al., 2008; Randolph et al., 2014) and BD (Randolph et al., 2014) as a continuous variable. One study solely treated pH as continuous (Piercy, 2019).

In selecting the study group, three of eight studies utilized an umbilical cord pH of < 7.0 to ascertain severe acidosis (Randoloph et al., 2013; Lavrijsen et al., 2004; Hüseman et al., 2011). The remaining studies used pH values < 7.10 (Beeby et al., 1994), and 7.20 (Kato et al., 1996, Mittendorf et al., 2008) as thresholds for group classification (i.e., acidotic versus nonacidotic). Three of these studies also included a base deficit threshold to ascertain metabolic acidosis; < -8.6 mEq/L (Baalbaki et al., 2021), < -12mq/L (Randolph et al., 2014), and < -16 mEq/L (Hüseman et al., 2011).

First Newborn Blood Acid-Base Measurements and Neuropsychological Outcome in Preterm-Born Children

As Table 1b shows, three studies investigated the relationship between initial arterial pH (i.e*., within the first hours of life*) and developmental or neuropsychological outcome of preterm-born children (Espy et al., 2007; Hopkins-Golighty et al., 2003; Hüseman et al., 2011). Two studies (Hopkins-Golighty et al., 2003; Hüseman et al., 2011) added initial arterial BD as a variable of interest. One of the studies (Hüseman et al., 2011) focused on infancy and used infancy development measures to assess infant cognitive or motor outcomes. The other two studies focused on preschool-age (Espy et al., 2007) and early school-age (Hopkins-Golightly et al., 2003). Espy and colleagues (2007) included academic and executive measures, while Hopkins-Golightly and colleagues (2003) studied intelligence and language measures.

Overall, two of the three research groups (Espy et al., 2007; Hopkins-Golightly et al., 2003) found that lower arterial pH values obtained *immediately after birth* (within 2-3 hours) were linked to lower scores on neuropsychological measures. Out of the two studies that included BD

(Hüseman et al., 2011; Hopkins-Golightly et al., 2003), one study (Hüseman et al., 2011) documented a significant association between severity of BD and global neurodevelopmental impairment, while the other group of researchers (Hopkins-Golightly et al., 2003) was not.

The three studies all included a wide gestational age range, including moderately preterm, very preterm, and extremely preterm-born children, but differed in terms of using an additional birthweight criterion. One used a low birth weight cutoff (< 2500g; Espy et al., 2007) while the other specified only very low birth weight (< 1500 g) infants (Hüseman et al., 2011). Of the three studies, two (Espy et al., 2007; Hopkins-Golightly et al., 2003) excluded children with brain lesions (e.g., IVH, PVL), chronic lung disease (e.g., bronchopulmonary dysplasia), and various neonatal complications experienced after the infant's immediate adjustment (e.g., sepsis). Hopkins-Golightly and colleagues (2003) also excluded infants with chromosomal or genetic defects. The remaining study (Hüseman et al., 2011) did not mention exclusion criteria.

Investigators adjusted for gestational age (Espy et al., 2007; Hüseman et al., 2011), chronological age (Espy et al., 2007), birthweight (Hüseman et al., 2011), antenatal and neonatal complications (Hopkins-Golightly et al., 2003), and sociodemographic variables (age, parent education, SES, maternal IQ, sex, race, and multiples; Hopkins-Golightly et al., 2003). All three studies (Espy et al., 2007; Hopkins-Golightly et al., 2003; Hüseman et al., 2011) treated pH and/or severity of BD as continuous variables, yet the pH thresholds for the target group varied. Whereas one study (Hüseman et al., 2011) used a severe acidosis cutoff (pH < 7.0 and BD ≤ -16 mEq/L), others (Espy et al., 2007; Hopkins-Golightly et al., 2003) used mild acidosis (pH = 7.3) as a cutoff to define their target group.

Neonatal Blood Acid-Base Measurements Obtained During the First Week of Life and Neuropsychological Outcome in Preterm-Born Children

As a part of the Extremely Low Gestational Age Newborn (ELGAN) study, the research group (Leviton et al., 2010, 2017; see Table 1c for study characteristics and results) investigated the relationships between lowest arterial pH values in the first 72 hours of life and neuropsychological outcome in two- and ten-year old extremely preterm-born children (< 28 weeks gestation), respectively. As shown in Table 1c, Leviton and colleagues (2010) focused on binary classifications of brain pathology (ICH, other brain lesions, microcephaly) and diagnosis of developmental delay. This study found that lowest arterial pH levels within the first 72 hours of life were associated with increased risk of mental, but not motor, dysfunction (MDI or PDI < 70). The later study (2017) from the same group (see Table 1c) documented a significant association between lowest arterial pH recorded within the first 72 hours of life and academic and executive skills, but not language outcomes (Leviton et al., 2017).

Participants with CP, ICH, and other brain lesions were included in the earlier ELGAN study (Leviton et al., 2010). It is unclear whether children with perinatal brain lesions were included in their later study (Leviton et al., 2017). Both ELGAN studies statistically adjusted for standardized birth weight and antenatal complications. However, in their earlier study (2010), which focused on prediction of neurological diagnoses, SES or level of education were not used to predict severe developmental delay. In their later study (2017) of neuropsychological outcome, adjustment was made for SES. Both studies classified infants into categories based on whether values obtained through acid base analysis of (mostly) arterial blood fell within the extreme quartile for gestational age.

Blood Carbon Dioxide (pCO_2) Levels and Neonatal Outcome in the Preterm Infant

As mentioned above (see page 6, *Abnormal Carbon Dioxide Levels*), hypercapnia refers to abnormally high levels of pCO_2 in the blood and is frequently observed in hypoxia (Brouillette & Waxman, 1997; Wong et al., 2022). Elevated pCO_2 can lead to cerebral vasodilation and an increase in cerebral blood flow in the fetus (Bonnin et al., 1992) and preterm infant (Kaiser et al., 2005). Cerebral vasodilation and increased blood flow increases intracranial pressure (Kety & Schmidt, 1948; Lassen & Christensen, 1976; Raper et al., 1971). Consequently, abnormally high pCO_2 levels have been linked with mortality (Ambalavanan et al., 2015; Thome et al., 2017), brain lesions (Altaany et al., 2015; Brown et al., 2018; Kaiser et al., 2006; Kenny et al., 1978; Khodapanahandeh et al., 2008; Kim et al., 2010; Lampe et al., 2020; Levene et al., 1982; Leviton et al., 2010; Ma et al., 2015; Van De Bor et al., 1986; Vela-Huerta et al., 2009; Zayek et al., 2014), as well as a subsequent CP diagnosis (Leviton et al., 2010) in preterm infants. However, of importance, there is no consensus on optimal target pCO_2 levels nor safe parameters (Wong et al., 2022) for preterm infants and some research suggests that permissive hypercapnia, or a mechanical ventilation strategy that tolerates the arterial pCO_2 levels ($pCO_2 > 45$ mmHg) above the normal range (45.90 ± 10.16 mmHg; Brodkorb et al., 2022; see Table 2 for blood gas reference ranges), may be beneficial in the prevention of lung trauma (Ozawa et al., 2022). A meta-analytic review by Ozawa and colleagues (2022) concluded that permissive hypercapnia (target pCO_2 range = 45 – 55 mmHg or 55 – 65 mmHg) does not increase the risk of brain lesions in preterm neonates, like severe hypercapnia does (Ma & Ye et al., 2016; Ozawa et al., 2022). However, other research suggests that permissive hypercapnia may be associated with an increased neurologic risk in preterm infants (Thome et al., 2006). A comprehensive review of permissive hypercapnia is beyond the scope of this study.

Fetal Blood Carbon Dioxide (pCO_2) Levels and Neonatal Outcome in the Preterm Infant

During labor and delivery, fetal hypercapnia is not uncommonly seen due transient compression of the umbilical cord (Tomimatsu et al., 2006). Nonetheless, umbilical cord pCO_2 is commonly used as a measure of pathological hypercapnia present at the time of birth and delivery (Kenny et al., 1978). Though there is a lack of consensus on the pCO_2 threshold associated with pathological sequelae, hypercapnic risk (as indexed by cord pCO_2 levels) observed during the birth and delivery period has been linked to IVH (Kenny et al., 1978).

Neonatal Blood Carbon Dioxide (pCO_2) Levels in the Preterm Newborn and Neonatal Outcome

pCO_2 measurements obtained within the first few days of life are commonly used as a tool to determine the presence of hypercapnia in the postnatal adjustment period (Zhou & Liu, 2008). Hypercapnia can range from mild (pCO_2 = 45 – 55 mmHg) to severe ($pCO_2 \geq$ 65 mmHg; Brown et al., 2018; see Table 3). Severe hypercapnia has been shown to be associated with neurological signs such as decreased alertness (Week et al., 2017; Zhou & Liu, 2008), spasms (Week et al., 2017; Zhou & Liu, 2008), suppressed cortical activity (Week et al., 2017; Zhou & Liu, 2008) in preterm infants. Even more so, higher arterial pCO_2 values obtained in the first hour of life (Ma et al., 2015) as well as within the first week of life (Altaany et al., 2015; Brown et al., 2018; Kaiser et al., 2006; Khodapanahandeh et al., 2008; Kim et al., 2010; Lampe et al., 2020; Levene et al., 1982; Leviton et al., 2010; Van De Bor et al., 1986; Vela-Huerta et al., 2009; Zayek et al., 2014) have been linked to ICH (Altaany et al., 2015; Brown et al., 2018; Kaiser et al., 2006; Khodapanahandeh et al., 2008; Kim et al., 2010; Lampe et al., 2020; Levene et al., 1982; Ma et al., 2015; Van De Bor et al., 1986; Vela-Huerta et al., 2009; Zayek et al., 2014), PVL (Ma et al., 2015), and later diagnosis of CP (Leviton et al., 2010) in preterm infants.

Blood Carbon Dioxide (pCO_2) Measurements and Neuropsychological Outcome in Preterm-Born Children: Systematic Review

The methodological characteristics and results of five studies that investigated the link between hypercapnic risk and neuropsychological outcome are described in Tables 1a through 1c. Table 1a includes studies of *during the birth and delivery period*. Table 1b includes studies based on neonatal blood gases obtained *immediately after birth*. Table 1c includes studies *during the infant's first week of life*.

Cord Blood Carbon Dioxide (pCO_2) Measurements and Neuropsychological Outcome in Preterm-Born Children

As Table 1a reveals, only one study investigated the neurodevelopmental outcome of preterm-born children, with arterial cord pCO_2 values as the variable of interest (Baalbaki et al., 2021; see Table 1a). Baalbaki and colleagues (2021) did not find a significant association between elevated arterial cord pCO_2 (pCO_2 > 77 mmHg) and diagnosis of developmental disability (CP, blindness, deafness, impaired balance, dystonia or IQ < 70).

First Newborn Blood Carbon Dioxide (pCO_2) Measurements and Neuropsychological Outcome in Preterm-Born Children

As shown in Table 1b, only one study investigated the relationships between initial arterial pCO_2 and cognitive and language outcomes of preterm-born children (Hopkins-Golightly et al., 2003). The authors did not document a significant association between initial arterial pCO_2 values and the measured outcomes.

Neonatal Blood Carbon Dioxide (pCO_2) Measurements Obtained During the First Week of Life and Neuropsychological Outcome in Preterm-Born Children

Three studies (Leviton et al., 2010, 2017; McKee et al., 2009) investigated the link between lowest pCO_2 within the first three (Leviton et al., 2010; 2017) to four (McKee et al., 2009) days of life and neuropsychological outcome of preterm-born children. As Table 1c shows, the studies varied in participants' age, which ranged from toddlerhood (McKee et al., 2009; Leviton et al., 2010) to ten years (Leviton et al., 2017). McKee and colleagues used infancy measures to assess infant cognitive and motor outcomes. All three studies documented a significant relationship between abnormally high arterial pCO_2 levels and lower scores on developmental (McKee et al., 2009) or neuropsychological measures (Leviton et al., 2010, 2017).

The methodological characteristics of two of the three studies above (i.e., Leviton et al., 2010, 2017) are discussed above (see page 20, *Neonatal Acid-Base Measurements Obtained During the First Week of Life and Neuropsychological Outcome)*. Hence, only the study by McKee and colleagues (2009) is discussed here. In their multivariate analyses, the researchers statistically adjusted for sociodemographic factors (e.g., sex, race) as well as some medical risk factors (PPROM, severe IVH, sepsis). They classified participants as having a neurodevelopmental disability or not (dichotomized dependent variable) but also performed analyses treating psychomotor outcome (PDI) as a continuous variable.

Blood Oxygenation (pO_2) and Neonatal Outcome in the Preterm Infant

As mentioned above (see page 5, *Abnormal Oxygen Levels*), hypoxemia is defined as abnormally low concentrations of pO_2 in the blood and often causes hypoxia (Samuel & Franklin, 2008). Hypoxemia, negatively affects cerebral oxidative metabolism which, in turn, results in depletion of energy reserves in tissues and subsequent cell death (Piesova & Mach, 2020).

Fetal Blood Oxygenation (pO_2) and Neonatal Outcome in the Preterm Infant

The key defining characteristic of labor is brief but repeated hypoxemia due to uterine contractions (Huch et al., 1977). The fetus has an impressive ability to adapt to hypoxemia with the brain-sparing response (Lear et al., 2018), an adaptation in which blood supply is preferentially perfused to the brain at the expense of peripheral organs. There has been a paucity of research examining fetal hypoxemia, as indexed by umbilical cord pO_2 values, and its association with neurologic and neuropsychological outcome in preterm infants. The dearth of studies is perhaps because maternal supplemental oxygen is commonly administered to women at the time of delivery and fetal cord pO_2 levels have been shown to be reflective of maternal oxygenation, rather than fetal oxygenation (Raghuraman et al., 2021). Likewise, because of the hemoglobin's high affinity for pO_2 in fetal blood, changes in pO_2 may be misinterpreted as changes in oxygenation, despite adequate or inadequate blood perfusion (Arikan et al., 2000). Thus, umbilical cord pO_2 levels may not be an accurate representation of fetal oxygenation, and thus will not be included in the current study.

Blood Oxygenation (pO_2) in the Preterm Newborn and Neonatal Outcome

Preterm infants, including those receiving supplemental oxygen or mechanical ventilation, commonly experience hypoxemia in the postnatal adjustment period, mostly owing to apnea of prematurity or cardiorespiratory instability (Di Fiore et al., 2019; Martin et al., 2007). In the unventilated, spontaneously breathing preterm infant, episodes of hypoxemia are usually credited to hypoventilation due to apnea (Bancalari & Claure, 2018). In the mechanically ventilated preterm infant, hypoxemia is frequently the result of forced exhalations produced by contractions of the abdominal musculature that increase intrathoracic pressure and result in a reduction in lung volume and hypoventilation (Esquer et al., 2007). Neonatal hypoxemia in the preterm neonate has been

linked to bronchopulmonary dysplasia (Jensen et al., 2021), a chronic lung disease, as well as to mortality (Poets et al., 2015). Lower arterial pO_2 values, obtained in the first hour of life (Ma et al., 2015) or within the first 72 hours of life (Van De Bor et al., 1986; Leviton et al., 2010) have been linked to diagnosis of brain lesions in the preterm neonate, including IVH (Ma et al., 2015; Van De Bor et al., 1986), PVL (Ma et al., 2015), and ventriculomegaly (Leviton et al., 2010).

Blood Oxygenation (pO_2) and Neuropsychological Outcome in Preterm-Born Children: Systematic Review

The next section will focus on neonatal blood oxygenation. Table 1b includes studies of blood oxygenation *immediately after birth*. Table 1c includes studies *during the first week of life*.

First Newborn Blood Oxygenation (pO_2) Measurements and Neuropsychological Outcome in Preterm-Born Children

As Table 1b *s*hows, only one study (Hopkins-Golightly et al., 2003) investigated the link between initial blood oxygenation and neuropsychological outcome. Hopkins-Golightly and colleagues were unable to document a significant relationship between arterial pO_2 obtained within 2 hours of birth and language or cognitive outcome at five years of age.

Neonatal Blood Oxygenation (pO_2) Measurements Obtained During the First Week of Life and Neuropsychological Outcome in Preterm-Born Children

As Table 1c shows, researchers from the ELGAN group (Leviton et al., 2010, 2017) documented associations between lowest arterial pO_2 in the first 72 hours of life and the outcome of preterm-born children. While the former investigation focused on toddlers, the latter focused on school-age. Leviton and colleagues' (2010) reported that lowest arterial pO_2 levels within the first 72 hours of life were associated with an increased risk of mental and motor dysfunction (MDI or PDI < 70). They also documented a significant association between lowest arterial pO_2 levels

within the first 72 hours of life and academic and executive skills, but not language outcome (Leviton et al., 2017). Both studies classified infants based on whether the lowest pO_2 fell within the lowest quartile.

Hypotheses and Rationale

Hypothesis 1 (Birth and Delivery)

It is predicted that severity of umbilical cord gas and acid-base derangements, thought to reflect fetal well-being in the last stage of birth and delivery, will explain a unique portion of variance in language and motor skills of preterm-born preschoolers.

Hypothesis 1a (Acid-Base Status). It is hypothesized that derangement in acid-base status occurring during birth and delivery, as indexed by arterial umbilical cord pH or BD, will explain a unique portion of variance in measures of language and motor skills.

Rationale. As discussed (see page 11, *Hypoxic-Ischemic Brain Injury in the Preterm Infant*), preterm infants appear to be at increased risk for primarily subcortical hypoxic-ischemic damage (e.g., Barkovich & Truit, 1990; Goplerud & Delivoria-Papadopoulos, 1993), rather than cortical (Barkovich & Truit, 1990; Goplerud & Delivoria-Papadopoulos, 1993). Neuropathological correlates of brain damage due to hypoxia and ischemia in preterm infants include various brain lesions, including PVL (Folkerth, 2006) and IVH (Ment et al., 2013). Acidemia and acidosis are both indicators of oxygen deprivation and hypoxia in the fetus (American College of Obstetricians & Gynecologists, 2014). It has been widely documented that lower umbilical artery pH or severity of BD are associated with hypoxic ischemic brain lesions in preterm infants, including PVL (J. Huang et al., 2017; Malin et al. 2010; Victory et al., 2003) and IVH (Lavrijsen et al., 2005; Malin et al. 2010; Randolph et al., 2014; Victory et al., 2003), as well as neuromotor impairment (i.e., CP; Baalbaki et al., 2021; Malin et al. 2010; Randolph et al., 2014).

Only one study (Piercy, 2019) documented a linear association between arterial cord pH and motor and language functioning in 151 preterm preschoolers. The current study is an extension of Piercy (2019) and will include arterial cord BD as an index of acid-base status, blood gas data (pO_2 and pCO_2), and a larger sample size (Piercy, 2019, total n = 189).

Hypothesis 1b (Blood Gases: Carbon Dioxide). It is hypothesized that severity of hypercapnia during birth and delivery, as indexed by arterial umbilical cord pCO_2 values, will explain a unique portion of variance in measures of language and motor skills.

Rationale. As described (see page 21, *Blood Carbon Dioxide (pCO_2) Levels and Neonatal Outcome in the Preterm Infant*), hypercapnia is associated with cerebral vasodilation and an increase in cerebral blood flow (CBF) in the fetus (Bonnin et al., 1992). Cerebral vasodilation and an increase in CBF ultimately increase intracranial pressure (Kety & Schmidt, 1948; Lassen & Christensen, 1976; Raper et al., 1971) and may result in hypoxic injury (Kasirer et al., 2022). Fetal hypercapnia (as indexed by cord pCO_2) has been linked to IVH in preterm infants (Kenny et al., 1978). Only one study (Baalbaki et al., 2021) investigated the relationship between diagnosis of hypercapnia (defined categorically as cord pCO_2 values > 77mg) and quality of performance on neurodevelopmental measures in preterm-born children (Baalbaki et al., 2021). As described in Table 1a (and see page 23, *Cord Blood Carbon Dioxide Measurements and Neuropsychological Outcome)*, Baalbaki and colleagues (2021) documented a significant association between pCO_2 values (pCO_2 > 77 mmHg) and global neurodevelopmental impairment (CP, blindness, deafness and intellectual disability) in very preterm singletons (ages 5-8). No studies have investigated the relationships between degree of hypercapnia at birth (based on arterial umbilical cord blood sample) and neuropsychological measures of fine and gross motor skills or language skills. As noted above (see page 11, *Hypoxic-Ischemic Brain Injury in the Preterm Infant*), motor and

language functioning are highly sensitive to hypoxic-ischemic damage in the preterm neonate (Barkovich & Truit, 1990; Goplerud & Delivoria-Papadopoulos, 1993).

Hypothesis 2 (Immediate Neonatal Adjustment)

It is predicted that severity of blood gas and acid-base derangements in the preterm newborn, measured soon after delivery, will explain a unique portion of the variance in language and motor skills at preschool age, over and above the variance explained by other perinatal risk factors.

Hypothesis 2a (Acid-Base Status). It is hypothesized that derangement in acid-base status, assessed immediately after birth and indexed by initial neonatal blood pH or BD, will explain a unique portion of variance in measures of language and motor skills.

Rationale. Initial newborn blood gas measurements are critical to providing essential information about the immediate functioning of an infant's newly assumed, independent cardiorespiratory responsibilities. As described (see page 15, *Neonatal Acid-Base Status and Neonatal Outcome*), both acidosis (Lee et al., 2018; Ma et al., 2015) and base deficit (Lee et al., 2018; Ma et al., 2015; Mires et al., 1991) observed during the immediate neonatal adjustment period have been linked to brain lesions in preterm newborns, including PVL (Ma et al., 2015; Mires et al., 1991) and IVH (Lee et al., 2018; Ma et al., 2015; Mires et al., 1991). Only one study (Hopkins-Golightly et al., 2003) investigated the link between initial arterial pH or BD and language functioning in preterm children at age five (Hopkins-Golightly et al., 2003; see Table 1b). This study included children with initial pH values in the mild to moderate acidosis range (pH ranged from 7.1 – 7.3) but was still able to document an association between pH and language outcome despite absence of severely acidotic cases. However, as noted above (see page 18, *First Newborn Blood Acid-Base Measurements and Neuropsychological Outcome;* see Table 1b), the

authors did not find the predicted inverse relationship between severity of BD and language functioning. The current study includes indices of fine and gross motor functioning, which are skills that are very vulnerable to perinatal hypoxic-ischemic injury (Barkovich & Truit, 1990; Goplerud & Delivoria-Papadopoulos, 1993) and have yet to be explored in the context of initial infant pH and BD.

Hypothesis 2b (Blood Gases: Carbon Dioxide). It is hypothesized that severity of hypercapnia, assessed immediately after birth and indexed by initial neonatal blood pCO_2 values, will explain a unique portion of variance in measures of language and motor skills.

Rationale. As mentioned, (see page 22, *Neonatal Blood Carbon Dioxide Levels and Neonatal Outcome*), severity of hypercapnia (as indexed by arterial pCO_2 values obtained within the first hour of life) has been associated with IVH and PVL in preterm infants (Ma et al., 2015). Only one study investigated the relationship between initial arterial pCO_2 values (obtained within the first 2 hours of life; Hopkins-Golightly et al., 2003) and language functioning (see Table 1b). This study did not find a significant relationship between initial hypercapnic risk and language skills in preterm-born preschoolers. The current study includes indices of fine and gross motor functioning, which have yet to be explored in the context of initial infant pCO_2 values. The current study also uses a sample that benefited from the advent of technological changes in the NICU (e.g., gentle ventilators).

Hypothesis 2c (Blood Gases: Oxygen). It is hypothesized that severity of hypoxemia, assessed immediately after birth and indexed by initial neonatal blood pO_2 values, will explain a unique portion of variance in measures of language and motor skills.

Rationale. As described (see page 24, *Blood Oxygenation and Neonatal Outcome)*, neonatal hypoxemia, as indexed by low arterial pO_2 values obtained within the first hour of life,

has been associated with IVH and PVL in preterm infants (Ma et al., 2015). Yet only one study (Hopkins-Golightly et al., 2003) investigated the relationships between degree of hypoxemia (observed immediately after birth) and neuropsychological sequalae (see Table 1b). Hopkins-Golightly and colleagues (2003) did not find a significant relationship between initial pO_2 values within 2 hours of birth and language skills obtained at kindergarten age (see Table 1b). Nonetheless, given that hypoxemia during the first week of life has been linked to CP (Leviton et al., 2010), PVL (Ma et al., 2015), ventriculomegaly (Leviton et al., 2010), and IVH (Ma et al., 2015; Van De Bor et al., 1986) in preterm infants, it is possible that a link to language and motor functioning can also be established.

Hypothesis 3 (Initial Neonatal Adjustment Within the First Week of Life)

It is hypothesized that severity of blood gas and acid-base derangement during the initial neonatal adjustment period (within the first week of life) will explain a unique portion of variance in measures of language and motor skills in a sample of preterm-born preschoolers, over and above the variance explained by other perinatal risk factors.

Hypothesis 3a (Acid-Base Status). It is hypothesized that the lowest pH or BD observed within the first week of life will explain a unique portion of variance in measures of language and motor skills.

Rationale. The first week of life is a period of the highest frequency of respiratory, cardiovascular, and metabolic pathology in preterm infants (Greisen, 1986). Blood-gas and acid-base status conveys important information to providers about physiological functioning. As noted above (see page 15, *Neonatal Acid-Base Status and Neonatal Outcome*), there is an abundance of literature that documents the associations between acidosis (Brown et al., 2018; Goswami et al., 2021; Graziani et al., 1992; Leviton et al., 2010; Van De Bor et al., 1986; Vela Huerta et al., 2009;

Zayek et al., 2014) or severity of base deficit (Goswami et al., 2021; Van De Bor et al., 1986; Vela Huerta et al., 2009; Zayek et al., 2014) observed during the first 72 hours of life and brain lesions in preterm-born infants, including IVH (Brown et al., 2018; Goswami et al., 2021; Graziani et al., 1992; Levene et al.. 1982; Van De Bor et al., 1986; Vela Huerta et al., 2009; Zayek et al., 2014), and ventriculomegaly (Leviton et al., 2010). Lowest arterial pH has also been linked with CP (Leviton et al., 2010) in preterm infants. Only one study (Leviton et al., 2010) investigated the relationship between acidemia (categorically defined by most extreme pH) during the first 72 hours of life and motor outcome at age two (Leviton et al., 2010; see Table 1c). Similarly, the same research group (Leviton et al., 2017) investigated the relationship between lowest pH (categorically defined by most extreme pH) and language outcome at age ten (Leviton et al., 2017; see Table 1c). Neither study documented a significant association between lowest pH and outcome. Both studies categorically classified pH measurements. The current study includes an additional measure of acid-base status, BD, as well as treats pH and BD as continuous variables. The current study also includes fine and gross motor functioning measures at preschool age (Bolisetty et al., 2014; Imamura et al., 2013; O'Shea et al., 2012; van Haastert et al., 2008).

Hypothesis 3b (Blood Gases: Carbon Dioxide). It is hypothesized that the highest pCO_2 will explain a unique portion of variance in measures of language and motor skills.

Rationale. As mentioned on page 22 (*Neonatal Blood Carbon Dioxide Levels and Neonatal Outcome*), severity of hypercapnia (indexed by blood pCO_2) during the early neonatal adjustment period (first three days or first week of life) has been consistently linked to IVH (Altaany et al., 2015; Brown et al., 2018; Kaiser et al., 2006; Khodapanahandeh et al., 2008; Kim et al., 2010; Lampe et al., 2020; Levene et al., 1982; Ma et al., 2015; Van De Bor et al., 1986; Vela-Huerta et al., 2009; Zayek et al., 2014) as well as a subsequent diagnosis of CP (Leviton et

al., 2010) in preterm infants. As Table 1c shows, two studies (Leviton et al., 2010; McKee et al., 2009) have investigated the link between abnormally high arterial pCO_2 levels during the first three to four days of life and motor development in preterm-born toddlers. Both studies documented a significant association. Only one study (Leviton et al., 2017) investigated the relationship between highest pCO_2 and language outcome at age ten (see Table 1c), but did not document an association. The current study includes measures of fine and gross motor functioning (not studied by Leviton et al., 2017; Bolisetty et al., 2014; Imamura et al., 2013; O'Shea et al., 2012; van Haastert et al., 2008).

Hypothesis 3c (Blood Gases: Oxygen). It is hypothesized that the lowest blood pO_2 will explain a unique portion of variance in measures of language and motor skills.

Rationale. As mentioned on page 24 (*Blood Oxygenation and Neonatal Outcome*), lower arterial pO_2 values obtained within the first 72 hours of life have been linked to perinatal brain lesions, such as IVH (Van De Bor et al., 1986), and ventriculomegaly (Leviton et al., 2010) in preterm-born infants, as well as to subsequent diagnosis of CP (Leviton et al., 2010). Only one study (Leviton et al., 2010) investigated the relationship between hypoxemia (categorically defined by most extreme pO_2) during the first 72 hours of life and motor outcome at age two (Leviton et al., 2010; see Table 1c). This research group documented a significant association. The same research group (Leviton et al., 2017) investigated the relationship between lowest pO_2 and language outcome at age ten (Leviton et al., 2017; see Table 1c), but did not document an association. Both studies categorically classified pO_2 values. The current study explores the linear relationship between extreme pO_2 values and fine and gross motor functioning, which are highly sensitive to hypoxic insult (Bolisetty et al., 2014; Imamura et al., 2013; O'Shea et al., 2012; van Haastert et al., 2008).

Hypothesis 4 (Birth and Delivery Period versus Neonatal Adjustment Period)

It is hypothesized that indices of risk for postnatal hypoxia-ischemia will explain a greater portion of variance in language and motor performance, compared to indices of fetal risk.

Rationale. Exposure to *cumulative* perinatal complications has been associated with increased vulnerability for white matter injury in preterm infants (Barnett et al., 2017). *Neonatal* blood gas and acid-base measures likely reflect negative sequalae of fetal adversity that is carried forward (De Franco et al., 2007), plus the sequelae of risk factors unique to the neonatal period. In other words, neonatal measures may actually reflect cumulative risk.

CHAPTER 2: METHOD

Participants

Inclusion Criteria

Children were recruited as a part of a larger collaborative study between William Beaumont Hospital (WBH) and Wayne State University (WSU) that examines the relationships between perinatal complications and neuropsychological outcome at preschool and school age. The study was approved by both WBH and WSU Human Investigation Committees. Families of preterm-born (< 34 weeks gestation) preschoolers who were previously served in the WBH Neonatal Intensive Care Unit (NICU) in Royal Oak, Michigan were contacted. Participants were born between September 2007 and September 2015 and evaluated between three and four years of age.

Exclusion Criteria

Infants with congenital anomalies, chromosomal disorders, neurosensory impairment, or need for mechanical ventilation following discharge from the NICU were excluded from the study and not contacted. Infants were also excluded if they were born in another hospital and transported to WBH. The families of 43.4% of 1270 cases were successfully contacted for recruitment attempt (see Recruitment Process Flow Chart for complete description in Figure 1). As the figure shows, 42.1% of successfully contacted families were not interested for various reasons. Three hundred and ten cases were scheduled for testing. Seventy-two scheduled cases no-showed two or more times and were not rescheduled. In total, 239 scheduled cases were evaluated at preschool age. Of the 239 cases that were evaluated, 16 participants were not included in the sample due to either unavailable maternal medical background data, lack of cooperation or were untestable with our neuropsychological instruments due to very low function, or suspected maternal substance use in utero.

Sample Characteristics

The total sample size available for analysis was 224 children. Analyses were also performed after the exclusion of 13 cases with severe neurological deficits, including diagnosis of cerebral palsy (n = 6), severe intracranial hemorrhage (ICH > Grade 2) or other intracranial pathology (n = 3), or both conditions (n = 1). Cases with seizures were also excluded (n = 3). Table 4 displays socio-demographic data for the total sample of 224 cases and the subsample of 211, without cases with known neurological complications, disorders, or deficits. As shown in the table, the sample predominantly consisted of middle-class families, with race (White = 76%, Black/Asian/Indian = 24%), and sex (Male = 45%) representations reflective of the general population. Perinatal complications and intervention procedures for the samples are presented in Tables 5 and 6.

Neuropsychological Assessment

Assessment Procedures

Evaluations were administered between May 2011 and March 2020 by clinical psychology graduate students who were extensively trained in developmental neuropsychological assessment. The examiners were kept uninformed about participants' medical history during the evaluation, except for being aware that the children were NICU graduates. All children were evaluated in one to three sessions, with attention to the child's fatigue level. Breaks were taken as needed.

Neuropsychological Measures

Language Skills. The Clinical Evaluation of Language Fundamentals— Preschool, Second Edition (CELF-P2; Wiig et al., 2004) was used as a measure of expressive (i.e., language production) and receptive (i.e., understanding of spoken language) language skills. Reliability and validity information for the sample's chronological age is presented in Table 7.

The CELF-P2 includes six core subtests which make up five index scores. The three indices of interest (i.e., core language, receptive language, expressive language) for the current study are described below. The Core Language Index (CLI), a composite measure of overall language performance, is comprised of three subtests: Sentence Structure, Word Structure, and Expressive Vocabulary. The Receptive Language Index (RLI) is an index of auditory comprehension, and it is comprised of Sentence Structure, Concepts and Following Directions, and Basic Concepts. The Expressive Language Index (ELI) is a measure of language production, and it is comprised of Word Structure, Expressive Vocabulary, and Recalling Sentences.

Motor Skills. Gross and fine motor functioning were evaluated using the Peabody Developmental Motor Scales—Second Edition (PDMS-2; Folio & Fewell, 2000). Reliability and validity properties may be found in Table 7. The Gross Motor Quotient (GMQ) is comprised of three subtests: Stationary, Locomotion, and Object Manipulation, and assesses a child's ability to maintain balance, run, jump, throw, catch, and kick a ball. The Fine Motor Quotient (FMQ) is comprised of the Grasping and Visual-Motor Integration subtests and assesses a child's ability to grasp objects, control finger movements, and eye-hand coordination.

Newborn Variables

Blood Sampled from the Umbilical Cord

Arterial cord blood gas values and acid-base data analyzed in ≤ 60 minutes from sample collection were retrospectively retrieved from medical records. Beyond this time frame, the acid-base balance data is presumed unreliable (Armstrong & Stenson, 2007). An exception to the rule were three cases that were slightly, though not significantly, above the 60-minute predetermined threshold ($M_{ThreeCases}$ = 62.3 minutes). Altogether, a total of 175 cases had arterial umbilical cord

blood gas and acid-base measurements available for analysis. Table 8 provides descriptive statistics of these cord blood values.

Blood Sampled from the Newborn

Arterial or capillary blood gas and acid-base data from two collection periods were used for this study. The initial blood gas and acid-base balance data derived from blood sampling within the first three hours of life were available for 98 cases. Additionally, the most extreme blood gas values and acid-base balance data derived from blood sampling within the first week of life (3 completed hours of life to 7 completed days of life) were available for 116 cases. Table 8 provides descriptive statistics for both collection periods (i.e., first 3 hours of life; 3 completed hours of life to 7 completed days of life).

Comparability Between Infant Blood Gas Measurements. Whereas arterial blood gas is typically available when cord blood samples are obtained, there are several methods to obtain blood samples in preterm infants (see page 8, *Blood Gas and Acid-Base Measurement from the Preterm Neonate*). Several studies comparing arterial and capillary blood gas analysis in preterm newborns reported no significant differences between arterial and capillary values for pH (McLain et al., 1988; Yang et al., 2018), pCO_2 (Brodkorb et al., 2022; McLain et al., 1988; Yang et al., 2018), and BD (Yang et al., 2018). Based on these investigations, using capillary blood as a source for pH, BD, and pCO_2 values may be an acceptable alternative for arterial blood gas measurements in preterm-born infants. However, capillary pO_2 measurements have consistently been reported to be significantly lower than arterial pO_2 values in preterm-born infants (Brodkorb et al., 2022; McLain et al., 1988; Yang et al., 2018; Yapıcıoğlu et al., 2014). Thus, capillary pO_2 values were adjusted to reflect arterial pO_2 values ($pO_2^{adjusted} = 0.64 \cdot pO_2^{capillary} + 28.32$ mmHg) using a correction formula proposed by Brodkorb and colleagues (2022).

CHAPTER 3: RESULTS

General Statistical Considerations

Mixed effects linear regression analyses were conducted to test Hypotheses 1 through 3. For these hypotheses, blood gas (pO_2 and pCO_2) and acid-base balance (pH and BD), four predictors of interest, were used separately in mixed regression models with family membership (i.e., belonging to a twin pair or a triplet) serving as a random factor (see additional explanation below). Corrected standard scores (adjusted for gestational age at birth) from three outcome measures reflecting language performance (CELF-P2 Core Language Index, Expressive Language Index, Receptive Language Index) and two reflecting motor performance (PDMS-2 Gross Motor Quotient, Fine Motor Quotient) were the dependent variables (see Table 9). As noted above, scores on outcome measures were adjusted for degree of prematurity. The gestational age correction was performed to ensure that scores were reflective of each participant's true biological age. Follow-up analyses of subtest scores were conducted when significant associations were found between one of the four predictors of interest and a language or motor performance index. Additional analyses using Steiger's *Z* Test for dependent correlations were performed when significant associations were found between a biochemical parameter and outcome variable. These analyses were performed in order to determine if the significant observed relationship between a blood-gas or acid base value with an outcome measure was stronger than the same parameter's relationship with another outcome variable. Umbilical cord blood pH, BD, and pCO_2 values were used as the independent variables for Hypothesis 1. Neonatal blood pH, BD, pCO_2, and pO_2 values were used as the independent variables for Hypotheses 2 and 3.

Sociodemographic (sex and socioeconomic status) and perinatal (gestational age, standardized birth weight, and sum of antenatal complications) variables were included as

covariates in all regression analyses for Hypotheses 1 through 3. All predictors of interest and covariates were screened for multicollinearity, as high correlations between predictors can lead to issues with model fit and spurious results. The sum of perinatal (antenatal + neonatal) complications and the sum of neonatal complications highly correlated with gestational age (total complications, $r = -0.65$, $p < .001$; neonatal complications, $r = -0.74$, $p < .001$) and were therefore not included in any models. Oromotor functioning, as assessed with the NEPSY-2 Oromotor Sequences subtest score (classified into categories based on performance percentile), was a covariate in all analyses that include expressive language (CLI, ELI) as the dependent variable in order to adjust for the oral-motor component required to produce spoken language. All covariates were simultaneously entered into the model with each predictor of interest. Prior to data analyses, interactions between sex and blood gas/acid-base parameters were also examined for each outcome measures and were included in the relevant models when $p < .05$.

Statistical analyses were performed separately for the total sample of 224 cases and the reduced (non-neurological) sample of 211 cases following exclusion of 13 cases. Information about bivariate correlations among the predictors may be found in Tables 10 and 11 for the total sample and reduced subsample, respectively. Bivariate correlations between blood gas and acid-base measurements can be found in Tables 12 and 13, respectively.

Fixed and Random Factors

As the sample includes participants of multiple gestation (Twins, $n = 93$; Triplets, $n = 9$), mixed effects linear regression analyses were utilized to test Hypotheses 1 – 3, with multiple gestation (i.e., family membership) used as a random effect. Individual multiples within each twin or triplet set were treated as replications. Singleton children or multiples without an evaluated co-multiple did not have replicates and were considered a random block with size one. This model

allowed both co-multiples and singletons to be included in the same analysis without violating independence assumptions or discarding information by including only one member of a set.

Missing Data

Missing data and assumption violations were also considered. Participants whose blood gas measurements were not obtained for one of the three collection periods (birth & delivery, 0 – 3 hours of life, or 3 hours to 7 completed days of life) were deleted from the relevant analysis via listwise deletion (see Table 14 for the percent of unavailable blood-gas and acid-base values). With regard to language and motor outcome, a missing values pattern analysis for outcome measures with greater than 5% missingness revealed missing values to be "missing at random" (MAR; see Tables 15 and 16 for percent missingness for covariates and outcome variables, respectively). To maintain the integrity of our data, I chose not to impute and opted to use pairwise deletion instead. Violations of normality, independence of observations, linearity, and homoscedasticity were not detected following extensive screening. Multivariate outliers were screened using Mahalanobis' distance. Statistical analyses were performed with and without multivariate outliers for the total and reduced sample. All results tables show analyses after the removal of these outliers. Analyses with the inclusion of outliers are provided in footnotes. Power calculations (Faul et al., 2009) revealed that for multiple regression analyses with six predictors and a power of 0.80, a sample of 98 is necessary to detect a medium effect and a sample of 688 is necessary for detection of a small effect. The available sample size for the birth and delivery period was 175. The available sample sizes for the immediate adjustment (0 to 3 hours of life) and initial adjustment (3 hours of life to 7 completed days of life) were 98 and 116, respectively.

Findings by Hypothesis

Hypothesis 1 (Birth and Delivery)

Tables 17a-b to 19a-b present findings pertaining to Hypothesis 1 for the total sample, and after exclusion of cases with neurological deficits.

Hypothesis 1a (Acid-Base Status). It was hypothesized that derangement in acid-base status occurring during birth and delivery, as indexed by arterial umbilical cord pH or BD, would explain a unique portion of variance in measures of language and motor skills. Tables 17a-b and 18a present the findings for cord pH and cord BD after removal of outliers, respectively (see footnote e in Tables 17a and 18a and footnote d in Table 17b for analyses that include outliers).

Cord pH. Consistent with predictions, umbilical cord pH was significantly associated with the GMQ in the reduced sample (p = .038) and trended in the same observed direction in the total sample (p = .076; see Table 17a). Consistent with Hypothesis 1a, lower cord pH values were associated with lower scores on the GMQ (see Figures 2 and 3). Cord pH accounted for 2.2% and 4.2% of the variance in the GMQ in the reduced sample and total sample, respectively (see Table 17a). However, contrary to predictions, cord pH was not significantly associated with FMQ nor any of the language measures in either the total or reduced sample after exclusion of "neurological" cases (see Table 17a).

Based on the relationship observed between cord pH and GMQ, follow-up analyses were conducted using subtest scores comprising the gross motor index as outcomes of interest (see Table 17b). Cord pH was significantly associated with the Locomotion subtest score in the total (p = .010, ΔR^2 = .121) and reduced (p = .001, ΔR^2 = .142) sample (see Figures 4 and 5). Cord pH was not significantly associated with Stationary or Object Manipulation scores in the total or reduced sample (see Table 17b). Again, lower cord pH values were associated with lower scores.

Follow-up analyses using Steiger's *Z* Test for dependent correlations were conducted to determine if the relationship between cord pH and GMQ was significantly stronger than the relationships between cord pH and the four other measured outcomes (FMQ, CLI, ELI, RLI). The correlation between cord pH and GMQ was significantly stronger than that of cord pH and CLI in the reduced sample (Steiger $Z = 2.06$, $p = .019$), and trended in the same direction in the total sample (Steiger $Z = 1.38$, $p = .080$). The difference in correlations between cord pH with performance on GMQ and FMQ approached significance in the total (Steiger $Z = 1.12$, $p = .131$) and reduced sample (Steiger $Z = 1.28$, $p = .101$). The difference in correlations between cord pH and performance on GMQ versus ELI trended towards significance in the reduced sample (Steiger $Z = 1.48$, $p = .069$), and was nonsignificant in the total sample (Steiger $Z = 0.68$, $p = .248$). The difference in correlations between cord pH and performance on GMQ versus RLI was nonsignificant in the total (Steiger $Z = 0.40$, $p = .345$) and reduced (Steiger $Z = 0.74$, $p = .229$) sample.

Follow-up analyses using Steiger's *Z* Test for dependent correlations were also conducted to determine if the relationship between cord pH and Locomotion score was significantly stronger than the relationships between cord pH and the two other gross motor subtest scores (Stationary and Object Manipulation). The difference in correlations between cord pH with performance on the Locomotion and Stationary subtests was marginally significant in the total (Steiger $Z = 1.34$, $p = .089$) and reduced sample (Steiger $Z = 1.38$, $p = .084$). The difference in correlations between cord pH and performance on Locomotion versus Object Manipulation was nonsignificant in the total (Steiger $Z = 0.01$, $p = .495$) and reduced (Steiger $Z = 0.73$, $p = .232$) sample.

Cord BD. Contrary to predictions, umbilical cord BD was not significantly associated with any of the motor or language indices in the total or reduced sample (see Table 18a).

Hypothesis 1b (Blood Gases: Carbon Dioxide). It was hypothesized that severity of hypercapnia during birth and delivery, as indexed by arterial umbilical cord pCO_2 values, would explain a unique portion of variance in measures of language and motor skills. Tables 19a-b present the findings for cord pCO_2 after removal of an outlier (see footnotes e and d in Tables 19a and 19b, respectively, for analyses that include the outlier).

Consistent with predictions, umbilical cord pCO_2 was significantly associated with GMQ score in the total sample (p = .049) and reduced (non-neurological) sample (p = .029; see Table 19a). In accord with Hypothesis 1b, higher cord blood pCO_2 values were associated with lower scores on the GMQ and accounted for 4.3% and 2.2% of the variance in the total and reduced sample, respectively (see Figures 6 and 7). However, contrary to predictions, cord pCO_2 was not significantly associated with FMQ scores or any of the language measures in either sample (see Table 19a).

Follow-up analyses were conducted using subtest scores comprising the gross motor index as outcomes of interest (see Table 19b). Cord pCO_2 was significantly associated with Locomotion score in the total (p = .010, ΔR^2 = .119; see Figure 8) and reduced sample (p = .004, ΔR^2 = .128; see Figure 9). The relationship between cord pCO_2 and Object Manipulation score trended in the direction of significance in the total sample (p = .095, ΔR^2 = .010). Cord pCO_2 was not significantly associated with Object Manipulation scores in the reduced sample (p = .190) nor Stationary scores in the total or reduced sample. Higher cord pCO_2 values were associated with lower scores on both the Locomotion and Object Manipulation subtests (see Table 19b).

Follow-up analyses using Steiger's Z Test for dependent correlations were conducted to determine if the relationship between cord pCO_2 and GMQ was significantly stronger than the relationships between cord pCO_2 and the other four measured outcomes (FMQ, CLI, ELI, RLI).

The correlation between cord pCO_2 and GMQ was significantly stronger than that of cord pCO_2 and CLI in the reduced (Steiger Z = -2.80, p = .003) and total sample (Steiger Z = -2.15, p = .016). The correlation between cord pCO_2 and GMQ was also significantly stronger than the correlation between cord pCO_2 and ELI in the reduced sample (Steiger Z = -2.06, p = .020), and trended in the same direction in the total sample (Steiger Z = -1.43, p = .076). The differences in correlations between cord pCO_2 and performance on GMQ versus FMQ and GMQ versus RLI were nonsignificant in the total (FMQ; Steiger Z = -0.76, p = .224; RLI, Steiger Z = -1.00, p = .159) and reduced (FMQ; Steiger Z = -0.90, p = .182; RLI, Steiger Z = -1.14, p = .127) sample.

Follow-up analyses using Steiger's Z Test for dependent correlations were also conducted to determine if the relationship between cord pCO_2 and Locomotion score was significantly stronger than the relationships between cord pCO_2 and the two other gross motor subtest scores (Stationary and Object Manipulation). The difference in correlations between cord pCO_2 with performance on the Locomotion versus Stationary subtests and Locomotion versus Object Manipulation subtests was nonsignificant in the total (Stationary; Steiger Z = -1.13, p = .129; Object Manipulation, Steiger Z = -0.01, p = .494) and reduced sample (Stationary; Steiger Z = -0.85, p = .195; Object Manipulation, Steiger Z = -0.58, p = .280).

Hypothesis 2 (Neonatal Adjustment Immediately After Birth)

Tables 20-23 show the findings pertaining to Hypothesis 2 for the total sample, and after exclusion of cases with neurological deficits.

Hypothesis 2a (Acid-Base Status). It was hypothesized that derangement in acid-base status, assessed immediately after birth and indexed by neonatal blood pH or BD obtained within the first three hours of life, would explain a unique portion of the variance in measures of preschool language and motor skills. Tables 20 and 21a-b present the findings for initial neonatal pH or BD,

obtained within the first three hours of life, respectively. Tables 21a-b present the findings for initial BD after removal of an outlier (see footnotes e and d in Tables 21a and 21b, respectively, for analyses that include the outlier).

Initial Neonatal pH. Contrary to prediction, initial neonatal blood pH obtained within the first three hours of life was not significantly associated with either motor or language indices in the total nor reduced sample after adjustment for covariates (see Table 20).

Initial Neonatal BD. Consistent with predictions, initial neonatal BD was significantly associated with GMQ scores in the total sample (p = .028; see Table 21a). This relationship was not significant in the reduced sample (p = .188). In accord with Hypothesis 2a, lower initial BD values were associated with lower scores on the GMQ (see Figure 10) and accounted for 1.1% of the variance in GMQ in the total sample (see Table 21a). However, contrary to predictions, initial BD was not significantly associated with FMQ scores nor any of the language measures in the total or reduced sample (see Table 21a).

Follow-up analyses were conducted using subtest scores comprising the gross motor index as outcomes of interest (see Table 21b). Initial BD was significantly associated with the Stationary subtest score in the total (p = .049, ΔR^2 = .032; see Figure 11) sample and trended in the similar observed direction in the reduced sample (p = .097, ΔR^2 = .028). Initial BD was not significantly associated with Locomotion or Object Manipulation scores in the total or reduced sample (see Table 21b). Again, lower initial BD values were associated with lower scores.

Follow-up analyses using Steiger's Z Test for dependent correlations were conducted to determine if the relationship between initial BD and GMQ was significantly stronger than the relationships between initial BD and the other four measured outcomes in the total sample (FMQ, CLI, ELI, RLI). The correlation between initial BD and GMQ was significantly stronger than the

correlations between initial BD and all four measured outcomes in the total sample (FMQ, Steiger $Z = 2.60$, $p = .004$; CLI, Steiger $Z = 2.51$, $p = .006$; ELI, Steiger $Z = 2.20$, $p = .013$; RLI, Steiger $Z = 3.34$, $p < .001$).

Follow-up analyses using Steiger's Z Test for dependent correlations were also conducted to determine if the relationship between initial BD and Stationary score was significantly stronger than the relationships between initial BD and the two other gross motor subtest scores in the total sample (Locomotion and Object Manipulation). The difference in correlations between initial BD with performance on the Stationary versus Locomotion subtests trended in the direction of significance in the total sample (Steiger $Z = 1.20$, $p = .115$). The difference in correlations between initial BD with performance on the Stationary versus Object Manipulation subtests was nonsignificant in the total sample (Steiger $Z = 0.11$, $p = .455$).

Hypothesis 2b (Blood Gases: Carbon Dioxide). It was hypothesized that severity of hypercapnia, assessed immediately after birth and indexed by initial pCO_2 values, would explain a unique portion of variance in measures of language and motor skills. Table 22 presents the findings for initial neonatal pCO_2.

Contrary to predictions, initial neonatal pCO_2 was not significantly associated with any of the motor nor language indices in the total or reduced sample (see Table 22). Of note, significant interactions were observed between sex and initial pCO_2 values when GMQ score was the outcome variable of interest in the total and reduced sample. A significant interaction was observed between sex and initial pCO_2 when FMQ score was the outcome of interest in the reduced sample as well. For both outcome variables, higher pCO_2 values tended to be associated with lower GMQ and FMQ scores in boys. However, for girls, lower neonatal pCO_2 values were associated with lower scores on the GMQ and FMQ. Importantly, in the girls only sample, initial pCO_2 values were

restricted in range (pCO_2 range = 28 - 68). This is in comparison to the boys only sample, that included a wide range of initial pCO_2 values (pCO_2 range = 35 - 93). Nonetheless, when the interaction between sex and initial pCO_2 was not included in analyses, the relationship between initial pCO_2 and all outcome variables remained nonsignificant.

Hypothesis 2c (Blood Gases: Oxygen). It was hypothesized that severity of hypoxemia, assessed immediately after birth and indexed by initial neonatal blood pO_2, would explain a unique portion of variance in measures of language and motor skills. Table 23 presents the findings for initial neonatal blood pO_2 after removal of outliers (see footnote e for analyses that include outliers).

Contrary to predictions, initial neonatal blood pO_2 obtained within the first three hours of life was not significantly associated with either motor or language indices in the total nor reduced sample after adjustment for covariates (see Table 23).

Hypothesis 3 (Initial Neonatal Adjustment Within the First Week of Life)

Tables 24-27a show the findings pertaining to Hypothesis 3 for the total sample, and for the reduced sample, after exclusion of cases with neurological deficits.

Hypothesis 3a (Acid-Base Status). It was hypothesized that the lowest pH or BD observed within the first week of life (3 hours of life to 7 days of life) would explain a unique portion of variance in measures of language and motor skills. Tables 24 and 25a-b present the findings of multiple regression analyses examining the relationships between the two acid-base parameters and preschool outcome indices. Tables 25a-b present the findings for lowest BD after removal of an outlier (see footnotes e and d in Tables 25a and 25b, respectively, for analyses that include the outlier).

Lowest pH. Contrary to predictions, after adjustment for covariates, lowest pH was not associated with any motor or language indices in the total sample, nor in the reduced sample, following exclusion of neurological cases (see Table 24).

Lowest BD. Consistent with predictions, the relationship between lowest neonatal BD and RLI scores approached significance in the total sample (p = .069). In accord with Hypothesis 3a, lower BD values were associated with lower scores on the RLI and accounted for 0.6% of the variance in RLI in the total sample (see Table 25a; see Figure 12). However, contrary to predictions, lowest BD was not significantly associated with RLI in the reduced sample (p = .116), nor GMQ, FMQ, CLI, or ELI scores in the total or reduced sample (see Table 25a).

Follow-up analyses were conducted using subtest scores comprising the receptive language index as outcomes of interest (see Table 25b). Lowest BD was significantly associated with the Concepts and Following Directions subtest score in the total (p = .045, ΔR^2 = .010) sample and trended in the similar observed direction in the reduced sample (p = .100). The relationship between lowest BD and Basic Concepts scores also trended in a similar observed direction in the total sample (p = .059, ΔR^2 = .012), but was not significant in the reduced sample (p = .112). Lowest BD was not significantly associated with Sentence Structure scores in the total or reduced sample (see Table 25b). Again, lower BD values were associated with lower scores (see Figures 13 and 14).

Follow-up analyses using Steiger's Z Test for dependent correlations were conducted to determine if the relationship between lowest BD and RLI was significantly stronger than the relationships between lowest BD and the other four measured outcomes in the total sample (GMQ, FMQ, CLI, ELI). The correlation between lowest BD and RLI was significantly stronger than the correlation between lowest BD and FMQ in the total sample (FMQ, Steiger Z = 1.95, p = .025).

The difference in correlations between lowest BD and RLI versus GMQ was marginally significant in the total sample (Steiger $Z = 1.48$, $p = .069$). The difference in correlations between lowest BD and performance on RLI versus CLI and RLI versus ELI was nonsignificant in the total sample (CLI, Steiger $Z = 0.07$ $p = .473$; ELI, Steiger $Z = 0.91$ $p = .182$).

Follow-up analyses using Steiger's *Z* Test for dependent correlations were also conducted to determine if the relationships between lowest BD and performances on the Concepts and Following Directions and Basic Concepts subtest were significantly stronger than the correlation between lowest BD and performance on the Sentence Structure subtest in the total sample. The differences in correlations between lowest BD and performance on the three subtests was nonsignificant in the total sample (CFD versus SS, Steiger $Z = 0.48$, $p = .316$; CFD versus BC, Steiger $Z = 0.16$ $p = .435$; BC versus SS, Steiger $Z = 0.35$ $p = .364$).

Hypothesis 3b (Blood Gases: Carbon Dioxide). It was hypothesized that the highest pCO_2 would explain a unique portion of variance in measures of language and motor skills. Table 26 presents the findings for highest pCO_2. Contrary to predictions, highest pCO_2 was not associated with any motor or language indices in the total or reduced sample after adjustment for covariates (see Table 26).

Hypothesis 3c (Blood Gases: Oxygen). It was hypothesized that the lowest blood pO_2 would explain a unique portion of variance in measures of language and motor skills. Table 27a presents the findings for lowest pO_2 obtained within the first week of life after removal of an outlier (see footnote e for analyses that include the outlier).

Contrary to predictions, lowest pO_2 was not associated with any motor or language indices in the total or reduced sample after adjustment for covariates (see Table 27a).

Hypothesis 4 (Birth and Delivery Period versus Neonatal Adjustment Period)

It was hypothesized that indices of risk for postnatal hypoxia-ischemia would explain a greater portion of variance in language and motor performance, compared to indices of fetal risk. This hypothesis was not explored, as significant associations were only found between cord pH, cord pCO_2, and initial neonatal BD with GMQ. Likewise, only the lowest BD was marginally associated with RLI. Thus, comparisons were not made across collection time periods because significant associations were not observed between the same blood-gas parameter with the same outcome measure at different collection times (i.e., birth and delivery, first three hours of life, first week of life).

Language Re-Analysis of Hypotheses 1 through 3 without the Oromotor Sequences Score

The Oromotor Sequences subtest score was included as a covariate in all analyses with an expressive language task as the outcome variable. Inclusion of this subtest controlled for the motor demand that is required in expressive language tasks. As noted above, none of the associations between blood-gas or acid-base values and CLI or ELI scores were significant when Oromotor Sequences score was included as a covariate. As demonstrated in Tables 17a, 18a, 19a, 20-23, and 24-27a, significant associations were found between Oromotor Sequences score and both core (CLI) and expressive language indices (ELI) across all analyses. A lower Oromotor Sequences score was associated with a lower score on CLI and ELI. Throughout analyses, Oromotor Sequences performance accounted for 23.9% to 44.8% of unique variance in expressive language tasks. Analyses of language outcome were repeated without the Oromotor Sequences score as a covariate to determine the impact of the previously excluded oral motor component underlying expressive language skills on the (null) findings.

Language Re-Analysis of Hypothesis 1 (Birth and Delivery)

Tables 17c, 18b, and 19c present the findings of language measures pertaining to Hypothesis 1 after the Oromotor Sequences score was excluded as a covariate.

Language Re-Analysis of Hypothesis 1a (Acid-Base Status).

Cord pH (Language Re-Analysis). As expected, when the Oromotor Sequences score was not included as a covariate in analyses of language outcome, cord pH was significantly associated with ELI scores in the total sample (p = .047; see Table 17c) as well as the reduced sample (p = .027; see Table 17c). Consistent with Hypothesis 1a, lower cord pH values were associated with lower ELI scores. Cord pH accounted for 4.3% and 5.8% of the variance in the total and reduced sample, respectively (see Figures 15 and 16). Contrary to predictions, cord pH was not significantly associated with CLI in the total or reduced sample (see Table 17c).

Cord BD (Language Re-Analysis). Contrary to expectations, cord BD was not significantly associated with CLI or ELI scores in the total or reduced sample when Oromotor Sequences score was not included as a covariate (see Table 18b).

Language Re-Analysis of Hypothesis 1b (Blood Gases: Carbon Dioxide). In accord with expectations, the relationship between cord pCO_2 and ELI trended towards significance (p = .076) in the reduced sample (see Table 19c) in the predicted direction. Consistent with Hypothesis 1b, higher cord pCO_2 values were associated with lower ELI scores and accounted for 4.5% of the variance in the reduced sample (see Figure 17). Contrary to expectations, cord pCO_2 values were not significantly associated with ELI in the total sample. Cord pCO_2 values were not significantly associated with CLI in the total or reduced sample either (Table 19c).

Language Re-Analysis of Hypothesis 2 (Neonatal Adjustment Immediately After Birth)

Footnote e in Tables 20 and 22 and footnote f in Tables 21a and 23 present the findings of language measures pertaining to Hypothesis 2 after the Oromotor Sequences score was excluded as a covariate. Contrary to expectations, initial neonatal blood pH (Hypothesis 2a), BD (Hypothesis 2a), pCO_2 (Hypothesis 2b), or pO_2 (Hypothesis 2c) values obtained within the first three hours of life were not significantly associated with either CLI or ELI scores in the total nor reduced sample after the Oromotor Sequences score was excluded as a covariate (initial pH, see footnote e in Table 20; initial BD, see footnote f in Table 21a; initial pCO_2, see footnote e in Table 22; initial pO_2, see footnote f in Table 23).

Language Re-Analysis of Hypothesis 3 (Initial Neonatal Adjustment Within the First Week of Life)

Table 27b, footnote e in Tables 24 and 26, and footnote f in Table 25a present the findings of language measures pertaining to Hypothesis 3 after the Oromotor Sequences score was excluded as a covariate.

Language Re-Analysis of Hypothesis 3a (Acid-Base Status).

Lowest pH (Language Re-Analysis). Contrary to predictions, lowest pH was not associated with either CLI or ELI scores in the total nor reduced sample after the Oromotor Sequences score was excluded as a covariate (see footnote e in Table 24).

Lowest BD (Language Re-Analysis). Contrary to predictions, lowest BD was not associated with either CLI or ELI scores in the total nor reduced sample after the Oromotor Sequences score was excluded as a covariate (see footnote f in Table 25a).

Language Re-Analysis of Hypothesis 3b (Blood Gases: Carbon Dioxide). Contrary to expectations, highest pCO_2 was not associated with either CLI or ELI scores in the total nor

reduced sample after the Oromotor Sequences score was excluded as a covariate (see footnote e in Table 26).

Language Re-Analysis of Hypothesis 3c (Blood Gases: Oxygen). The relationship between lowest pO_2 and both CLI and ELI trended towards significance in the reduced sample (CLI; $p = .088$; ELI, $p = .052$; see Table 27b). Contrary to expectations, higher pO_2 values were associated with lower CLI and ELI scores, and accounted for 2.4% and 2.5% of the variance in the reduced sample (see Figures 18 and 19). The relationship between lowest pO_2 values and CLI or ELI was not significant in the total sample after exclusion of the Oromotor Sequences score as a covariate.

Comments on Sociodemographic and Perinatal Covariates

Participant Sex

As demonstrated in Tables 17a through 27a, significant associations were found between participant sex and motor and language outcome measures across most analyses. In 29 out of 55 analyses in the total sample and 25 out of 55 analyses in the reduced sample, females outperformed males.

Familial Socioeconomic Status

As demonstrated in Tables 17a through 27a, significant associations were found between familial socioeconomic status (Hollingshead, 1975) and both motor and language outcomes across almost all analyses. Specifically, in 43 out of 55 analyses in the total sample and 42 out of 55 analyses in the reduced sample, children with higher socioeconomic status consistently obtained higher scores on outcome measures.

CHAPTER 4: DISCUSSION

Overview of Dissertation Project

In this study, I examined the contribution of four early biochemical indexes of hypoxic-ischemic risk, two blood gas measures and two measures of acid-base balance, to neuropsychological outcome in a large sample of preterm-born preschool-age children. I was interested in the link between biochemical risk indices reflecting neonatal status at birth, immediately after birth, or within the first week of life and neuropsychological functioning. The outcomes of interest included measures of gross and fine motor skills, as well as receptive and expressive language skills. Hypothesis 1 addressed preschool outcome correlates of hypoxic-ischemic risk during the birth and delivery period, as indexed by cord blood pH, BD, and pCO_2 values. Hypothesis 2 addressed preschool outcome correlates of hypoxic-ischemic risk during the immediate neonatal adjustment period, as indexed by pH, BD, pCO_2, or pO_2 values obtained within the first three hours of life. Hypothesis 3 addressed outcome correlates of hypoxic-ischemic risk during the initial neonatal adjustment period, as indexed by lowest pH, lowest BD, highest pCO_2, or lowest pO_2 values obtained within the first week of life (3 hours of life to 7 completed days of life).

Discussion of Findings Pertaining to Hypothesis 1

It was hypothesized that acid-base and blood-gas status during birth and delivery, as indexed by arterial umbilical cord pH, BD, or pCO_2, would explain a unique portion of variance in measures of motor and language skills. Consistent with expectations, lower cord pH values were significantly associated with lower GMQ in the non-neurological subsample (following exclusion of cases with CP or moderate to severe perinatal brain injury; $p = .038$), and trended in the same direction in the total sample ($p = .076$). Cord pH accounted for 2.2% and 4.2% of the variance in

the GMQ in the reduced sample and total sample, respectively (see Table 17a), a small-to-medium effect size. Likewise, as predicted, higher cord pCO_2 values were also significantly associated with lower GMQ scores in the total ($p = .049$) and reduced sample ($p = .029$), accounting for 4.3% and 2.2% of the variance, respectively (see Table 19a). The statistical effect of cord pCO_2 on GMQ is consistent with a small-to-medium effect size as well. In contrast with predictions, none of the biochemical measures obtained from cord blood were significantly associated with fine motor measures. A comparison of the correlations between cord pH with GMQ versus FMQ revealed that the relationship between cord pH with GMQ was marginally stronger than with that of FMQ in the reduced sample (see page 43, *Findings by Hypothesis, Hypothesis 1a*). Furthermore, a comparison of the correlations between cord pCO_2 with GMQ versus FMQ showed a nonsignificant difference between the two relationships (see page 45, *Findings by Hypothesis, Hypothesis 1b*).

Follow-up analyses revealed that the relationships between cord pH and pCO_2 with GMQ may be primarily attributable to the statistical effect of these two biochemical indices on the Locomotion scaled scores (see Tables 17b and 19b). Cord pH and pCO_2 accounted for approximately 14.2% and 12.8% of the variance (medium effect sizes) in Locomotion performance, respectively. Of note, a comparison of the correlations between cord pH with gross motor subtest scores revealed a marginally significant difference between Locomotion versus Stationary scores, and a nonsignificant difference between Locomotion versus Object Manipulation scores (see page 43, *Findings by Hypothesis, Hypothesis 1a*). The correlation between cord pCO_2 and Locomotion score was not significantly different from the correlations between cord pCO_2 and the other two gross motor subtests (see page 45, *Findings by Hypothesis, Hypothesis 1b*). These results indicate that gross motor skills, particularly locomotor skills, rather

than fine motor skills, may be increasingly vulnerable to hypoxic-ischemic risk. Thus, the findings of the current study suggest that severity of acidosis and hypercapnia during the birth and delivery period (as indexed by cord pH and pCO_2 values) are linearly associated with gross motor skills in a preterm born sample at preschool age.

Inconsistent with predictions, none of the associations between cord blood-gas or acid-base values and language outcomes were significant when Oromotor Sequences score was included as a covariate. The Oromotor Sequences score accounted for a *very significant* portion of expressive language score variance (23% - 44%). When it was removed from analyses, as expected, lower cord pH was significantly associated with a lower score on ELI in the total (p = .047) and reduced (p = .027) sample, accounting for 4.3% and 5.8% of the variance (small effect sizes; see Table 17c), respectively. Likewise, the relationship between cord pCO_2 and ELI trended in the expected direction of significance in the reduced sample (p = .076; see Table 19c), and accounted for 4.5% of the variance (small effect size). Higher cord pCO_2 values were associated with lower ELI scores. Expressive language requires several different skill sets, including oral motor planning and control, semantics, grammar, and pragmatics. Inclusion of the Oromotor Sequences score controlled for the motor demand that is required in expressive language tasks. The present results suggest that the motor demand involved in linguistic expression may underpin language levels, acting as a catalyst or constraint on linguistic expression (Green & Nip, 2010; Nip et al., 2009; Nip & Green, 2006). Nonetheless, the findings of the current study suggest that severity of acidosis and hypercapnia during the birth and delivery period (as indexed by cord pH and pCO_2 values) are linearly associated with expressive language skills in a preterm born sample at preschool age.

The above findings add to the literature investigating outcomes related to hypoxic-ischemic risk during the birth and delivery period in preterm infants. A majority of the studies that examined

arterial cord blood-gas and acid-base values did so in a preterm *infant* sample (chronological age < 2 years), where outcome variables were global neurodevelopmental indices (Beeby et al., 1994; Hüseman et al., 2011; Kato et al., 1996; Lavrijsen et al., 2003; Mittendorf et al., 2008; Randolph et al., 2014). I was able to find only two studies that investigated the relationship between cord blood-gas or acid-base values and either motor or language outcome in children at preschool to school age (Baalbaki et al., 2021; Piercy, 2019).

The current findings are consistent with reported associations between arterial cord pH and motor and language outcomes at preschool age, as documented by Piercy (2019). The current study extended Piercy's contributions by shedding light on the specific language skills (oral-motor control) that may be exceedingly vulnerable to changes in cord blood pH. Furthermore, the current results extend the findings reported by Baalbaki and colleagues (2021), who documented a significant association between diagnosis of acidosis (categorized as cord pH < 7.1) and general neurodevelopmental impairment. This investigation's findings show that severity of acidosis is linearly associated with gross motor and expressive language skills. It should be noted that the sample in the current study predominantly represented infants with mild acidemia, as only three infants in the current study experienced moderate-to-severe acidemia (defined by cord pH values < 7.1). Thus, the findings should be interpreted and generalized respective to this representation. Even in a sample with relatively few cases with extreme cord pH levels, degree of acidosis was associated with poorer gross motor and expressive language outcome at preschool-age in a preterm sample. Future research may be devoted to elucidating the role of oral-motor functioning in expressive language development in preterm born children compared to their term counterparts.

I was able to find only one other study that included cord pCO_2 values as the predictor of interest (Baalbaki et al., 2021), yet the investigators reported no significant association between

diagnosis of hypercapnia (defined categorically as arterial cord pCO_2 values > 77mg) and global developmental impairment (Baalbaki et al., 2021). In contrast, the current investigation, using linear regression methodology, revealed that the severity of hypercapnia was inversely related to the quality of gross motor performance and expressive language performance in a non-neurological sample. In other words, the aforementioned relationships were observed even in a "nonhandicapped" sample, after removal of cases with perinatal brain injury, postnatal seizures, and CP.

The current study did not find cord BD significantly associated with motor or language indices. I was able to find two prior studies that documented significant relationships between diagnosis of moderate-to-severe-acidemia (defined categorically as cord BD < -8.6mEq/L (Baalbaki et al., 2021) and -12Eq/L (Randolph et al., 2014)) and neurodevelopmental impairment. The absence of statistically significant results in the current investigation may be due to the small number of cases with extreme cord BD values. Only nine infants who experienced extreme cord BD values consistent with moderate-to-severe acidemia (cord BD < -8mEq/L) were available for analysis in the current study, of which only one infant had a cord BD value consistent with severe acidemia (cord BD < -12mEq/L; lowest cord BD = -16mEq/L). As will be discussed below (see page 74, *Limitations and Future Directions*), the limited sample size of infants who experienced moderate-to-severe metabolic acidemia is generally unsurprising, as the current study only included children who were able to participate and complete testing. Future studies may investigate this relationship by including a larger sample of infants with moderate-to-severe metabolic acidemia, as indexed by cord BD levels, to further understand the influence of hypoxia on motor and language outcomes.

Discussion of Findings Pertaining to Hypothesis 2

Consistent with predictions, initial BD values were significantly associated with the GMQ in the total sample (p = .028; see Table 21a). As expected, lower BD values were associated with lower scores on the GMQ and accounted for 1.1% of the variance in GMQ in the total sample (small effect size). Follow-up analyses with gross motor subtest scores as the outcome variables revealed that this relationship may be primarily due to the statistical effect of initial BD on the Stationary score (p = .049; see Table 21b). Initial BD values accounted for 3.2% of the variance in Stationary scores in the total sample (small effect size). However, of note, a comparison of the correlations between initial BD and subtest performances revealed a marginally significant difference between performance on Stationary versus Locomotion subtests, and a nonsignificant difference between performance on Stationary and Object Manipulation subtests. The relationship between initial BD values and GMQ scores trended in the same direction in the reduced sample (p = .188), though did not reach statistical significance perhaps as a result of the smaller sample size (n = 93 compared to n = 84 for the total and reduced sample, respectively). Contrary to predictions, initial neonatal pH, pCO_2, and pO_2 values obtained within the first three hours of life were not significantly associated with either motor or language indices in the reduced nor total sample. Thus, the results suggest that the degree of metabolic acidosis (indexed by initial BD values) during the infant's immediate adjustment period is linearly associated with gross motor skills in a preterm sample that includes children with known neurological complications. A larger sample size may be needed to demonstrate this modest effect size in "non-handicapped" children without major neurological complications.

These findings add to the literature investigating outcomes related to hypoxic-ischemic risk during the preterm infant's immediate neonatal adjustment period. The results are broadly

consistent with the findings documented in Hüseman and colleagues (2011), who documented a significant relationship between severe metabolic acidosis during the first 12 hours of life (categorically defined as BD ≤ 16 mmol/L) and global neurodevelopmental impairment in preterm infants at 12 and 20 months of age. The current study extends the findings of Hüseman and colleagues (2011) to show that the severity of metabolic acidosis (defined by initial BD values) is linearly related to gross motor skills at preschool-age in a preterm sample that included cases with neurological complications. Similar to the observed findings here, Hüseman and colleagues did not document a significant relationship between severe acidosis within the first 12 hours of life, categorically defined as pH < 7.0, and neurodevelopmental impairment at 12 and 20 months of age in preterm infants. The two other research groups (Espy et al., 2007; Hopkins-Golightly et al., 2003) who investigated the relationship between initial blood-gas and acid-base measurements with neuropsychological outcome did so within a restricted range of pH values (pH = 7.1-7.3). The two studies documented a significant relationship between mild to moderate acidosis (defined as initial pH values) in the first hours of life and academic performance (Espy et al., 2007), executive functioning (Espy et al., 2007), and intelligence (Hopkins-Golightly et al., 2003). No significant linear associations were found between BD, pCO_2, or pO_2 values and cognitive or language outcomes within the restricted range of pH values investigated (Hopkins-Golightly et al., 2003). It should be noted that BD < -16mEq/L is classified as severe metabolic acidosis (see Table 3; Hüseman et al., 2011), with unclear cutoffs for BD values in moderate and mild metabolic acidosis. As may be seen, the BD values in our samples ranged from +6 to -13 mEq/L, thus omitting children with values falling below the severe range. Even in a sample with a restricted range in initial BD levels, lower initial neonatal BD was associated with poorer gross motor outcome at preschool-age in a preterm sample. Of note, none of these studies that included initial blood-gas and acid

base values as a predictor of interest (Espy et al., 2007; Hopkins-Golightly et al., 2003; Hüseman et al., 2011) investigated the relationship of these initial parameters with motor outcome. Future studies may investigate this relationship with unrestricted blood-gas or acid-base values to further elucidate the influence of hypoxia on motor and language outcomes.

Discussion of Findings Pertaining to Hypothesis 3

It was hypothesized that the lowest pH, lowest BD, highest pCO_2, and lowest pO_2 observed within the first week of life would explain a unique portion of variance in measures of language and motor skills. Consistent with expectations, the relationship between lowest BD and RLI scores trended towards significance in the total sample (p = .069; see Table 25a). Lower BD values were associated with lower scores on the RLI and accounted for 0.6% of the variance in RLI in the total sample (small effect size). Follow-up analyses revealed this relationship appeared primarily attributable to the statistical effect of lowest BD values on the Concepts and Following Directions and Basic Concepts scaled scores (see Table 25b), though the correlations between lowest BD and these two subtests were not significantly stronger than its correlation with the Sentence Structure subtest score (see page 49, *Findings by Hypothesis, Lowest BD*). Lowest BD values accounted for 1.0% to 1.2% of the variance in these subtest scores in the total sample (small effect size). The relationship between lowest BD and RLI trended in the same direction in the reduced sample (p = .116), though did not reach statistical significance perhaps as a result of the smaller sample size (n = 107 compared to n = 98 for the total and reduced sample, respectively). Contrary to predictions, lowest BD was not significantly associated with motor indices. A larger sample size may be needed to demonstrate this modest effect size in "non-handicapped" children without major neurological complications.

Lowest BD was not significantly associated with the CLI or ELI in either the total or reduced sample. Similarly, in contrast with Hypothesis 3a, lowest pH, highest pCO_2, and lowest pO_2 were not associated with any motor or language indices neither in the total, nor in the reduced, sample. However, when oral motor functioning was not included as a covariate in expressive language tasks, lowest pO_2 was significantly associated with expressive language performance. Contrary to predictions, higher pO_2 values were associated with lower scores (see Table 27b). Thus, the results suggest that the degree of metabolic acidosis (indexed by lowest BD values) during the infant's first week of life may be linearly associated with receptive language skills in a preterm sample.

The marginally significant relationship documented between lowest BD values and receptive language skills add to the literature investigating outcomes related to hypoxic-ischemic risk during the initial adjustment period (first week of life) in preterm infants. I was able to retrieve three prior studies (Mckee et al., 2009; Leviton et al., 2010, 2017) that included extreme blood-gas or acid-base parameters collected within the first week of life as the predictor of interest. Two of these studies (Mckee et al, 2009; Leviton et al., 2010) examined these extreme blood-gas or acid-base parameters within the first week of life in a preterm *infant* sample (chronological age < 2 years), where outcome variables were global neurodevelopmental indices (see Table 1c). One study investigated these relationships at school age (Leviton et al., 2017; age 10), using neuropsychological measures as the outcome variable (see Table 1c).

The results of this study are broadly inconsistent with the significant relationships reported by all three aforementioned studies (Mckee et al., 2009; Leviton et al., 2010, 2017). The absence of significant findings for lowest pH, highest pCO_2, and lowest pO_2 could be related to numerous methodological differences, including chronological age, the inclusion of different outcome

measures, or the treatment of blood-gas or acid-base parameters as continuous variables. Furthermore, it should also be noted that the current study's definition of an infant's first week of life differed from the aforementioned studies, as this investigation excluded blood-gas and acid-base values obtained within the first three hours of life from analyses for Hypothesis 3. It is possible that some blood-gas and acid-base values may have been more extreme within the infant's first three hours of life as the infant transitioned to the extrauterine environment. However, the current investigation extends the findings of the aforementioned studies (Mckee et al., 2009; Leviton et al., 2010, 2017) to show that the relationship between *severity* of metabolic acidosis (as indexed by lowest BD values) during the first week of life may be related to language outcome at preschool age.

In regards to the observed relationship between higher pO_2 values and lower language scores, there is evidence to suggest that hyperoxia (high oxygen levels) may be linked to poorer neuropsychological outcome in preterm children (Leviton et al., 2017). Of note, none of the 99 children included in language analyses in the current study fell within the hyperoxic range (pO_2 > 80 mmHg; H. Huang et al., 2017). Likewise, all but seven cases fell within a normoxia (normal oxygen) range (pO_2 = 40 – 80 mmHg; Castillo et al., 2008). Cutoffs for mild, moderate, and severe hypoxemia are unclear, and as a result, it is uncertain what range the lowest observed value of the current study fell within (pO_2 range = 36 – 62 mmHg). Future research should explore the relationship between low pO_2 levels and language functioning within a preterm sample and include a wider representation of oxygenation values.

The Relationship between Hypoxia, Specificity of Outcome Measures, and Fetal and Neonatal Brain Injury

In the preterm brain, hypoxic-ischemic brain injuries often result in periventricular white matter injury as a result of periventricular leukomalacia (PVL) or germinal-matrix hemorrhage (GMH; Varghese et al., 2016). Most periventricular injury occurs in the region of the white matter that is traversed by descending fibers from the motor cortex corresponding to the legs (Volpe, 2001). Studies utilizing diffusion tensor imaging (DTI) have noted decreased connectivity in the cerebral peduncle, posterior limb of the internal capsule, corona radiata, and posterior corpus callosum (Gao et al., 2012; Lvov et al., 2019; Varghese et al., 2016) in mild hypoxic-ischemic preterm neonates. Importantly, many of these regions (cerebral peduncle, corona radiata, internal capsule) house the corticospinal tract, the major neuronal pathway that functions in voluntary motor function, especially gross motor function. In fact, one study (Rha et al., 2012) noted reduced volume and number of fibers in the corticospinal tract in children with CP caused by PVL, and the reduced connectivity of the tract was associated with poorer gross motor performance. The corpus callosum connects the bilateral hemispheres and its splenium connects the primary motor, premotor, and supplementary motor cortices (Wahl et al., 2007). The splenium of the corpus callosum has also been shown to be uniquely affected by periventricular injury, with radial diffusivity and shorter fiber lengths shown on DTI, and associated with gross motor scores in preterm infants (De Bruïne et al., 2013). Thus, it is unsurprising that cord pH, cord pCO_2, and initial neonatal BD values were significantly associated with gross motor functioning, rather than fine motor, given the neuroanatomical vulnerabilities associated with hypoxic-ischemic events. That is not to say that fine motor functioning is not also affected by hypoxic-ischemic events, but

that given the small sample size and restricted range of blood-gas and acid-base values, gross motor skills may be especially vulnerable in a preterm population.

It was also found that the relationship between initial neonatal BD values and gross motor skills appeared primarily attributable to the statistical effect of initial BD on the Stationary scaled scores. Furthermore, the relationships between either cord pH or cord pCO_2 values and GMQ appeared primarily attributable to effect of these biochemical indices of hypoxic risk on the Locomotion scaled scores. The Stationary subtest measures a child's ability to sustain control of his or her body within its center of gravity and retain equilibrium. The Locomotion subtest measures a child's ability to move from one place to another by walking, running, hopping, and jumping. Both of these subtests require balance and proprioception (awareness of one's body in space), with the later placing a higher demand on proprioception due to the movement component. As white matter injury in preterm infants preferentially involves thalamocortical pathways, decreased connectivity and fractional anisotropy has been observed in the posterior thalamic radiations in preterm infants (Li et al., 2014). Posterior thalamic radiations play a main role in sensory perception, and more importantly, proprioception, and have been linked to motor outcome as well (Hoone et al., 2009). Thus, the relationship between cord pH and cord pCO_2 values with the Locomotion subtest, and initial neonatal BD with the Stationary subtest, may be linked to the increased vulnerability of both the corticospinal tract and posterior thalamic radiations to hypoxic-ischemic injury in preterm infants.

The relationship between lowest neonatal BD values and RLI trended towards significance in the total sample. It should also be noted that when the Oromotor Sequences subtest score was not included as a covariate in analyses of language tasks, cord pH was significantly associated with ELI scores in the total and reduced sample, and the relationship between cord pCO_2 with ELI

trended towards significance in the reduced sample. This is generally unsurprising, especially given the corticobulbar tract and corpus callosum's known roles in oromotor skills and language processing (Northam et al., 2012; Stipdonk et al., 2018). The corticobulbar tract receives projections from the precentral gyrus that descend through the internal capsule, cerebral peduncles, pons, and medulla oblongata. As previously stated, the internal capsule and cerebral peduncles are highly susceptible to hypoxic-ischemic injury in preterm infants (Gao et al., 2012; Lvov et al., 2019; Varghese et al., 2016). The corticobulbar tract sits adjacent to the corticospinal tract and innervates nerves of the face, tongue, and jaw. Given these functions, reduced fractional anisotropy of the corticobulbar tract has been linked to poorer oromotor functioning in preterm children (Northam et al., 2012, 2019). Similarly, slower mean diffusivity and radial diffusivity rates of change within the internal capsule have been linked to lower language scores at age 4 in preterm children as well (Young et al., 2017). As mentioned above, the corpus callosum integrates information from both hemispheres and allows for improved interhemispheric connectivity to promote language (Bartha-Doering et al., 2020). The volume of the corpus callosum has been found to be significantly associated with oral language skills and verbal fluency in school-age preterm children (see meta-analysis by Stipdonk et al., 2018). Furthermore, the fractional anisotropy of the splenium of the corpus callosum has been linked to composite language skills in preterm children at age 2 as well (Dubner et al., 2020). Nonetheless, it is important to highlight the relatively widespread language network connections for expressive and language processing, with both periventricular and non-periventricular region involvement. Expressive and receptive language skills have both been significantly associated with bilateral arcuate fasciculi, white matter within the cerebellum, corpus callosum, bilateral corticospinal tracts, bilateral corticothalamic tracts, internal and external capsules, and bilateral inferior fronto-occipial fasciculi in preterm

children (Barnes-Davis et al., 2020; Dubner et al., 2020; Young et al., 2017). There is also some evidence to suggest increased tract fractional anisotropy in anterior thalamic radiation, inferior fronto-occipital fasciculi, and inferior longitudinal fasciculi in preterm children, compared to their full-term counterparts (Dodson et al., 2017). While this evidence may suggest increased myelination as a compensatory mechanism due to early brain injury, increased myelination does not necessarily indicate increased maturity or greater white matter integrity (Dodson et al., 2017). Thus, the relatively wide-spread language network connectome as well as the possibility of increased connectivity in some non-periventricular language-associated regions may explain why language processing was not more robustly associated with biochemical indices of hypoxic-ischemic risk in this preterm sample. Nonetheless, future research should examine the relationship between language network connectivity, compensatory mechanisms, and language outcomes in preterm children.

Together, the dose-response relationship observed here between biochemical indices of hypoxic-ischemic risk and motor and language outcome support the idea that there is a continuum of brain injury related to hypoxia, rather than an "all-or-nothing" phenomenon (Casaer et al., 1991). It had been previously suggested that birth hypoxia was a distinct state, occurring only when duration and severity of hypoxia surpassed a specified biochemical level (Johnston, Trescher, & Taylor, 1995). This distinct state was presumed to be accompanied and followed by significant impairment, including intellectual disability and cerebral palsy (American College of Obstetricians & Gynecologists, 2014; Ravarino et al., 2014). However, the current study, along with several others (Espy et al., 2007; Hopkins-Golightly et al., 2003) provide evidence for a dose-response relationship, rather than categorical, between hypoxic-ischemic risk and later

neuropsychological outcome. Even slight risk for birth-related hypoxic injury exerts a considerable effect on motor and language outcome.

Timing of Blood-Gas and Acid-Base Measurement and Relation to Motor and Language Outcome

Together, the current findings suggest that blood-gas and acid-base measurements collected from the infant's birth and delivery period and/or immediate adjustment period may convey important information in regards to vulnerability to future gross motor difficulties and relatedly, expressive language difficulties though its oral-motor underpinnings. Derangement in blood-gas and acid-base status are often the result of a stimulus or some stimuli leading to physiologic instability (Leviton et al., 2010, 2017), and similarly, are indicators of underlying immaturity and/or vulnerability (Leviton et al., 2010, 2017). Because of this, it is difficult to parse apart the direct and indirect effects between blood-gas and acid-base abnormalities and the presumed preceding stimulus. Nonetheless, immaturity can be the equivalent of vulnerability when an early developmental process is particularly prone to perturbation. With this in mind, it is noteworthy to highlight the brain pre-myelination patterns in typical development, as different sites myelinate at distinctive times (Gilles et al., 1983). The highest-risk period for white matter injury precedes the onset of myelination and occurs when white matter is populated primarily by pre-myelinating oligodendrocytes between approximately 23-32 weeks gestation (preOLs; Back, 2017). The decline in risk for white matter injury related to hypoxia coincides with the differentiation of preOLs to immature OLs that initiate myelination (Back et al., 2002). PreOLs are particularly susceptible to maturation-dependent mechanisms of free-radical mediated injury, whereas later OL stages are more resistant to oxidative stress (Back et al., 2002). Likewise, portions of white matter tracts begin to rapidly pre-myelinate beginning at 27-28 weeks (corona

radiata), and continue to pre-myelinate throughout the course of the third trimester (internal capsule, posterior limb [29-30 weeks]; corticospinal tract [29-30 weeks]; corpus callosum [32 weeks]; Gilles et al., 1983). If hypoxic-ischemic events occur during this pre-myelination, the expected phase of rapid myelination may fail to occur, resulting in a lack of expected increase in white matter volume and connectivity (du Plessis & Volpe, 2002), and relatedly, motor and language dysfunction. Thus, the sensitivity of the biochemical indices of hypoxic-ischemic risk collected during the birth and delivery period and/or immediate neonatal adjustment period may be reflective of early fetal adversity (De Franco et al., 2007). Likewise, the current results may suggest that hypoxic-ischemic risk experienced in-utero and/or during the birth and delivery are associated with increased vulnerability to later motor and expressive language difficulties.

Sensitivity of Blood-Gas and Acid-Base Measurements to Outcome

The sensitivity of pH, BD, and pCO_2 to hypoxia and/or developmental outcome alludes to their biochemical underpinnings in acid-base balance.

When oxygen is deficient, the body resorts to anaerobic metabolism and eventually produces lactic acid (McNamara & El-Khuffash, 2017). Given that lactic acid separates into lactate and H^+ ions, its increased production exceeds the body's capacity to metabolize it. Thus, oxygen deprivation can lead to high levels of H^+ in the body, decreasing pH and increasing the acidity of the blood. BD represents the represents the amount of base required to titrate a whole arterial blood to a normal pH and is useful in quantifying the metabolic or respiratory component of acidosis, with lower BD levels related to metabolic issues and higher BD levels related to respiratory causes (Berend, 2018; Carter et al., 1993; Ouellet et al., 2021). The BD values available for the current study represented a restricted range (cord BD, range = -16 to +4; initial BD, range = -13 to + 6; first week BD, range = -19 to +4; Dickinson et al., 1992; Yang et al., 2002), showcasing greater

deficit, rather than excess. It is possible that this restricted range may allude to primarily metabolic instabilities, rather than respiratory, in relation to acidosis for some individual cases. Metabolic acidosis is often the result of an underlying physiological issue (i.e., immature kidneys in preterm infants) and strongly linked to hypoxic-ischemic brain damage (Baalbaki et al., 2021; Malin et al. 2010; Ouellet et al., 2021; Randolph et al., 2014). Thus, the observed relationships between cord pH, initial BD, and lowest BD with neuropsychological outcome highlights the linear relationship between severity of metabolic acidosis and later skill development. Furthermore, there is also some evidence to suggest that BD levels may provide some information about the duration of an insulting event (Knutzen et al., 2015). Thus, the relationship between initial and lowest BD values, rather than initial and lowest pH values, and outcome may allude to the importance of the length of hypoxic-ischemic risk, rather than acute episodes.

Carbon dioxide is a regulator of blood pH and respiration (Messina & Patrick, 2021), and is most commonly observed in the context of reduced clearance due to umbilical cord compression and/or hypoventilation, and relatedly, hypoxia. In both the fetal and newborn metabolism, when carbon dioxide enters the blood stream, it is converted into carbonic acid (Messina & Patrick, 2021) which, in turn, rapidly converts to HCO3- and H+. As a result, when the fetus or newborn is unable to eliminate pCO_2 via the umbilical cord or respiration, the H+ concentration increases, decreasing pH and increasing the acidity of the blood. Elevated pCO_2 (hypercapnia) can lead to cerebral vasodilation and an increase in cerebral blood flow in the fetus (Bonnin et al., 1992) and preterm infant (Kaiser et al., 2005). Cerebral vasodilation and increased blood flow increases intracranial pressure (Kety & Schmidt, 1948; Lassen & Christensen, 1976; Raper et al., 1971). Thus, the observed relationship between cord pCO_2 and gross motor skills may allude to the

transient hypercapnic risk associated with umbilical cord compression, and related hypoxia, during the birth and delivery period.

In regards to pO_2 values, it should also be noted that pO_2 levels refer to the amount of oxygen in the blood, but not the amount of oxygen-carrying hemoglobin (oxygen saturation). With this in mind, though there may be a low amount of oxygen in the blood, oxygen saturation may be broadly within normal limits if an adequate amount of hemoglobin is bound to the available oxygen. Furthermore, the absence of significant findings may also be related to the preponderance of capillary pO_2 values compared to arterial pO_2 values (initial pO_2, $n^{arterial} = 23$, $n^{adjusted\ capillary} = 75$; first week pO_2, $n^{arterial} = 20$, $n^{adjusted\ capillary} = 96$). As it has been established that capillary pO_2 measurements are significantly lower than arterial pO_2 values in preterm-born infants (Brodkorb et al., 2022; McLain et al., 1988; Yang et al., 2018; Yapıcıoğlu et al., 2014), capillary pO_2 values were adjusted to reflect arterial pO_2 values in the current study (Brodkorb et al., 2022). Though the conversion formula was shown to be a reliable predictor of arterial pO_2 levels (Brodkorb et al., 2022), each infant's true arterial pO_2 values were unknown and the adjustment of capillary values may have introduced some error into the analyses. Future research may investigate the relationship between solely arterial pO_2 values and motor and language outcomes.

Blood Gas and Acid-Base Abnormalities as Protective Factors?

There is some preliminary, emerging evidence that moderate hypoxia in the early postnatal period may provide some type of neuroprotective effect for the developing brain (Hagberg et al., 2004). The theoretical underpinnings of this line of research are based in preconditioning, which suggests that a subthreshold exposure to a certain damaging stimulus may render the brain less sensitive to successive insults (Hagberg et al., 2004). Though application of this idea is difficult to explore in a clinical setting due to risk, numerous studies have documented possible benefits of

hypoxic, acidosis, and hypercapnic preconditioning postnatally in animal models (Chen et al., 2015; Ladilov, 2012; Sheldon et al., 2014; Suryana & Jones, 2014; Tregub et al., 2016). For example, in a mouse model of apnea of prematurity, one study (Bouslama et al., 2015) documented that moderate intermittent hypoxia during the early postnatal period stimulated hippocampal neurogenesis and angiogenesis. Another study (Tregub et al., 2023) also showed that hypercapnic preconditioning inhibited the signaling pathways of neuronal apoptosis due to ischemia in rats. Though the mechanisms of hypoxic preconditioning remain largely unclear, these observations suggest that moderate abnormalities in blood-gas and acid-base status that are typically associated with later dysfunction, may also provide some type of neuroprotection. As previously discussed, permissive hypercapnia may follow this same line of thinking, with some possible neuroprotective properties during a hypoxic-ischemic insult (Ozawa et al., 2022). However, it is important to note that there is some evidence to suggest that hypoxic preconditioning may render the developing brain more vulnerable to damaging exposures (Deng et al., 2003). Though the current study does not necessarily confirm or disconfirm either idea, future research may consider the link between biochemical indices of hypoxic-ischemic risk and potential neuroprotective benefits for later exposures in preterm infants.

Comments Pertaining to Socio-Demographic Variables

Socioeconomic status and participant sex were included as covariates in all of my hypotheses. Across most analyses, both covariates were associated with motor and language outcome at preschool age. Specifically, children with higher socioeconomic status obtained higher scores on outcome measures. There was a clear female advantage across numerous measures as well. It has been well-established that socioeconomic status is a critical predictor in the development of preterm-born children (e.g., Raz et al., 2015; Taylor et al., 2011), as environmental enrichment

and early access to intervention services may function to support or accelerate maturational processes (Salmaso et al., 2014). Likewise, the observed female advantage in the current study is consistent with findings in previous studies involving preterm children as well (e.g., Skiold et al., 2014; Raz et al., 2015), along with studies examining solely outcomes following hypoxic-ischemic injury (Carrel & Willard, 2005; Hagberg et al., 2004; Rosen et al., 1999). It appears that hormonal modulation as well as genetically-linked apoptotic mechanisms afford perinatal females an advantage and some protection against perinatal complications and/or hypoxic-ischemic injury, in comparison to their male counterparts (Carrel & Willard, 2005; Hagberg et al., 2004; Rosen et al., 1999).

Limitations and Future Directions

The results of the current study should be considered in the context of several limitations. The current study is limited by a considerable amount of unavailable or missing data. It should be noted that infants who are medically stable after birth are less likely to have blood gas and acid-base analyses collected during the birth and delivery period (i.e., cord), within their immediate adjustment period (e.g., infant blood from the first few hours), and within the first week of life, as it was not medically needed. Similarly, the declining sample size following each sequential collection period likely reflects the improving medical status of the newborns as neonatal age increases. With this in mind, the available blood-gas and acid-base data used in the current study represent a biased sample of values, as cases who did not have blood-gas sampled in a certain collection period were not able to be represented in analyses. Thus, the current investigation was limited to studying the dose-response relationships within a sample of preterm newborns who medically needed blood-gas and acid-base measurements at that time due to their more unstable neonatal medical status. The omission of those infants who did not have blood gas measurements

taken, who may be expected to show better outcome, may have resulted in an underestimation of the observed effects of biochemical indices of hypoxic risk on language and motor outcome. It is also important to note that children who were unable to complete or participate in testing for other reasons, such as cooperation difficulties or very low functioning, were also not included in the current study. As a result, the collected scores on motor and language measures may not fully represent the lower end of the range of scores due to the inability to capture their level of functioning. Socio-demographically, it should be noted that my sample was largely composed of middle-class families. Thus, generalizability to a lower stratum is uncertain and future research should include a more socioeconomically diverse sample.

APPENDIX A

Table 1a

Methodological comparisons of studies examining umbilical cord acid-base and blood gas values in relation to neurodevelopmental or neuropsychological outcome in cohorts of preterm-born children

Authors, Year	GA/BW cut-off & CA	Acid-Base / Blood Gas Variable & cutoff	At-Risk Group	Control Group	Exclusion	Outcome Measures	Covariance / Matching	Results
Randolph et al., 2014	ELBW (<1000g) CA: 1 year	ACpH < 7.0 or BD < -12	249 ELBW infants with acidosis	3730 ELBW infants without acidosis	Infants born with congenital heart defects, chromosomal anomalies, and CNS abnormalities	NDI, defined as Bayley Scales of Infant Development – II (MDI or PDI <70) or III (cognitive < 85), moderate to severe CP, GMFCS > 2, bilateral vision loss worse than 20/200, deafness, or bilateral hearing loss requiring amplification	GA, BW, 5-min apgar, multiple gestation, sex, maternal insurance status, maternal hypertension, antenatal steroids	ACpH<7 or BD<−12 were both significantly associated with death/NDI in ELBW infants. Inclusion of ACpH or BD did not improve the ability of the multivariable model to predict death/NDI, over and above covariates.
Lavrijsen et al., 2005	<32 weeks <1500 grams CA: 1 year	Acidemia ACpH < 7.00	44 preterm infants with acidosis	67 preterm infants without acidosis	Congenital anomalies, infants transferred to another hospital, GA unclear, missing follow up data	Griffiths Developmental Scale (DQ < 85), CP, IVH, PVL, seizures	GA, BW, SGA, Apgar, Seizures	Severe IVH and seizures occurred significantly more in infants with Severe umbilical cord acidemia not a significant risk factor for long-term outcome (developmental delay).
Beeby et al., 1994	<32 weeks CA: 1 year	ACpH <7.10	58 preterm infants with ACpH <7.10	565 preterm infants with ACpH > 7.1	Congenital anomalies	Griffiths Developmental Scale (DQ), CP diagnosis	Grade III/IV IVH, BW, HMD, antenatal steroids	A low ACpH was not significantly associated with neonatal death, DQ, or CP diagnosis.
Kato et al., 1996	<1500 grams	ACpH <7.2	23 infants with ACpH <7.2	124 infants with ACpH >7.2	Congenital anomalies, multiples, death	CP, ID	Malpresentation, tocolytics, cord ph	Mean ACpH significantly lower in the CP/ID group.
Hüseman et al., 2011	< 35 weeks <1500 grams 12 mos (N = 820) & 20 mos (N= 551)	ACpH < 7.0	1137 VLBW infants with severe acidosis (pH < 7.0)			NDI, defined as Griffiths Developmental Scale, DQ < 75, death	GA, BW	ACpH not significantly associated with DI or death. Weak predictive power of ACpH and death and NDI at 12 or 20 months.

Mittendorf et al., 2008	<34 weeks CA: 18 months	ACpH <7.20	17 infants with ACpH <7.20	83 infants with ACpH >7.20	Maternal infection, preeclampsia, antenatal steroid use, requiring reassuring fetal assessment.	Bayley Psychomotor Developmental Index (PDI)		No significant relationship between ACpH and PDI scores when dichotomized or analyses continuously.
Piercy, 2019	< 34 weeks CA: 3-4 years	ACpH (continuous; range = 6.95 – 7.42)	197 preterm infants	NA	Congenital anomalies, chromosomal disorders, neonatal meningitis, need for mechanical ventilation following discharge from NICU	WPPSI-III/IV FSIQ, Information & Block Design; CELF-P2 CLI, ELI, & RLI; PDMS-2 GMQ & FMQ; NEPSY-2 Word Generation	Sex, GA, SES, total complications, standardized BW	After adjustments, ACpH was significantly associated with FSIQ, Information score, CLI, ELI, GMQ, & Word Generation. It was not significantly associated with Block Design score, RLI, or FMQ.
Baalbaki et al. 2021	23-31 weeks CA: 5-8 years	ACpH < 7.1 BD < -8.6 mEq/L pCO_2 > 77mmHg	259 preterm singletons	NA	Neurodevelopmental disorders / anomalies at birth	NDD, which consisted of IQ < 70 (WISC-IV/DAS), CP, blindness, deafness or other major deficits such as abnormal balance, impaired cognition, dystonia, and seizure disorder	Race, caregiver IQ, GA	Children with abnormal pH and BD had significantly higher rates of NDD than those children with normal cord gas parameters, after adjustment for covariates. Abnormal pCO_2 not significantly related to NDD after adjustment.

Note. ACpH = Arterial Cord pH; BD = Base Deficit; BW = Birthweight; CA = Chronological Age; CELF-P2 = Clinical Evaluation of Language Fundamentals, Preschool, Second Edition; CLI = Core Language; CNS = Central Nervous System; CP = Cerebral Palsy; DQ = Developmental Quotient; ELI = Expressive Language Index; ELBQ = Extremely Low Birthweight; FMQ = Fine Motor Quotient; FSIQ = Full Scale Intelligence Quotient; GA = Gestational Age; GMFCS = Gross Motor Function Classification Scale; GMQ = Gross Motor Quotient; HMD = Hyaline Membrane Disease; ID = Intellectual Disability; IVH = Intraventricular Hemorrhage; MDI = Mental Development Index; NA = Not Applicable; NDI = Neurodevelopmental Impairment; NDD = Neurodevelopmental Disorder; NEPSY-2 = Neuropsychological Assessment for Children, Second Edition; PDI = Psychomotor Development Index; PDMS-2 = Peabody Developmental Motor Scales – Second Edition; PVL = Periventricular Leukomalacia; RLI = Receptive Language Index; SGA = Small for Gestational Age; VCpH = Venous Cord pH; VLBW = Very Low Birthweight; WPPSI-III/IV = Wechsler Preschool and Primary Scale of Intelligence – Third/Fourth Edition

Table 1b

Methodological comparisons of studies examining infant acid-base and blood gas values immediately after birth in relation to neurodevelopmental or neuropsychological outcome in cohorts of preterm-born children

Authors, Year	GA/BW cut-off & CA	Acid-Base / Blood Gas Variable & cutoff	At-Risk Group	Control Group	Exclusion	Outcome Measures	Covariance / Matching	Results
Hüseman et al., 2011	< 35 weeks <1500 grams 12 mos (N = 820) & 20 mos (N= 551)	pH and BD upon admission (unless admission occurred at an age later than 6 h) and most severe BD during first 12 hours of life (did not specify which source)	1137 VLBW infants with pH ≤ 7.0 and BD ≥ 16 mmol/l	NA	Not reported	Griffiths Developmental Scale; (NDI =DQ <75)	GA, BW	Infants with neurodevelopmental impairment at 12 or 20 months of age had lower BD during the first 12 h of life, compared to infants without impairment, and tended to have lower BD at admission. DQs at 12 and 20 months did not correlate with pH at admission.
Espy et al., 2007	≤ 35 weeks BW ≤ 2500 g CA: 3 yrs	Arterial blood pH within first 3 hours of life = 7.1-7.3	22 preschool preterm children	NA	Surgery, NEC, chronic lung disease, IVH or periventricular injury, sepsis, or seizure disorder	Picture Vocabulary & Applied Problems subtest from WJ-R, Six Boxes, Self Control, Visual Attention from NEPSY	GA, CA	Initial pH was related to performance on the WJ-R Picture Vocabulary & Applied Problems, NEPSY Visual Attention, with children with lower initial pH values obtaining lower scores. Initial pH was not related to performance on Six Boxes or Self Control.
Hopkins-Golightly et al., 2003	≤ 36 weeks Mean BW: 2,233.58 g Mean CA: 5.91 yrs	Arterial pH = 7.1-7.3	26 preterm children with initial arterial pH (within 2 hours of delivery) between 7.1-7.3	26 preterm children with initial arterial pH > 7.3 or infants without the need for acid-base assessment (unknown pH)	Infants with postrecovery drop in pH, supplemental oxygen > 1 week, chromosomal or genetic defects, placental abruption or previa, IUGR, ROP, IVH, BPD	WPPSI-R, WISC-III, PSL-3 (ACS & ECS)	Age, parental education, SES, maternal IQ, sex, racial composition, multiples, antenatal and neonatal complications	Group affiliation was significantly linked to both the VIQ and PIQ, with the at-risk group obtaining lower scores than the control group. No significant association between group affiliation and ACS & ECS. The only variable obtained within two hours of birth and related to cognitive outcome was pH. BD, pCO_2, and pO_2 values were not. The relationship between pH and cognitive outcome was significantly strengthened when a

								second order trend (pH^2) was added as a predictor, demonstrating a curvilinear relationship between pH and cognitive outcome.

Note. ACS = Auditory Comprehension Scale; BE = Base Excess; BPD = Bronchopulmonary Dysplasia; BW = Birthweight; CA = Chronological Age; CP = Cerebral Palsy; DQ = Developmental Quotient; ECS = Expressive Communication Scale; GA = Gestational Age; IQ = Intelligence Quotient; IUGR = Intrauterine Growth Restriction; IVH = Intraventricular Hemorrhage; NA = Not Applicable; NDI = Neurodevelopmental Impairment; NEC = Necrotizing Enterocolitis; NEPSY = Neuropsychological Assessment for Children; PIQ = Performance Intelligence Quotient; PLS-3 = Preschool Language Scale – Third Edition; ROP = Retinopathy of Prematurity; SES = Socioeconomic Status; VIQ = Verbal Intelligence Quotient; VLBW = Very Low Birthweight; WJ-R = Woodcock Johnson Educational Battery-Revised; WPPSI-III = Wechsler Preschool and Primary Scale of Intelligence – Third Edition; WPPSI-R = Wechsler Preschool and Primary Scale of Intelligence – Revised

Table 1c

Methodological comparisons of studies examining infant acid-base and blood gas values within the first week of life in relation to neurodevelopmental or neuropsychological outcome in cohorts of preterm-born children

Authors, Year	GA/BW cut-off & CA	Acid-Base / Blood Gas Variable & cutoff	At-Risk Group	Control Group	Exclusion	Outcome Measures	Covariance / Matching	Results
McKee et al., 2009	< 1000g CA: 18-22 months	Highest and lowest arterial pCO_2 obtained within the first 4 days of life, along with average pCO_2 and the difference between the two (fluctuation)	400 ELBW infants	NA	None reported; analyses reported for infants with and without IMV and CPAP	Bayley Scales of Infant Development – II; MDI, PDI, or NDI	Sex, race, PPROM, Severe IVH, Sepsis	All pCO_2 variables significantly associated with NDI, except lowest pCO_2 was not. Higher pCO_2 difference associated with a lower MDI. A higher average pCO_2 was associated with a lower PDI. In a univariate analysis, the number of blood gas measurements was significantly higher in the NDI group than the non-NDI group.
Leviton et al., 2010	< 28 weeks CA: 2 yrs	Lowest Arterial pH Lowest and highest p_aO_2, & p_aCO_2 within the first 3 days of life; 7 had venous blood for pH and pCO_2 ; classified by extreme quintiles by gestational age	1504 ELGA children	NA	None reported	Bayley Scales of Infant Development-II; MDI or PDI < 70	Conception assistance, maternal fever during pregnancy, use of nonsteroidal anti-inflammatory drugs during pregnancy, BW z score, preeclampsia, recovery of Mycoplasma from the placenta, and thrombosis of fetal stem vessels in the placenta.	Low p_aO_2, low pH, and high p_aCO_2 were related to an increased risk of MDI < 70. Low p_aO_2 and high p_aCO_2 were related to an increased risk of PDI < 70.
Leviton et al., 2017	< 28 weeks CA: 10 yrs	Lowest Arterial pH Lowest and highest p_aO_2, & p_aCO_2 within the first 3 days of life; 7 had venous blood for pH and pCO_2 ; classified by extreme quintiles by gestational age; recorded how many days each blood gas was low	740 ELGA children	NA	None reported	DAS-II Verbal and Nonverbal Reasoning, Recall of Digits Backward, and Recall of Sequential Order; OWLS; NEPSY-II Auditory Attention, Response Set, Inhibition, Inhibition Switching, Animal Sorting, Inhibition Naming, Arrows, Geometric Puzzles, and Visuomotor Precision; WIAT-III Word Recognition and Pseudoword Decoding, Spelling, and	Sex, BW Z score, antenatal glucocorticoids, race, years of formal education, marital status, insurance, SNAP-II score	Lowest p_aO_2 occurring on two out of three days was associated with Spelling and Arrows. Lowest p_aO_2 occurring on one out of three days was associated with Geometric Puzzles. Highest p_aO_2 occurring on two out of three days was associated with DAS-II Working Memory and Inhibition Switching. Lowest p_aCO_2 occurring on one out of three days was associated with Word Reading, Pseudoword

						Numeric Operations		Decoding, and Geometric Puzzles. Highest p_aCO_2 occurring on two out of three days was associated with Auditory Attention and Geometric Puzzles. Highest p_aCO_2 occurring on one out of three days was associated with Pseudoword Decoding, Spelling, Numerical Operations, Inhibition Switching, and Naming. Lowest pH occurring on two out of three days was associated with Spelling, and Geometric Puzzles. Lowest pH occurring on one out of three days was associated with Auditory Response and Inhibition Switching. None of the blood-gas or acid-base measures were associated with language outcome.

Note. BW = Birthweight; CA = Chronological Age; CPAP = Continuous Positive Airway Pressure; DAS-II = Differential Abilities Scales – Second Edition; ELBW = Extremely Low Birth Weight; ELGA = Extremely Low Gestational Age; GA = Gestational Age; IMV = Intermittent Mechanical Ventilation; IVH = Intraventricular Hemorrhage; MDI = Mental Development Index; NA = Not Applicable; NDI = Neurodevelopmental Impairment; NEPSY-II = Neuropsychological Assessment for Children, Second Edition; OWLS = Oral and Written Language Scales; PDI = Psychomotor Development Index; PIQ = Performance Intelligence Quotient; PPROM = Premature Rupture of Membranes; SES = Socioeconomic Status; SNAP-II = Score for Neonatal Acute Physiology – Second Edition; WIAT-III = Wechsler Individual Achievement Test – Third Edition

Table 2
Reference ranges for blood gas and acid-base values in the fetus and preterm infant

Source	Value	Overall Preterm Reference Range	Reference Range by Gestational Age
Umbilical arterial	pH	7.26 ± 0.08[d]	*24-28 weeks*: 7.27 ± 0.10 [d] *29-32 weeks*: 7.27 ± 0.08 [d] *33-36 weeks*: 7.26 ± 0.08 [d]
	BD[a]	-3.20 ± 2.90 mEq/L[d]	*24-28 weeks*: -3.3 ± 3.4 [d] *29-32 weeks*: -3.0 ± 3.0 [d] *33-36 weeks*: -3.2 ± 2.8 [d]
	pCO_2[b]	53.00 ± 10.00 mmHg[d]	*24-28 weeks*: 50.4 ± 11.2 [d] *29-32 weeks*: 52.4 ± 9.7 [d] *33-36 weeks*: 53.5 ± 9.9 [d]
	pO_2[c]	19.00 ± 7.90 mmHg[d]	*24-28 weeks*: 20.7 ± 7.8 [d] *29-32 weeks*: 18.9 ± 7.5 [d] *33-36 weeks*: 18.8 ± 6.7 [d]
Umbilical venous	pH	7.33 ± 0.07[d]	25-31 weeks: 7.33 ± 0.08[g] 32-37 weeks: 7.33 ± 0.06 [g]
	BD[a]	-2.60 ± 2.50 mEq/L[d]	
	pCO_2[b]	43.30 ± 8.30 mmHg[d]	
	pO_2[c]	29.20 ± 9.70 mmHg[d]	
Infant arterial	pH	7.39 ± 0.09[f]	
	BD[a]	-3.10 ± 6.20 mEq/L[e]	
	pCO_2[b]	45.90 ± 10.16 mmHg[f]	
	pO_2[c]	52.11 ± 11.84 mmHg[f]	
Infant capillary	pH	7.37 ± 0.08[f]	
	BD[a]	-3.70 ± 5.70 mEq/L[e]	
	pCO_2[b]	46.42 ± 9.13 mmHg[f]	
	pO_2[c]	36.96 ± 5.85 mmHg[f]	

Note. Means ± standard deviation; Reference ranges by gestational age that were left blank were unavailable.
[a]Base Deficit; [b]Partial pressure of carbon dioxide; [c]Partial pressure of oxygen; [d]Dickinson et al., 1992; [e]Yang et al., 2002 [f]Brodkorb et al., 2022; [g] Victory et al., 2003.

Table 3
Blood gas and acid-base value cutoffs by severity in the fetus and preterm infant

Source	Value	Severity	Range
Umbilical arterial	pH	Mild Acidemia	pH = 7.1 – 7.2[d]
		Moderate Acidemia	pH = 7.1 – 7.0[d]
		Severe Acidemia	pH < 7.0[d]
	BD[a]	Mild Acidemia	
		Moderate Acidemia	
		Severe Acidemia	BD ≤ -12 to -16 mEq/L[e]
	pCO_2[b]	Mild Hypercapnia	
		Moderate Hypercapnia	
		Severe Hypercapnia	
	pO_2[c]	Mild Hypoxemia	
		Moderate Hypoxemia	
		Severe Hypoxemia	
Infant arterial	pH	Mild Acidemia	pH = 7.2 – 7.3[f]
		Moderate Acidemia	pH = 7.1-7.2[f]
		Severe Acidemia	pH < 7.1[f]
	BD[a]	Mild Metabolic Acidemia	
		Moderate Metabolic Acidemia	
		Severe Metabolic Acidemia	BD < -16 mEq/L[g]
	pCO_2[b]	Mild Hypercapnia	pCO_2 = 45-55 mmHg[h]
		Moderate Hypercapnia	pCO_2 = 55-65 mmHg[h]
		Severe Hypercapnia	pCO_2 > 65 mmHg[h]
	pO_2[c]	Mild Hypoxemia	
		Moderate Hypoxemia	
		Severe Hypoxemia	pO_2 < 11.25 mmHg[i]

Note. If a range is left blank, the severity range was unable to be found in preterm (or term) infants.
[a]Base Deficit; [b]Partial pressure of carbon dioxide; [c]Partial pressure of oxygen; [d]Leuthner et al., 2004; [e]Jonsson et al., 2009; [f]Korones, 1981; [g]Hüseman et al., 2011; [h]Brown et al., 2018; [i] Greisen, 1992.

Table 4

Demographic and socio-familial characteristics of total sample and non-neurological subsample

Characteristics	*Total Sample* (N = 224)	*Non-Neurological Subsample* (N = 211)
Adjusted age (months)[a]	45.08 ± 3.08 [38.6-53.1]	45.08 ± 3.07 [38.6-53.1]
Multiples (S:M)[b]	122 : 102 [55:45%]	109 : 102 [52:48%]
Race (W:O)[c]	171 : 53 [76:24%]	171 : 40 [81:19%]
Sex (M: F)	100 : 124 [45:55%]	97 : 114 [46:54%]
Maternal Height	65.13 ± 3.12 (215) ([48-72]	65.14 ± 3.11 (203) [48-72]
SES[d]	49.50 ± 10.11 [24-66]	49.44 ± 10.10 [24-66]
Parental VIQ[e]	100.18 ± 11.44 (196) [70-136]	99.71 ± 11.32 (183) [70-134]
Mother's education (yrs.)	16.29 ± 1.83 (219) [12-20]	16.27 ± 1.86 (207) [12-20]
Father's education (yrs.)	15.58 ± 2.24 (222) [10-20]	15.61 ± 2.21 (209) [10-20]

Note. Frequencies are reported for discrete data, means and standard deviations for continuous data. In the case of missing data, number of participants used is provided in parentheses. Ranges and percentages by group are provided in brackets.

[a] Age adjusted for prematurity at first testing session.

[b] S = single, M = multiple (Twins, n = 93 [including 7 single cases in which other twin was not evaluated; Triplets, n = 9)

[c] W=White (at least one parent considered Caucasian), O = Other

[d] Hollingshead's (1975) Four Factor Index of Social Status.

[e] Prorated parental IQ based on three subtests (Vocabulary, Similarities, and Information) of the Wechsler Adult Intelligence Scale-IV; Testing was administered to the biological mothers.

Table 5
Antenatal and neonatal data for total sample and non-neurological subsample

Characteristics	*Total Sample* (N = 224)	*Non-Neurological Subsample* (N = 211)
Antenatal Factors		
Pregnancy - general		
Mother's age at delivery (years)	32.73 ± 4.78 (223) [21-46]	32.62 ± 4.80 (210) [21-46]
Parity	0.75 ± 0.96 [0-5]	0.74 ± 0.97 [0-5]
Smoking (≥ 1 cigarette per day)	5 (216) [2.3%]	5 (203) [2.5%]
Abruption of placenta[a]	23 [10.3%]	19 [9.0%]
Diabetes[b]	30 [13.4%]	28 [13.3%]
HELLP syndrome[c]	13 [5.8%]	11 [5.2%]
Hypertension in pregnancy[d]	74 [33.0%]	68 [32.2%]
Hypothyroidism[e] (requiring hormone replacement)	44 [19.6%]	41 [19.4%]
Small for gestational age[f] (< 10th centile)	24 [10.7%]	24 [11.4%]
Membranes ruptured > 12hr[g]	62 [27.7%]	58 [27.5%]
Placenta previa	18 [8.0%]	18 [8.5%]
Chorioamnionitis (Histological)[h]	41 [18.3%]	37 [17.5%]
Total antenatal complications[i]	1.47 ± 1.03 [0-4]	1.60 ± 1.11 [0-5]
Neonatal Factors		
Birth and delivery		
Abnormal presentation[j]	91 (222) [41.0%]	85 (209) [40.7%]
Birthweight (g)	1465.56 ± 482.21 [490-3070]	1496.05 ± 471.14 [575-3070]
Gestational age (wks)[k]	30.52 ± 2.71 [23.6-33.9]	30.73 ± 2.57 [23.7-33.9]
5-minute Apgar	8.23 ± 1.02 [3-9]	8.27 ± 1.01 [3-9]
Anemia at birth[l]	29 [12.9%]	25 [11.8%]
Bacterial Infection[m]	13 [5.8%]	9 [4.3%]
Bronchopulmonary Dysplasia[n]	39 [17.4%]	32 [15.2%]
Hyaline Membrane Disease[o]	128 [57.1%]	116 [55.0%]
Intracranial Pathology[p]	33 [14.7%]	25 [11.8%]
Oxygenation following discharge[q]	25 [11.2%]	20 [9.5%]
Patent Ductus Arteriosus[r]	45 [20.1%]	36 [17.1%]
Hypogylcemia[s]	38 [17.0%]	33 [15.6%]
Hyperbilirubinemia[t]	22 [9.8%]	22 [10.4%]
Total Neonatal Complications[u]	1.66 ± 1.58 [0-7]	1.35 ± 1.41 [0-7]
Total Complications[v]	3.13 ± 2.01 [0-9]	2.95 ± 1.81 [0-9]

Note. Frequencies are reported for discrete data, means and standard deviations for continuous data. In the case of missing data, number of participants used is provided in parentheses. Ranges and percentages by group are provided in brackets.

[a] Determined at delivery or by placental pathology

[b] Includes both gestational diabetes and diabetes mellitus.

[c] Hemolysis, elevated liver enzymes and low platelets.

[d] Including diagnoses of preeclampsia, chronic hypertension, and pregnancy induced hypertension

[e] All cases requiring treatment with Levothyroxine.

[f] According to sex-specific, birthweight-for-gestational-age, reference norms (birthweight SD) published by Kramer et al. (2001).
[g] Time from spontaneous or artificial rupture of membranes to delivery.
[h] Includes only cases confirmed via histopathology (with or without funisitis)
[i] Summary score for the nine above listed antenatal complications
[j] Includes various atypical presentations such as breech, transverse lie, footling, etc.
[k] As determined by obstetrician; > 95% of cases were corroborated by antenatal ultrasound.
[l] Initial hematocrit < 40%
[m] Established by positive blood culture
[n] Chronic lung disease: supplemental oxygen required at 36 weeks gestation or discharge for infants
[o] Based on a chest roentgenogram and clinical evaluation
[p] Documented on the basis of cranial ultrasound. (Mild = Bleed Grade 1 & 2; Severe = Grade 3 & 4 using grading criteria by Volpe, 2001). Routine cranial ultrasound given to all infants with gestational age ≤ 32 weeks, and when clinically indicated to infants with gestational age > 32 weeks.
[q] Infants discharged on the ventilator were not included in the current study
[r] Diagnosed by clinical manifestations and echocardiographic information
[s] Diagnosed at least once during NICU stay
[t] Peak bilirubin ≥ 12 mg/dl
[u] Summary score for the nine above listed perinatal complications
[v] Summary score for the 18 above listed antenatal and perinatal complications.

Table 6

Antenatal and neonatal diagnostic and intervention procedures for total sample and non-neurological subsample

Procedures	*Total Sample* (N = 224)	*Non-Neurological Subsample* (N = 211)
Antenatal magnesium sulfate[a]	169 (223) [75.8%]	157 (210) [74.8%]
Antenatal steroids dose[b]	1.61 ± 0.66 (221) [0-2]	1.60 ± 0.67 (208) [0-2]
General anesthesia during delivery	18 (223) [8.1%]	16 (210) [7.6%]
Hypertension medications in pregnancy	51 (213) [23.9%]	46 (200) [23.0%]
Surfactant therapy	64 [28.6%]	55 [26.1%]
Ventilation days	4.09 ± 13.46 (223) [0-91]	2.29 ± 8.80 [0-91]
Days in Neonatal Intensive Care Unit	41.63 ± 31.82 [5-170]	38.01 ± 25.94 [5-141]

Note. Frequencies are reported for discrete data, means and standard deviations for continuous data. In the case of missing data, number of participants used is provided in parentheses. Ranges and percentages by group are provided in brackets.

[a] Magnesium sulfate, administered to inhibit preterm labor and/or control seizures in preeclampsia.

[b] Betamethasone, to promote fetal lung maturation.

Table 7
Psychometric properties of neuropsychological measures

Instrument	Outcome Measure	Internal Consistency		Test-Retest Reliability	
		3-year-olds	4-year-olds	3-year-olds	4-year-olds
PDMS-2[a]	*Gross Motor Quotient*	.93 (3:0-3:11)	.94 (4:0-4:11)	NA	NA
	Stationary	.71 (3:0-3:11)	.77 (4:0-4:11)	NA	NA
	Locomotion	.95 (3:0-3:11)	.96 (4:0-4:11)	NA	NA
	Object Manipulation	.90 (3:0-3:11)	.92 (4:0-4:11)	NA	NA
	Fine Motor Quotient	.91 (3:0-3:11)	.98 (4:0-4:11)	NA	NA
	Grasping	.74 (3:0-3:11)	.96 (4:0-4:11)	NA	NA
	Visual-Motor Integration	.94 (3:0-3:11)	.96 (4:0-4:11)	NA	NA
CELF-P2[b]	*Core Language Index*	.91 (3:0-3:5)	.93 (4:0-4:5)	.92	.89
		.91 (3:6-3:11)	.93 (4:6-4:11)		
	Receptive Language	.91 (3:0-3:5)	.94 (4:0-4:5)	.92	.95
		.92 (3:6-3:11)	.91 (4:6-4:11)		
	Sentence Structure	.78 (3:0-3:5)	.83 (4:0-4:5)	.77	.80
		.79 (3:6-3:11)	.81 (4:6-4:11)		
	Concepts & Following Directions	.85 (3:0-3:5)	.85 (4:0-4:5)	.85	.83
		.84 (3:6-3:11)	.84 (4:6-4:11)		
	Basic Concepts	.82 (3:0-3:5)	.87 (4:0-4:5)	.90	.80
		.81 (3:6-3:11)	.72 (4:6-4:11)		
	Expressive Language Index	.93 (3:0-3:5)	.94 (4:0-4:5)	.95	.92
		.92 (3:6-3:11)	.94 (4:6-4:11)		
	Word Structure	.86 (3:0-3:5)	.86 (4:0-4:5)	.92	.77
		.84 (3:6-3:11)	.83 (4:6-4:11)		
	Expressive Vocabulary	.78 (3:0-3:5)	.83 (4:0-4:5)	.88	.90
		.77 (3:6-3:11)	.84 (4:6-4:11)		
	Recalling Sentences	.88 (3:0-3:5)	.91 (4:0-4:5)	.89	.87
		.87 (3:6-3:11)	.90 (4:6-4:11)		
NEPSY-2[c]	*Oromotor Sequences*	NA	NA	NA	NA

Note: Internal consistency coefficients are provided for each index and subtest, with appropriate age range in parentheses. Test-retest reliability coefficients provided for each index and subtest. NA = Not Available.
[a]PDMS-2 = Peabody Developmental Motor Scales – Second Edition
[b]CELF-P2 = Clinical Evaluation of Language Fundamentals, Preschool, Second Edition

Table 8
Means and standard deviations (range) for predictor variables for the total sample and non-neurological subsample

	Total Sample		*Non-Neurological Subsample*	
	N	*M* ± SD [range]	*N*	*M* ± SD [range]
Arterial Umbilical Cord [a]				
Cord blood pH	*N* = 175	7.29 ± 0.07 [6.95-7.44]	*N* = 163	7.29 ± 0.07 [7.08-7.44]
Cord blood pCO_2	*N* = 175	53.45 ± 9.98 [32-103]	*N* = 163	53.27 ± 9.14 [32-80]
Cord blood BD	*N* = 173	-2.31 ± 2.90 [-16-4]	*N* = 161	-2.22 ± 2.68 [-12-4]
Time from Birth[b] (min)		28.89 ± 91.81 [0-738]		30.02 ± 94.94 [0-738]
Initial (First Three Hours of Life)[c]				
Arterial pH	*n* = 23	7.29 ± 0.07 [7.19-7.47]	*n* = 19	7.29 ± 0.07 [7.19-7.47]
Capillary pH	*n* = 75	7.33 ± 0.06 [7.16-7.49]	*n* = 69	7.33 ± 0.06 [7.16-7.49]
pH (Total)[d]	*N* = 98	7.32 ± 0.07 [7.16-7.49]	*N* = 88	7.32 ± 0.07 [7.16-7.49]
Arterial pCO_2	*n* = 23	52.26 ± 11.11 [35-77]	*n* = 19	51.95 ± 11.04 [35-77]
Capillary pCO_2	*n* = 75	54.55 ± 9.55 [28-93]	*n* = 69	55.13 ± 9.53 [28-93]
pCO_2 (Total)[e]	*N* = 98	54.01 ± 9.92 [28-93]	*N* = 88	54.44 ± 9.89 [28-93]
Arterial pO_2	*n* = 23	78.09 ± 54.04 [41-270]	*n* = 19	82.26 ± 58.75 [41-270]
Adjusted Capillary pO_2[f]	*n* = 75	56.00 ± 5.86 [43-79]	*n* = 69	55.74 ± 5.37 [43-79]
pO_2 (Total)[g]	*N* = 98	51.43 ± 30.76 [24-270]	*N* = 88	51.35 ± 32.18 [24-270]
Arterial BD	*n* = 23	-2.87 ± 2.78 [-13 to +2]	*n* = 19	-2.79 ± 2.90 [-13 to +2]
Capillary BD	*n* = 75	+0.53 ± 2.32 [-6 to +6]	*n* = 69	+0.57 ± 2.23 [-5 to +6]
BD (Total)[h]	*N* = 98	-0.27 ± 2.81 [-13 to +6]	*N* = 88	-0.16 ± 2.75 [-13 to +6]
Time From Birth[i] (min)		92.57 ± 32.00 [43-176]		94.81 ± 32.41 [43-176]
First Week of Life[j]				
Lowest Arterial pH	*n* = 17	7.10 ± 0.07 [6.98-7.25]	*n* = 12	7.10 ± 0.08 [6.98-7.25]
Lowest Capillary pH	*n* = 99	7.27 ± 0.09 [6.95-7.47]	*n* = 93	7.27 ± 0.09 [6.95-7.47]
Lowest pH (Total)[k]	*N* = 116	7.24 ± 0.11 [6.95-7.47]	*N* = 105	7.25 ± 0.10 [6.95-7.47]
Time From Birth[l] (hr)		55.87 ± 44.30 [1.8-158.3]		54.13 ± 44.89 [1.8-158.3]
Highest Arterial pCO_2	*n* = 15	72.07 ± 16.85 [49-114]	*n* = 12	71.75 ± 18.14 [49-114]
Highest Capillary pCO_2	*n* = 100	59.45 ± 14.29 [36-119]	*n* = 92	58.47 ± 13.92 [36-119]
Highest pCO_2 (Total)[m]	*N* = 115	61.10 ± 15.18 [36-119]	*N* = 104	60.00 ± 14.99 [36-119]
Time From Birth[l] (hr)		46.61 ± 45.90 [1.8-165.9]		41.12 ± 41.46 [1.8-165.5]
Lowest Arterial pO_2	*n* = 20	41.60 ± 4.25 [36-50]	*n* = 16	41.50 ± 4.46 [36-50]
Lowest Adjusted Capillary pO_2[f]	*n* = 96	50.03 ± 4.34 [41-62]	*n* = 89	50.14 ± 4.30 [41-62]
Lowest pO_2 (Total)[n]	*N* = 116	48.58 ± 5.36 [36-62]	*N* = 105	48.83 ± 5.31 [36-62]
Time From Birth[l] (hr)		43.33 ± 41.66 [1.0-168.9]		40.00 ± 38.64 [1.0-168.9]
Lowest Arterial BD	*n* = 21	-10.29 ± 3.27 [-19 to -3]	*n* = 16	-10.06 ± 3.68 [-19 to -3]
Capillary Lowest BD	*n* = 95	-3.26 ± 3.42 [-10 to +4]	*n* = 89	-3.15 ± 3.47 [-10 to +4]

Lowest BD (Total)[o]	*N* = 116	-4.53 ± 4.34 [-19 to +4]	*N* = 105	-4.20 ± 4.29 [-19 to +4]
Time From Birth[l] (hr)		62.72 ± 43.41 [2.5-163.4]		60.75 ± 43.50 [2.5-158.4]

Note. Sample size, means, and standard deviations. Ranges are provided in brackets.
[a] Cases with available arterial umbilical cord blood gas measurements.
[b] Time in minutes from birth to the collection of a cord blood sample.
[c] Cases with available neonatal arterial or capillary blood gas measurements obtained within the first three hours of life. Breakdown of arterial and capillary blood gas measurements provided with sample size, means, standard deviations, and ranges.
[d] Total cases = sum of cases with arterial or capillary pH measurements obtained within the first three hours of life.
[e] Total cases = sum of cases with arterial or capillary pCO_2 measurements obtained within the first three hours of life.
[f] Capillary pO_2 values were adjusted using Brodkorb et al.'s (2022) conversion formula.
[g] Total cases = sum of cases with arterial or adjusted capillary pO_2 obtained within the first three hours of life.
[h] Total cases = sum of cases with arterial or capillary BD measurements obtained within the first three hours of life.
[i] Time in minutes from birth to the collection of an initial neonatal blood sample
[j] Cases with available neonatal arterial or capillary blood gas measurements obtained within the first week of life. Breakdown of arterial and capillary blood gas measurements provided with sample size, means, standard deviations, and ranges.
[k] Total cases = sum of cases with lowest arterial or lowest capillary pH measurements obtained within the first week of life (3 hours of life to 7 completed days of life).
[l] Time in hours from birth to collection of the blood sample containing the relevant biochemical index
[m] Total cases = sum of cases with highest arterial or highest capillary pCO_2 measurements obtained within the first week of life.
[n] Total = sum of cases with lowest arterial or lowest adjusted capillary pO_2 measurements obtained within the first week of life.
[o] Total cases = sum of cases with lowest arterial or lowest capillary BD measurements obtained within the first week of life.

Table 9
Independent variables for each hypothesis

Hypothesis	Independent Variable	Blood Source	Collection Period
Hypothesis 1 (Birth & Delivery)			
1a	Cord pH	Arterial	Delivery
	Cord BD[a]	Arterial	
1b	Cord pCO_2[b]	Arterial	
Hypothesis 2 (Immediate Neonatal Adjustment)			
2a	Neonatal pH	Arterial / Capillary	First 3 hours of life
	Neonatal BD[a]	Arterial / Capillary	
2b	Neonatal pCO_2[b]	Arterial / Capillary	
2c	Neonatal pO_2[c]	Arterial / Adjusted Capillary[d]	
Hypothesis 3 (Initial Neonatal Adjustment Within the First Week of Life)			
3a	Lowest neonatal pH	Arterial / Capillary	3 hours of life to 7 completed days of life
	Lowest neonatal BD[a]	Arterial / Capillary	
3b	Highest neonatal pCO_2[b]	Arterial / Capillary	
3c	Lowest neonatal pO_2[c]	Arterial / Adjusted Capillary[d]	
Hypothesis 4	All Infant Blood Gas Values	Arterial / Capillary / Adjusted Capillary	Birth & Delivery Period *vs* Immediate Neonatal Adjustment Period *vs* First Week of Life

[a]Base Deficit; [b]Partial pressure of carbon dioxide; [c]Partial pressure of oxygen; [d]Adjusted via Brodkorb et al.'s (2022) correction formula.

Table 10

Bivariate correlations between predictors and covariates in the total sample

	SES	Sex	Gestational Age	Standardized Birthweight	Antenatal Complications
SES[a]	—				
Sex	-.016	—			
Gestational Age	.118	.086	—		
Standardized Birthweight[b]	-.058	.024	-.108	—	
Antenatal Complications	.020	-.066	-.136*	-.194**	—
Arterial Umbilical Cord[c]					
Cord pH	.123 (176)	-.081 (176)	-.043 (176)	.007 (176)	.028 (176)
Cord pCO_2	.077 (175)	-.079 (175)	.236** (175)	-.075 (175)	.012 (175)
Cord BD	.052 (173)	.054 (173)	-.118 (173)	.053 (173)	-.052 (173)
Initial (First Three Hours of Life)[d]					
pH	.060 (107)	.088 (107)	-.020 (107)	.004 (107)	.028 (107)
pCO_2	.079 (107)	-.128 (107)	.225* (107)	.029 (107)	-.075 (107)
pO_2[e]	-.224* (107)	-.121 (107)	-.247* (107)	-.015 (107)	.280** (107)
BD	.186 (107)	-.011 (107)	.241* (107)	.038 (107)	-.036 (107)
First Week of Life[f]					
Lowest pH	-.001 (117)	.036 (117)	.447*** (117)	.205* (117)	-.186* (117)
Highest pCO_2	.047 (116)	-.093 (116)	-.204* (116)	-.199* (116)	.062 (116)
Lowest pO_2[e]	.032 (117)	.010 (117)	.372*** (117)	.090 (117)	-.062 (117)
Lowest BD	.064 (117)	-.028 (117)	.609*** (117)	.102 (117)	-.219* (117)

* $p < .05$; ** $p < .01$; *** $p < .001$

Note. In the case of missing data, sample size is provided in parentheses below each correlation. Neurological cases are included.

[a] Hollingshead's (1975) Four Factor Index of Social Status.

[b] According to sex-specific, birthweight-for-gestational-age, reference norms (birthweight SD) published by Kramer et al. (2001).

[c] Cases with available arterial umbilical cord blood gas measurements.

[d] Cases with available neonatal arterial or capillary blood gas measurements obtained within the first three hours of life.

[e] Capillary pO_2 values were adjusted to reflect arterial values using Brodkorb et al. (2022)'s conversion formula.

[f] Cases with available neonatal arterial or capillary blood gas measurements obtained within the first week of life.

Table 11

Bivariate correlations between predictors and covariates in the non-neurological subsample

	SES	Sex	Gestational Age	Standardized Birthweight	Antenatal Complications
SES[a]	—				
Sex	-.050	—			
Gestational Age	.118	.119	—		
Standardized Birthweight[b]	-.038	.044	-.109	—	
Antenatal Complications	.032	-.070	-.069	-.225**	—
Arterial Umbilical Cord[c]					
Cord pH	.129 (164)	-.081 (164)	-.055 (164)	.009 (164)	.028 (176)
Cord pCO_2	.027 (163)	-.117 (163)	.245** (163)	-.094 (163)	.012 (175)
Cord BD	.124 (161)	.071 (161)	-.129 (161)	.056 (161)	-.052 (173)
Initial (First Three Hours of Life)[d]					
pH	.088 (97)	.072 (97)	-.068 (97)	-.014 (97)	.028 (107)
pCO_2	.092 (97)	-.090 (97)	.224* (97)	.054 (97)	-.075 (107)
pO_2[e]	-.238* (97)	-.138 (97)	-.262* (97)	-.015 (97)	.280** (107)
BD	.247* (97)	.004 (97)	.166 (97)	.042 (97)	-.036 (107)
First Week of Life[f]					
Lowest pH	.033 (106)	.105 (106)	.408*** (106)	.178 (106)	-.186* (117)
Highest pCO_2	.041 (105)	-.156 (105)	-.133 (105)	-.149 (105)	.062 (116)
Lowest pO_2[e]	.084 (106)	.053 (106)	.346*** (106)	.038 (106)	-.062 (117)
Lowest BD	.091 (106)	.003 (106)	.588*** (106)	.092 (106)	-.219* (117)

* $p < .05$; ** $p < .01$; *** $p < .001$

Note. In the case of missing data, sample size is provided in parentheses below each correlation. Neurological cases are excluded.

[a] Hollingshead's (1975) Four Factor Index of Social Status.

[b] According to sex-specific, birthweight-for-gestational-age, reference norms (birthweight SD) published by Kramer et al. (2001).

[c] Cases with available arterial umbilical cord blood gas measurements.

[d] Cases with available neonatal arterial or capillary blood gas measurements obtained within the first three hours of life.

[e] Capillary pO_2 values were adjusted to reflect arterial values using Brodkorb et al. (2022)'s conversion formula.

[f] Cases with available neonatal arterial or capillary blood gas measurements obtained within the first week of life.

Table 12

Bivariate correlations between predictors in the total sample

		Arterial Umbilical Cord [a]			Initial (First Three Hours of Life)[c]			
		pH	pCO_2	BD	pH	pCO_2	pO_2[d]	BD
Initial (First Three Hours of Life)[b]	pH	.010 (78)	.146 (78)	.188 (78)				
	pCO_2	.081 (78)	-.044 (78)	.119 (78)				
	pO_2[d]	-.025 (78)	-.120 (78)	-.226* (78)				
	BD	.085 (78)	.198 (78)	.417*** (78)				
First Week of Life [c]	Lowest pH	.120 (91)	.221* (90)	.051 (89)	.317** (94)	-.068 (94)	-.200 (94)	.395*** (94)
	Highest pCO_2	-.153 (90)	-.054 (89)	.083 (88)	-.348*** (93)	.273** (93)	.092 (93)	-.205* (93)
	Lowest pO_2[d]	.079 (91)	.105 (90)	.052 (89)	.180 (94)	.050 (94)	-.111 (94)	.333** (94)
	Lowest BD	.057 (91)	.284** (90)	.295** (89)	.199 (94)	.155 (94)	-.194 (94)	.482*** (94)

* $p < .05$; ** $p < .01$; *** $p < .001$

Note. In the case of missing data, sample size is provided in parentheses below each correlation. Neurological cases are included.

[a] Cases with available arterial umbilical cord blood gas measurements.

[b] Cases with available neonatal arterial or capillary blood gas measurements obtained within the first three hours of life.

[c] Cases with available neonatal arterial or capillary blood gas measurements obtained within the first week of life.

[d] Capillary pO_2 values were adjusted to reflect arterial values using Brodkorb et al. (2022)'s correction formula.

Table 13

Bivariate correlations between predictors in the non-neurological subsample

		Arterial Umbilical Cord [a]			Initial (First Three Hours of Life)[c]			
		pH	pCO_2	BD	pH	pCO_2	pO_2[d]	BD
Initial (First Three Hours of Life)[b]	pH	.062 (69)	.118 (69)	.274* (69)				
	pCO_2	.117 (69)	-.043 (69)	.156 (69)				
	pO_2[d]	-.073 (69)	-.116 (69)	-.308* (69)				
	BD	.206 (69)	.159 (69)	.596*** (69)				
First Week of Life [c]	Lowest pH	.120 (61)	.248* (80)	-.036 (79)	.324** (85)	-.099 (85)	-.211 (85)	.373*** (85)
	Highest pCO_2	-.156 (80)	-.042 (79)	.183 (78)	-.366*** (84)	.311** (84)	.098 (84)	-.189 (84)
	Lowest pO_2[d]	.079 (81)	.160 (80)	-.026 (79)	.143 (85)	.069 (85)	-.117 (85)	.305** (85)
	Lowest BD	.051 (81)	.311** (80)	.243* (79)	.173 (85)	.161 (85)	-.200 (85)	.454*** (85)

* $p < .05$; ** $p < .01$; *** $p < .001$

Note. In the case of missing data, sample size is provided in parentheses below each correlation. Neurological cases are excluded.

[a] Cases with available arterial umbilical cord blood gas measurements.

[b] Cases with available neonatal arterial or capillary blood gas measurements obtained within the first three hours of life.

[c] Cases with available neonatal arterial or capillary blood gas measurements obtained within the first week of life.

[d] Capillary pO_2 values were adjusted to reflect arterial values using Brodkorb et al. (2022)'s correction formula.

Table 14

Available cases by period for each biochemical variable of interest for the total sample and the non-neurological subsample

	Total Sample $N = 224$	*Non-Neurological Subsample* $N = 211$
Birth and Delivery Period [a]		
Cord pH	175 (21.9%)	163 (22.7%)
Cord pCO_2	175 (21.9%)	163 (22.7%)
Cord BD	173 (22.8%)	161 (23.7%)
Immediate Neonatal Adjustment Period [b]		
pH	98 (56.3%)	88 (58.3%)
pCO_2	98 (56.3%)	88 (58.3%)
pO_2	98 (56.3%)	88 (58.3%)
BD	98 (56.3%)	88 (58.3%)
First Week of Life [c]		
Lowest pH	116 (48.2%)	105 (50.2%)
Highest pCO_2	115 (48.7%)	104 (50.7%)
Lowest pO_2	116 (48.2%)	105 (50.2%)
Lowest BD	116 (48.2%)	105 (50.2%)

Note. Sample size for each variable of interest with percent unavailable reported in parentheses. Percent unavailable was determined from a sample of 224 in the total sample and a sample of 211 in the non-neurological subsample.

[a] Cases with available arterial umbilical cord blood gas measurements.

[b] Cases with available neonatal arterial or capillary blood gas measurements obtained within the first three hours of life.

[c] Cases with available neonatal arterial or capillary blood gas measurements obtained within the first week of life (3 hours of life to 7 completed days of life).

Table 15
Missing values for covariate variables for the total sample and non-neurological subsample

	Total Sample $N = 224$	*Non-Neurological Subsample* $N = 211$
SES	224 (0%)	211 (0%)
Sex	224 (0%)	211 (0%)
Gestational Age	224 (0%)	211 (0%)
Standardized BW	224 (0%)	211 (0%)
Total Antenatal Complications	224 (0%)	211 (0%)
NEPSY-2 Oromotor Sequences[a]	191 (14.7%)	75 (14.2%)

Note. Sample size with percent missing in parentheses. Percent missingness was determined from a sample of 224 and 211 in the Total Sample and Non-Neurological Subsample, respectively.
[a] The NEPSY-2 Oromotor Sequences subtest score was used as a covariate in analyses with the CELF-P2 Core Language Index and Expressive Language Index as the outcome variables.

Table 16
Missing values for outcome variables for the total sample and non-neurological subsample

	Total Sample $N = 224$	*Non-Neurological Subsample* $N = 211$
Motor		
PDMS-2 Fine Motor Quotient	219 (2.2%)	206 (2.4%)
PDMS-2 Gross Motor Quotient	215 (4.0%)	203 (3.8%)
Language		
CELF-P2 Expressive Language Index	205 (8.5%)	194 (8.1%)
CELF-P2 Receptive Language Index	210 (6.3%)	199 (5.7%)
CELF-P2 Core Language Index	212 (5.4%)	201 (4.7%)

Note. Sample size with percent missing in parentheses. Percent missingness was determined from a sample of 224 and 211 in the Total Sample and Non-Neurological Subsample, respectively.

Table 17a

Summary of linear mixed model analyses of the relationships between arterial umbilical cord pH and preschool motor and language measures

		Total Sample[f]					Non-Neurological Subsample[f]				
Index	Source	*N*	*t*	*df*	*p*	ΔR^2	*N*	*t*	*df*	*p*	ΔR^2
Motor											
PDMS-2[a] Gross Motor Quotient	Cord pH[c, e]	165	1.79	1, 158.00	.076	.042	153	2.09	1, 146.00	.038	.022
	Gestational Age		1.56	1, 147.49	.122			0.9	1, 136.48	.368	
	Standardized BW		0.71	1, 158.00	.482			0.43	1, 146.00	.671	
	Antenatal		-0.10	1, 147.19	.924			0.84	1, 136.21	.403	
	Sex (F > M)		-0.70	1, 158.00	.485			-1.58	1, 146.00	.117	
	Socioeconomic Status		0.35	1, 143.81	.726			1.25	1, 133.58	.215	
PDMS-2[a] Fine Motor Quotient	Cord pH[c, e]	170	0.85	1, 162.47	.396		157	1.06	1, 148.39	.292	
	Gestational Age		3.37	1, 150.12	<.001	.064		3.21	1, 136.32	.002	.063
	Standardized BW		1.12	1, 161.37	.263			0.68	1, 148.11	.496	
	Antenatal		0.60	1, 145.84	.553			0.38	1, 134.30	.703	
	Sex (F > M)		-4.67	1, 163.00	<.001	.119		-5.2	1, 150.00	<.001	.152
	Socioeconomic Status		3.07	1, 145.62	.003	.054		3.67	1, 133.44	<.001	.081
Language											
CELF-P2[b] Core Language Index	Cord pH[c, e]	147	-0.33	1, 136.00	.740		136	-0.64	1, 126.00	.523	
	Gestational Age		0.34	1, 114.52	.733			0.04	1, 104.51	.967	
	Standardized BW		1.16	1, 136.00	.248			0.69	1, 126.00	.493	
	Antenatal		0.28	1, 125.09	.783			0.07	1, 112.55	.946	
	Sex (F > M)		-1.94	1, 136.00	.054	.023		-1.95	1, 126.00	.054	.024
	Socioeconomic Status		2.73	1, 119.52	.007	.064		2.91	1, 108.81	.004	.078
	Oromotor Sequences[d]		-5.91	4, 136.00	<.001	.380		-5.32	4, 126.00	<.001	.384
CELF-P2[b] Expressive Language Index	Cord pH[c, e]	142	0.69	1, 131.00	.490		131	0.45	1, 122.00	.655	
	Gestational Age		1.47	1, 113.53	.144			1.38	1, 106.00	.171	
	Standardized BW		0.86	1, 131.00	.390			0.45	1, 122.00	.651	
	Antenatal		0.22	1, 120.50	.826			-0.02	1, 111.19	.985	
	Sex (F > M)		-1.95	1, 131.00	.053	.022		-1.86	1, 122.00	.065	.022
	Socioeconomic Status		2.31	1, 118.31	.022	.047		2.66	1, 110.00	.009	.065
	Oromotor Sequences[d]		-7.18	4, 131.00	<.001	.441		-6.46	4, 122.00	<.001	.438
CELF-P2[b] Receptive Language Index	Cord pH[c, e]	161	1.53	1, 154.00	.128		149	1.28	1, 142.00	.203	
	Gestational Age		1.53	1, 129.14	.129			1.73	1, 117.56	.086	.020
	Standardized BW		0.58	1, 152.77	.562			0.12	1, 140.50	.908	
	Antenatal		-0.57	1, 134.96	.572			-0.66	1, 124.79	.513	
	Sex (F > M)		-2.57	1, 154.00	.011	.030		-2.35	1, 142.00	.020	.026
	Socioeconomic Status		4.20	1, 125.20	<.001	.111		3.96	1, 113.95	<.001	.107

[a]Peabody Developmental Motor Scales – Second Edition (Folio & Fewell, 2000)

[b]Clinical Evaluation of Language Fundamentals – Preschool Second Edition (CELF-P2; Wiig et al., 2004)

[c] Arterial umbilical cord pH

[d] NEPSY Second Edition (NEPSY-2; Korkman, Kirk, & Kemp, 1997)

[e] One case was noted to be a multivariate outlier (determined with Mahalanobis Distance; critical value, $\chi 2 = 20.52$ for GMQ, FMQ, and RLI; critical value, $\chi 2 = 24.32$ for CLI and ELI) across all five measured outcomes in the total sample (observed values for GMQ, $\chi 2 = 28.38$; FMQ, $\chi 2 = 29.07$; CLI, $\chi 2 = 28.28$; ELI, $\chi 2 = 30.48$; RLI, $\chi 2 = 28.65$; all $p < .001$). Two cases were noted to be multivariate outliers (determined with Mahalanobis Distance; critical value, $\chi 2 = 20.52$ for GMQ, FMQ, and RLI; critical value, $\chi 2 = 24.32$ for CLI and ELI) across all five measured outcomes in the reduced sample (observed values for GMQ, $\chi 2 = 21.22$, $\chi 2 = 21.12$; FMQ, $\chi 2 = 21.02$, $\chi 2 = 22.74$; CLI, $\chi 2 = 24.85$, $\chi 2 = 26.48$; ELI, $\chi 2 = 25.26$, $\chi 2 = 26.52$; RLI, $\chi 2 = 21.16$, $\chi 2 = 22.88$; all $p < .001$). When the outlier was included in the total sample, the relationship between cord pH and FMQ, CLI, ELI, and RLI remained nonsignificant, FMQ: ($t[164] = 1.18$, $p = .239$), CLI: ($t[137] = 0.30$, $p = .768$), ELI: ($t[132] = 1.44$, $p = .152$), RLI: ($t[154] = 1.66$, $p = .098$), and the relationship between cord pH and GMQ reached statistical significance (($t[159] = 2.61$, $p = .010$). When the two outliers were included in the reduced sample, the relationship between cord pH and GMQ, FMQ, CLI, ELI, and RLI were nonsignificant, GMQ: ($t[148] = 1.55$, $p = .123$), FMQ: ($t[151] = 0.62$, $p = .539$), CLI: ($t[127] = -0.44$, $p = .660$), ELI: ($t[122] = 0.45$, $p = .655$), RLI: ($t[144] = 1.42$, $p = .158$). The relationship between cord pH and GMQ no longer reached statistical significance.

[f] Outcome data missing for indices in the total sample ($N = 175$) and non-neurological subsample ($N = 163$):

GMQ: 9 cases from the total sample (5.1%) and 8 cases from the non-neurological subsample (4.9%).

FMQ: 4 cases from the total sample (2.3%) and 4 cases from the non-neurological subsample (2.5%).

CLI: 11 cases from the total sample (6.3%) and 10 cases from the non-neurological subsample (6.1%). 26 cases (14.9%) had missing data from the Oromotor Sequences subtest in the total sample, and 24 cases (14.7%) in the non-neurological subsample.

ELI: 16 cases from the total sample (9.1%) and 15 cases from the non-neurological subsample (9.2%). 26 (14.9%) cases had missing data from the Oromotor Sequences subtest in the total sample, and 24 cases (14.7%) in the non-neurological subsample.

RLI: 13 cases from the total sample (7.4%) and 12 cases from the non-neurological subsample (7.4%).

Table 17b

Summary of linear mixed model analyses of the relationships between arterial umbilical cord pH and preschool gross motor subtest scores

		Total Sample[e]					Non-Neurological Subsample[e]				
Subtest[a,b]	Source	*N*	*t*	*df*	*p*	ΔR^2	*N*	*t*	*df*	*p*	ΔR^2
Stationary	Cord pH[c, d]	168	-0.40	1, 161.00	.689		156	0.23	1, 149.00	.822	
Locomotion	Cord pH[c, d]	167	2.59	1, 160.00	.010	.121	155	3.24	1, 148.00	.001	.142
Object Manipulation	Cord pH[c, d]	165	1.53	1, 158.00	.129		153	1.21	1, 146.00	.228	

[a]Peabody Developmental Motor Scales – Second Edition (Folio & Fewell, 2000)

[b]All analyses included gestational age, standardized birthweight, total antenatal complications, sex, and socioeconomic status as covariates.

[c] Arterial umbilical cord pH

[d] One case was noted to be a multivariate outlier (determined with Mahalanobis Distance; critical value, $\chi2= 20.52$) across the three measured outcomes in the total sample (observed values for Stationary, $\chi2= 28.74$; Locomotion, $\chi2= 28.67$; Object Manipulation, $\chi2= 28.38$; all $p < .001$). Two cases were noted to be multivariate outliers (determined with Mahalanobis Distance; critical value, $\chi2= 20.52$) across all three measured outcomes in the reduced sample (observed values for Stationary, $\chi2= 21.13$, $\chi2= 22.51$; Locomotion, $\chi2= 21.33$, $\chi2= 22.36$; Object Manipulation, $\chi2= 21.22$, $\chi2= 22.12$; all $p < .001$). When the outlier was included in the total sample, the relationship between cord pH and the Stationary subtest score remained nonsignificant ($t[162] = 0.49$, $p = .628$), and the relationship between cord pH and Locomotion ($t[161] = 3.18$, $p = .002$) and Object Manipulation ($t[159] = 2.10$, $p = .037$) scores was significant. When the outliers were included in the reduced sample, the relationship between cord pH and Locomotion scores remained significant ($t[150] = 2.47$, $p = .015$), and the relationship between cord pH and Stationary ($t[151] = -0.31$, $p = .761$) and Object Manipulation ($t[148] = 0.86$, $p = .391$) scores remained nonsignificant.

[e] Outcome data missing for subtests in the total sample ($N = 175$) and non-neurological subsample ($N = 163$):
Stationary: 6 cases from the total sample (3.4%) and 5 cases from the non-neurological subsample (3.1%).
Locomotion: 7 cases from the total sample (4.0%) and 6 cases from the non-neurological subsample (3.7%).
Object Manipulation: 9 cases from the total sample (5.1%) and 8 cases from the non-neurological subsample (4.9%).

Table 17c

Summary of linear mixed model re-analysis of the relationships between arterial umbilical cord pH and preschool language measures following removal of a single covariate

Language		Total Sample[e]					Non-Neurological Subsample[e]				
Index[a,b]	Source	*N*	*t*	*df*	*p*	ΔR^2	*N*	*t*	*df*	*p*	ΔR^2
Core Language	Cord pH[c, d]	163	0.83	1, 156.00	.407		153	1.12	1, 145.00	.265	
Expressive Language	Cord pH[c, d]	158	2.00	1, 151.00	.047	.043	148	2.24	1, 141.00	.027	.058

Note. Re-analysis of language outcomes without the Oromotor Sequences score as a covariate.

[a] Clinical Evaluation of Language Fundamentals – Preschool Second Edition (CELF-P2; Wiig et al., 2004)

[b] All analyses included gestational age, standardized birthweight, total antenatal complications, sex, and socioeconomic status as covariates.

[c] Arterial umbilical cord pH

[d] One case was noted to be a multivariate outlier (determined with Mahalanobis Distance; critical value, $\chi 2 = 20.52$) across both measured outcomes in the total sample (observed values for CLI, $\chi 2 = 28.28$; ELI, $\chi 2 = 30.48$, both $p < .001$). One case was noted to be a multivariate outlier with CLI as the outcome variable in the reduced sample (observed value for CLI, $\chi 2 = 24.85$; $p < .001$). When the outlier was included in the total sample, the relationship between cord pH and CLI remained nonsignificant ($t[157] = 1.14$, $p = .255$) and the relationship between cord pH and ELI remained significant ($t[152] = 2.32$, $p = .021$). When the outlier was included in the reduced sample, the relationship between cord pH and CLI remained nonsignificant, ($t[146] = 0.97$, $p = .334$).

[e] Outcome data missing for subtests in the total sample ($N = 175$) and non-neurological subsample ($N = 163$):

CLI: 11 cases from the total sample (6.3%) and 10 cases from the non-neurological subsample (6.1%).

ELI: 16 cases from the total sample (9.1%) and 15 cases from the non-neurological subsample (9.2%).

Table 18a

Summary of linear mixed model analyses of the relationships between arterial umbilical cord base deficit and preschool motor and language measures

		Total Sample[f]					Non-Neurological Subsample[f]				
Index	Source	*N*	*t*	*df*	*p*	ΔR^2	*N*	*t*	*df*	*p*	ΔR^2
Motor											
PDMS-2[a] Gross Motor Quotient	Cord BD[c, e]	163	0.51	1, 150.82	.609		151	0.71	1, 138.34	.479	
	Gestational Age		1.47	1, 145.71	.145			0.57	1, 135.28	.572	
	Standardized BW		0.84	1, 156.00	.402			0.62	1, 144.00	.538	
	Antenatal		-0.23	1, 145.03	.815			0.76	1, 132.99	.447	
	Sex (F > M)		-0.75	1, 156.00	.457			-1.61	1, 144.00	.109	
	Socioeconomic Status		0.16	1, 141.64	.876			1.07	1, 130.83	.288	
PDMS-2[a] Fine Motor Quotient	Cord BD[c, e]	168	-0.08	1, 153.01	.936		155	0.03	1, 138.86	.974	
	Gestational Age		3.50	1, 150.31	<.001	.070		3.22	1, 138.00	.002	.064
	Standardized BW		1.35	1, 159.67	.180			0.95	1, 146.29	.345	
	Antenatal		0.62	1, 144.9	.539			0.43	1, 132.70	.669	
	Sex (F > M)		-4.79	1, 161.00	<.001	.125		-5.28	1, 148.00	<.001	.158
	Socioeconomic Status		2.85	1, 144.39	.005	.048		3.67	1, 133.441	<.001	.072
Language											
CELF-P2[b] Core Language Index	Cord BD[c, e]	147	1.09	1, 126.92	.279		136	0.64	1, 116.52	.521	
	Gestational Age		0.50	1, 113.76	.620			0.36	1, 103.34	.720	
	Standardized BW		1.09	1, 136.00	.277			0.60	1, 125.97	.552	
	Antenatal		0.29	1, 124.38	.774			0.10	1, 111.19	.920	
	Sex (F > M)		-1.82	1, 136.00	.071	.020		-1.88	1, 126.00	.062	.024
	Socioeconomic Status		2.75	1, 118.70	.007	.065		2.95	1, 106.97	.004	.080
	Oromotor Sequences[d]		-5.93	4, 136.00	<.001	.318		-5.24	4, 126.00	<.001	.316
CELF-P2[b] Expressive Language Index	Cord BD[c, e]	142	1.31	1, 123.53	.191		131	0.63	1, 116.28	.530	
	Gestational Age		1.54	1, 113.87	.127			1.41	1, 107.04	.163	
	Standardized BW		0.86	1, 131.00	.390			0.48	1, 122.00	.635	
	Antenatal		0.20	1, 120.05	.841			-0.03	1, 111.26	.978	
	Sex (F > M)		-1.95	1, 131.00	.054	.023		-1.88	1, 122.00	.063	.023
	Socioeconomic Status		2.29	1, 117.69	.024	.046		2.63	1, 109.48	.010	.063
	Oromotor Sequences[d]		-7.18	4, 131.00	<.001	.389		-6.48	4, 122.00	<.001	.385
CELF-P2[b] Receptive Language Index	Cord BD[c, e]	160	1.54	1, 140.19	.127		148	0.90	1, 128.93	.372	
	Gestational Age		1.74	1, 129.29	.084	.019		1.85	1, 117.79	.067	.023
	Standardized BW		1.08	1, 150.97	.281			0.67	1, 138.96	.507	
	Antenatal		-0.10	1, 133.64	.920			-0.16	1, 123.57	.871	
	Sex (F > M)		-2.91	1, 153.00	.004	.042		-2.67	1, 141.00	.008	.037
	Socioeconomic Status		3.84	1, 124.70	<.001	.094		3.61	1, 113.25	<.001	.090

[a]Peabody Developmental Motor Scales – Second Edition (Folio & Fewell, 2000)

[b]Clinical Evaluation of Language Fundamentals – Preschool Second Edition (CELF-P2; Wiig et al., 2004)

[c] Arterial umbilical cord base deficit

[d] NEPSY Second Edition (NEPSY-2; Korkman, Kirk, & Kemp, 1997)

[e] One case was noted to be a multivariate outlier (determined with Mahalanobis Distance; critical value, $\chi 2 = 20.52$ for GMQ, FMQ, and RLI; critical value, $\chi 2 = 24.32$ for CLI and ELI) across all five measured outcomes in the total sample (observed values for GMQ, $\chi 2 = 25.13$; FMQ, $\chi 2 = 25.24$; CLI, $\chi 2 = 24.98$; ELI, $\chi 2 = 25.42$; RLI, $\chi 2 = 24.52$; all $p < .001$). Two cases were noted to be multivariate outliers (determined with Mahalanobis Distance; critical value, $\chi 2 = 20.52$ for GMQ, FMQ, and RLI; critical value, $\chi 2 = 24.32$ for CLI and ELI) across all five measured outcomes in the reduced sample (observed values for GMQ, $\chi 2 = 21.98$, $\chi 2 = 21.71$; FMQ, $\chi 2 = 21.97$, $\chi 2 = 22.20$; CLI, $\chi 2 = 24.75$, $\chi 2 = 25.14$; ELI, $\chi 2 = 25.24$, $\chi 2 = 24.97$; RLI, $\chi 2 = 22.07$, $\chi 2 = 21.73$; all $p < .001$). When the outlier was included in the total sample, the relationship between cord BD and between the GMQ, FMQ, and CLI remained nonsignificant, GMQ: ($t[153] = 1.41$, $p = .161$), FMQ: ($t[156] = 0.32$, $p = .753$), CLI: ($t[128] = 1.56$, $p = .122$). The relationship between cord BD and ELI and between cord BD and RLI trended towards significance, ELI: ($t[125] = 1.96$, $p = .052$), RLI: ($t[143] = 1.70$, $p = .098$). When the two outliers were included in the reduced sample, the relationship between cord BD and all five measured outcomes remained nonsignificant, GMQ: ($t[140] = 0.27$, $p = .789$), FMQ: ($t[142] = -0.35$, $p = .730$), CLI: ($t[116] = 0.75$, $p = .455$), ELI: ($t[116] = 0.63$, $p = .530$), RLI: ($t[130] = 1.14$, $p = .257$).

[f] Outcome data missing for indices in the total sample ($N = 173$) and non-neurological subsample ($N = 161$):

GMQ: 9 cases from the total sample (5.2%) and 8 cases from the non-neurological subsample (5.0%).

FMQ: 4 cases from the total sample (2.3%) and 4 cases from the non-neurological subsample (2.5%).

CLI: 11 cases from the total sample (6.4%) and 10 cases from the non-neurological subsample (6.2%). 26 cases (13.9%) had missing data from the Oromotor Sequences subtest in the total sample, and 22 cases (13.7%) in the non-neurological subsample.

ELI: 16 cases from the total sample (9.2%) and 15 cases from the non-neurological subsample (9.3%). 26 (13.9%) cases had missing data from the Oromotor Sequences subtest in the total sample, and 22 cases (13.7%) in the non-neurological subsample.

RLI: 12 cases from the total sample (6.9%) and 11 cases from the non-neurological subsample (6.8%).

Table 18b

Summary of linear mixed model re-analysis of the relationships between arterial umbilical cord base deficit and preschool language measures following removal of a single covariate

Language Index[a,b]	Source	Total Sample[e]				Non-Neurological Subsample[e]			
		N	*t*	*df*	*p*	*N*	*t*	*df*	*p*
Core Language	Cord BD[c, d]	161	1.26	1, 149.68	.208	150	1.23	1, 140.41	.219
Expressive Language	Cord BD[c, d]	156	1.62	1, 143.62	.108	146	1.30	1, 133.74	.197

Note. Re-analysis of language outcomes without the Oromotor Sequences score as a covariate.

[a] Clinical Evaluation of Language Fundamentals – Preschool Second Edition (CELF-P2; Wiig et al., 2004)

[b] All analyses included gestational age, standardized birthweight, total antenatal complications, sex, and socioeconomic status as covariates.

[c] Arterial umbilical cord base deficit

[d] One case was noted to be a multivariate outlier (determined with Mahalanobis Distance; critical value, $\chi 2 = 20.52$) across both measured outcomes in the total sample (observed values for CLI, $\chi 2 = 24.98$; ELI, $\chi 2 = 25.42$; both $p < .001$). Two cases were noted to be multivariate outliers across both measured outcomes in the reduced sample (observed value for CLI, $\chi 2 = 24.75$, $\chi 2 = 25.14$; ELI, $\chi 2 = 25.24$; both $p < .001$). When the outlier was included in the total sample, the relationship between cord pH and CLI remained nonsignificant ($t[149] = 1.57$, $p = .118$), and the relationship between cord pH and ELI reached significance ($t[143] = 2.01$, $p = .046$). When the outlier was included in the reduced sample, the relationships between cord pH and both measured outcomes remained nonsignificant, (CLI, $t[140] = 1.09$, $p = .276$; ELI, $t[133] = 1.28$, $p = .200$).

[e] Outcome data missing for subtests in the total sample ($N = 173$) and non-neurological subsample ($N = 161$):

CLI: 11 cases from the total sample (6.3%) and 10 cases from the non-neurological subsample (6.1%).

ELI: 16 cases from the total sample (9.1%) and 15 cases from the non-neurological subsample (9.2%).

Table 19a

Summary of linear mixed model analyses of the relationships between arterial umbilical cord pCO_2 and preschool motor and language measures

		Total Sample[f]					Non-Neurological Subsample[f]				
Index	Source	*N*	*t*	*df*	*p*	ΔR^2	*N*	*t*	*df*	*p*	ΔR^2
Motor											
PDMS-2[a] Gross Motor Quotient	Cord pCO_2[c, e]	165	-1.99	1, 158.00	.049	.043	153	-2.21	1, 146.00	.029	.022
	Gestational Age		1.61	1, 145.92	.109			0.85	1, 134.90	.396	
	Standardized BW		0.73	1, 158.00	.465			0.48	1, 146.00	.631	
	Antenatal		-0.14	1, 147.69	.890			0.83	1, 136.43	.407	
	Sex (F > M)		-0.68	1, 158.00	.499			-1.50	1, 146.00	.135	
	Socioeconomic Status		0.44	1, 143.71	.664			1.33	1, 133.44	.185	
PDMS-2[a] Fine Motor Quotient	Cord pCO_2[c, e]	170	-1.31	1, 163.00	.192		157	-1.45	1, 150.00	.148	
	Gestational Age		3.49	1, 147.50	<.001	.068		3.33	1, 134.69	.001	.066
	Standardized BW		1.11	1, 161.33	.268			0.68	1, 148.17	.495	
	Antenatal		0.57	1, 146.48	.569			0.37	1, 134.87	.711	
	Sex (F > M)		-4.58	1, 163.00	<.001	.115		-5.09	1, 150.00	<.001	.148
	Socioeconomic Status		3.12	1, 145.75	.002	.056		3.72	1, 133.82	<.001	.083
Language											
CELF-P2[b] Core Language Index	Cord pCO_2[c, e, f]	147	1.35	1, 136.00	.181		136	1.29	1, 126.00	.201	
	Gestational Age		0.20	1, 113.58	.839			-0.07	1, 102.35	.944	
	Standardized BW		1.29	1, 136.00	.200			0.77	1, 125.63	.443	
	Antenatal		0.21	1, 124.22	.838			0.03	1, 111.64	.978	
	Sex (F > M)		-2.04	1, 136.00	.043	.025		-2.01	1, 126.00	.046	.027
	Socioeconomic Status		2.65	1, 119.77	.009	.060		2.86	1, 108.89	.005	.074
	Oromotor Sequences[d]		-5.92	4, 136.00	<.001	.391		-5.36	4, 126.00	<.001	.400
CELF-P2[b] Expressive Language Index	Cord pCO_2[c, e, f]	142	0.26	1, 131.00	.793		131	0.03	1, 122.00	.978	
	Gestational Age		1.29	1, 113.32	.201			1.26	1, 104.93	.210	
	Standardized BW		1.00	1, 131.00	.321			0.51	1, 122.00	.610	
	Antenatal		0.16	1, 121.44	.870			-0.04	1, 111.75	.969	
	Sex (F > M)		-2.00	1, 131.00	.047	.023		-1.89	1, 122.00	.062	.023
	Socioeconomic Status		2.20	1, 119.63	.030	.042		2.63	1, 110.91	.010	.063
	Oromotor Sequences[d]		-7.19	4, 131.00	<.001	.448		-6.52	4, 122.00	<.001	.448
CELF-P2[b] Receptive Language Index	Cord pCO_2[c, e]	161	-0.93	1, 154.00	.353		149	-1.04	1, 142.00	.300	
	Gestational Age		1.40	1, 128.25	.165			1.63	1, 116.32	.106	
	Standardized BW		0.61	1, 153.72	.541			0.14	1, 141.37	.886	
	Antenatal		-0.62	1, 136.68	.539			-0.66	1, 125.88	.509	
	Sex (F > M)		-2.66	1, 153.14	.009	.032		-2.37	1, 141.42	.019	.025
	Socioeconomic Status		4.23	1, 126.38	<.001	.113		4.00	1, 114.91	<.001	.108

[a]Peabody Developmental Motor Scales – Second Edition (Folio & Fewell, 2000)

[b]Clinical Evaluation of Language Fundamentals – Preschool Second Edition (CELF-P2; Wiig et al., 2004)

[c] Arterial umbilical cord partial pressure of carbon dioxide

[d] NEPSY Second Edition (NEPSY-2; Korkman, Kirk, & Kemp, 1997)

[e] One case was noted to be a multivariate outlier (determined with Mahalanobis Distance; critical value, $\chi 2 = 20.52$ for GMQ, FMQ, and RLI; critical value, $\chi 2 = 24.32$ for CLI and ELI) across all five measured outcomes in the total sample (observed values for GMQ, $\chi 2 = 28.05$; FMQ, $\chi 2 = 28.99$; CLI, $\chi 2 = 29.72$; ELI, $\chi 2 = 30.06$; RLI, $\chi 2 = 28.76$; all $p < .001$). When the outlier was included in the total sample, the relationship between cord pCO_2 and GMQ remained significant ($t[159] = -2.79$, $p = .006$), and the relationship between cord pCO_2 and FMQ, CLI, ELI, and RLI remained nonsignificant, FMQ: ($t[164] = -1.60$, $p = .112$), CLI: ($t[137] = 0.60$, $p = .553$), ELI: ($t[132] = -0.57$, $p = .569$), RLI: ($t[155] = -1.11$, $p = .268$).

[f] Outcome data missing for indices in the total sample ($N = 175$) and non-neurological subsample ($N = 163$):

GMQ: 9 cases from the total sample (5.1%) and 8 cases from the non-neurological subsample (4.9%).

FMQ: 4 cases from the total sample (2.3%) and 4 cases from the non-neurological subsample (2.5%).

CLI: 11 cases from the total sample (6.3%) and 10 cases from the non-neurological subsample (6.1%). 26 cases (14.9%) had missing data from the Oromotor Sequences subtest in the total sample, and 24 cases (14.7%) in the non-neurological subsample.

ELI: 16 cases from the total sample (9.1%) and 15 cases from the non-neurological subsample (9.2%). 26 (14.9%) cases had missing data from the Oromotor Sequences subtest in the total sample, and 24 cases (14.7%) in the non-neurological subsample.

RLI: 13 cases from the total sample (7.4%) and 12 cases from the non-neurological subsample (7.4%).

Table 19b

Summary of linear mixed model analyses of the relationships between arterial umbilical cord pCO_2 and preschool gross motor subtest scores

		Total Sample[e]					Non-Neurological Subsample[e]				
Subtest[a, b]		*N*	*t*	*df*	*p*	ΔR^2	*N*	*t*	*df*	*p*	ΔR^2
Stationary	Cord pCO_2[c, d]	168	-0.25	161.00	.803		156	-0.86	149.00	.391	
Locomotion	Cord pCO_2[c, d]	167	-2.61	160.00	.010	.119	155	-2.94	148.00	.004	.128
Object Manipulation	Cord pCO_2[c, d]	165	-1.680	156.85	.095	.010	153	-1.32	146.00	.190	

[a]Peabody Developmental Motor Scales – Second Edition (Folio & Fewell, 2000)

[b]All analyses included gestational age, standardized birthweight, total antenatal complications, sex, and socioeconomic status as covariates.

[c] Arterial umbilical cord partial pressure of carbon dioxide

[d] One case was noted to be a multivariate outlier (determined with Mahalanobis Distance; critical value, $\chi2$= 20.52) across the three measured outcomes in the total sample (observed values for Stationary, $\chi2$= 28.54; Locomotion, $\chi2$= 28.39; Object Manipulation, $\chi2$= 28.04; all $p < .001$). When the outlier was included in the total sample, the relationship between cord pCO_2 and the Stationary score remained nonsignificant (t[162] = -1.08, p = .282). The relationship between cord pCO_2 and Locomotion score remained significant (t[161] = -3.19, p = .002), and the relationship between cord pCO_2 and Object Manipulation score reached statistical significance, (t[159] = -2.25, p = .026).

[e] Outcome data missing for subtests in the total sample (N = 175) and non-neurological subsample (N = 163):
Stationary: 6 cases from the total sample (3.4%) and 5 cases from the non-neurological subsample (3.1%).
Locomotion: 7 cases from the total sample (4.0%) and 6 cases from the non-neurological subsample (3.7%).
Object Manipulation: 9 cases from the total sample (5.1%) and 8 cases from the non-neurological subsample (4.9%).

Table 19c

Summary of linear mixed model re-analysis of the relationships between arterial umbilical cord pCO_2 and preschool language measures following removal of a single covariate

Language		Total Sample[e]				Non-Neurological Subsample[e]				
Index[a,b]	Source	*N*	*t*	*df*	*p*	*N*	*t*	*df*	*p*	ΔR^2
Core Language	Cord pCO_2 [c, d]	163	-0.19	1, 156.00	.853	152	-0.57	1, 145.00	.570	
Expressive Language	Cord pCO_2 [c, d]	158	-1.31	1, 151.00	.192	148	-1.79	1, 141.00	.076	.045

Note. Re-analysis of language outcomes without the Oromotor Sequences score as a covariate.

[a] Clinical Evaluation of Language Fundamentals – Preschool Second Edition (CELF-P2; Wiig et al., 2004)

[b] All analyses included gestational age, standardized birthweight, total antenatal complications, sex, and socioeconomic status as covariates.

[c] Arterial umbilical cord partial pressure of carbon dioxide

[d] One case was noted to be a multivariate outlier (determined with Mahalanobis Distance; critical value, $\chi2= 20.52$) across both measured outcomes in the total sample (observed values for CLI, $\chi2= 29.72$; ELI, $\chi2= 30.06$; all $p < .001$). When the outlier was included in the total sample, the relationship between cord pCO_2 and both measured outcomes remained nonsignificant, CLI: ($t[157] = -0.54$, $p = .592$), ELI: ($t[152] = -1.68$, $p = .096$)).

[e] Outcome data missing for subtests in the total sample ($N = 175$) and non-neurological subsample ($N = 163$):
CLI: 11 cases from the total sample (6.3%) and 10 cases from the non-neurological subsample (6.1%).
ELI: 16 cases from the total sample (9.1%) and 15 cases from the non-neurological subsample (9.2%).

Table 20

Summary of linear mixed model analyses of the relationships between initial neonatal pH and preschool motor and language measures

		Total Sample[f]					Non-Neurological Subsample[f]				
Index	Source	*N*	*t*	*df*	*p*	ΔR^2	*N*	*t*	*df*	*p*	ΔR^2
Motor											
PDMS-2[a] Gross Motor Quotient	Initial pH[c]	94	0.28	1, 87.00	.782		85	-0.03	1, 78.00	.973	
	Gestational Age		1.05	1, 77.39	.298			0.05	1, 67.39	.957	
	Standardized BW		1.39	1, 87.00	.168			1.25	1, 78.00	.214	
	Antenatal		-1.28	1, 83.03	.204			0.09	1, 70.62	.926	
	Sex (F > M)		-0.43	1, 57.56	.668			-1.42	1, 61.31	.161	
	Socioeconomic Status		-0.49	1, 74.65	.624			0.49	1, 63.71	.628	
PDMS-2[a] Fine Motor Quotient	Initial pH[c]	96	-0.03	1, 89.00	.977		86	-0.70	1, 79.00	.489	
	Gestational Age		1.15	1, 89.00	.252			0.61	1, 79.00	.545	
	Standardized BW		1.04	1, 89.00	.303			0.82	1, 79.00	.417	
	Antenatal		-0.59	1, 89.00	.560			-0.26	1, 79.00	.798	
	Sex (F > M)		-3.90	1, 89.00	<.001	.137		-4.78	1, 79.00	<.001	.210
	Socioeconomic Status		2.83	1, 89.00	.006	.078		3.23	1, 79.00	.002	.108
Language											
CELF-P2[b] Core Language Index	Initial pH[c, e]	81	-0.45	1, 70.00	.651		74	-0.44	1, 63.00	.661	
	Gestational Age		0.23	1, 52.68	.817			0.43	1, 47.67	.672	
	Standardized BW		0.20	1, 70.00	.840			0.14	1, 63.00	.889	
	Antenatal		-1.16	1, 46.48	.252			-0.91	1, 45.43	.368	
	Sex (F > M)		-0.27	1, 70.00	.787			-0.27	1, 63.00	.789	
	Socioeconomic Status		2.87	1, 46.25	.006	.132		2.71	1, 43.74	.010	.134
	Oromotor Sequences[d]		-5.31	4, 59.82	<.001	.346		-4.37	4, 56.93	<.001	.321
CELF-P2[b] Expressive Language Index	Initial pH[c, e]	79	-0.21	1, 68.00	.834		72	-0.38	1, 61.00	.708	
	Gestational Age		0.79	1, 55.58	.435			1.07	1, 51.67	.289	
	Standardized BW		-0.46	1, 68.00	.649			-0.62	1, 61.00	.536	
	Antenatal		-1.41	1, 51.61	.166			-1.24	1, 52.03	.220	
	Sex (F > M)		-0.97	1, 68.00	.336			-0.88	1, 59.54	.380	
	Socioeconomic Status		2.24	1, 50.58	.030	.087		2.39	1, 48.77	.021	.107
	Oromotor Sequences[d]		-5.65	4, 62.59	<.001	.384		-4.64	4, 60.68	<.001	.368
CELF-P2[b] Receptive Language Index	Initial pH[c]	91	-0.10	1, 84.00	.921		83	-0.23	1, 76.00	.822	
	Gestational Age		0.55	1, 70.83	.586			1.17	1, 61.76	.246	
	Standardized BW		0.16	1, 84.00	.875			-0.16	1, 76.00	.876	
	Antenatal		-1.27	1, 66.51	.209			-1.49	1, 59.67	.141	
	Sex (F > M)		-2.15	1, 77.96	.035	.064		-1.89	1, 68.51	.063	.055
	Socioeconomic Status		3.41	1, 65.47	.001	.134		3.36	1, 56.65	.001	.146

[a]Peabody Developmental Motor Scales – Second Edition (Folio & Fewell, 2000)

[b]Clinical Evaluation of Language Fundamentals – Preschool Second Edition (CELF-P2; Wiig et al., 2004)

[c] Neonatal arterial or capillary blood pH obtained within the first three hours of life

[d] NEPSY Second Edition (NEPSY-2; Korkman, Kirk, & Kemp, 1997)

[e] When Oromotor Sequences score was not included as a covariate in analyses with CLI or ELI as the outcome variable,

the relationships between initial pH and CLI and ELI remained nonsignificant in the total (CLI: t[84] = -0.32, p = .753, ELI: t[81] = 0.001, p = .999) and reduced sample (CLI: t[76] = -0.31, p = .760, ELI: t[76] = 0.17, p = .865).

[f] Outcome data missing for subtest in the total sample (N = 98) and non-neurological subsample (N = 88):

GMQ: 4 cases from the total sample (4.1%) and 3 cases from the non-neurological subsample (3.4%).

FMQ: 2 cases from the total sample (2.0%) and 2 cases from the non-neurological subsample (2.3%).

CLI: 7 cases from the total sample (7.1%) and 5 cases from the non-neurological subsample (5.7%). 16 cases (16.3%) had missing data from the Oromotor Sequences subtest in the total sample, and 13 cases (14.8%) in the non-neurological subsample.

ELI: 10 cases from the total sample (10.2%) and 8 cases from the non-neurological subsample (9.1%). 16 (16.3%) cases had missing data from the Oromotor Sequences subtest in the total sample, and 13 cases (14.8%) in the non-neurological subsample.

RLI: 7 cases from the total sample (7.1%) and 5 cases from the non-neurological subsample (5.7%).

Table 21a

Summary of linear mixed model analyses of the relationships between initial neonatal base deficit and preschool motor and language measures

			Total Sample[g]					Non-Neurological Subsample[g]			
Index	Source	*N*	*t*	*df*	*p*	ΔR^2	*N*	*t*	*df*	*p*	ΔR^2
Motor											
PDMS-2[a] Gross Motor Quotient	Initial BD[c, e]	93	2.23	1, 82.92	.028	.011	84	1.33	1, 77.00	.188	
	Gestational Age		0.43	1, 77.53	.671			-0.15	1, 65.26	.880	
	Standardized BW		1.11	1, 86.00	.271			0.98	1, 77.00	.330	
	Antenatal		-1.36	1, 84.04	.177			-.001	1, 69.16	.999	
	Sex (F > M)		-0.10	1, 51.64	.925			-1.23	1, 58.66	.224	
	Socioeconomic Status		-0.65	1, 73.35	.517			0.30	1, 62.51	.763	
PDMS-2[a] Fine Motor Quotient	Initial BD[c, e]	95	0.27	1, 88.00	.791		85	-0.11	1, 78.00	.912	
	Gestational Age		1.09	1, 88.00	.280			0.71	1, 78.00	.482	
	Standardized BW		0.96	1, 88.00	.342			0.77	1, 78.00	.445	
	Antenatal		-0.53	1, 88.00	.595			-0.22	1, 78.00	.827	
	Sex (F > M)		-3.98	1, 88.00	<.001	.142		-4.74	1, 78.00	<.001	.209
	Socioeconomic Status		2.79	1, 88.00	.007	.077		3.13	1, 78.00	.002	.104
Language											
CELF-P2[b] Core Language Index	Initial BD[c, e, f]	80	-0.76	1, 69.00	.450		73	-0.71	1, 62.00	.481	
	Gestational Age		0.34	1, 44.09	.738			0.49	1, 40.18	.627	
	Standardized BW		0.28	1, 69.00	.784			0.23	1, 62.00	.817	
	Antenatal		-1.22	1, 43.14	.229			-0.92	1, 43.48	.363	
	Sex (F > M)		-0.18	1, 69.00	.856			-0.19	1, 62.00	.847	
	Socioeconomic Status		2.84	1, 43.45	.007	.134		2.67	1, 41.66	.011	.137
	Oromotor Sequences[d]		-5.32	4, 58.98	<.001	.350		-4.39	4, 59.31	<.001	.326
CELF-P2[b] Expressive Language Index	Initial BD[c, e, f]	78	-0.52	1, 68.00	.608		71	-0.47	1, 61.00	.640	
	Gestational Age		0.89	1, 49.26	.377			1.18	1, 44.89	.245	
	Standardized BW		-0.42	1, 68.00	.673			-0.56	1, 61.00	.576	
	Antenatal		-1.43	1, 49.53	.158			-1.26	1, 49.50	.215	
	Sex (F > M)		-0.99	1, 68.00	.328			-0.87	1, 61.00	.388	
	Socioeconomic Status		2.32	1, 49.13	.025	.095		2.44	1, 47.12	.019	.116
	Oromotor Sequences[d]		-5.70	4, 62.60	<.001	.390		-4.69	4, 61.00	<.001	.374
CELF-P2[b] Receptive Language Index	Initial BD[c, e]	90	-1.53	1, 83.00	.131		82	-1.47	1, 75.00	.146	
	Gestational Age		0.91	1, 70.41	.369			1.42	1, 61.93	.162	
	Standardized BW		0.29	1, 83.00	.774			0.001	1, 75.00	.999	
	Antenatal		-1.25	1, 68.80	.217			-1.36	1, 61.87	.180	
	Sex (F > M)		-2.32	1, 79.41	.023	.063		-2.08	1, 70.71	.042	.054
	Socioeconomic Status		3.50	1, 67.27	<.001	.139		3.55	1, 59.27	<.001	.155

[a]Peabody Developmental Motor Scales – Second Edition (Folio & Fewell, 2000)

[b]Clinical Evaluation of Language Fundamentals – Preschool Second Edition (CELF-P2; Wiig et al., 2004)

[c] Neonatal arterial or capillary blood base deficit obtained within the first three hours of life

[d] NEPSY Second Edition (NEPSY-2; Korkman, Kirk, & Kemp, 1997)

[e] One case was noted to be a multivariate outlier (determined with Mahalanobis Distance; critical value, $\chi 2 = 20.52$ for GMQ, FMQ, and RLI; critical value, $\chi 2 = 24.32$ for CLI and ELI) across all five measured outcomes in the total sample (observed values for GMQ, $\chi 2 = 23.73$; FMQ, $\chi 2 = 23.55$; CLI, $\chi 2 = 24.54$; ELI, $\chi 2 = 24.89$; RLI, $\chi 2 = 22.94$; all $p < .001$) and in the reduced sample (observed values for GMQ, $\chi 2 = 24.17$; FMQ, $\chi 2 = 24.55$; CLI, $\chi 2 = 24.99$; ELI, $\chi 2 = 25.48$; RLI, $\chi 2 = 24.22$; all $p < .001$). When the outlier was included in the total sample, the relationship between initial BD and FMQ, CLI, ELI, and RLI remained nonsignificant, (FMQ: ($t[89] = -0.03$, $p = .977$), CLI: ($t[70] = -0.51$, $p = .612$), ELI: ($t[68] = -0.52$, $p = .608$), RLI: ($t[84] = -1.28$, $p = .205$)). The relationship between initial BD and GMQ trended towards significance, ($t[87] = 1.67$, $p = .098$). When the outlier was included in the reduced sample, the relationship between initial BD and all five measured outcomes remained nonsignificant, GMQ: ($t[78] = 0.74$, $p = .464$), FMQ: ($t[79] = -0.42$, $p = .674$), CLI: ($t[63] = -0.47$, $p = .644$), ELI: ($t[61] = -0.47$, $p = .640$), RLI: ($t[76] = -1.30$, $p = .197$).

[f] When Oromotor Sequences score was not included as a covariate in analyses with CLI or ELI as the outcome variable, the relationships between initial BD and CLI and ELI remained nonsignificant in the total (CLI: $t[83] = -0.55$, $p = .582$, ELI: $t[81] = -0.10$, $p = .921$) and reduced sample (CLI: $t[75] = -0.30$, $p = .768$, ELI: $t[73] = 0.07$, $p = .947$).

[g] Outcome data missing for subtest in the total sample ($N = 98$) and non-neurological subsample ($N = 88$):

GMQ: 4 cases from the total sample (4.1%) and 3 cases from the non-neurological subsample (3.4%).

FMQ: 2 cases from the total sample (2.0%) and 2 cases from the non-neurological subsample (2.3%).

CLI: 7 cases from the total sample (7.1%) and 5 cases from the non-neurological subsample (5.7%). 16 cases (16.3%) had missing data from the Oromotor Sequences subtest in the total sample, and 13 cases (14.8%) in the non-neurological subsample.

ELI: 10 cases from the total sample (10.2%) and 8 cases from the non-neurological subsample (9.1%). 16 (16.3%) cases had missing data from the Oromotor Sequences subtest in the total sample, and 13 cases (14.8%) in the non-neurological subsample.

RLI: 7 cases from the total sample (7.1%) and 5 cases from the non-neurological subsample (5.7%).

Table 21b

Summary of linear mixed model analyses of the relationships between initial neonatal base deficit and preschool gross motor subtest scores

		Total Sample[e]					Non-Neurological Subsample[e]				
Subtest[a, b]	Source	*N*	*t*	*df*	*p*	ΔR^2	*N*	*t*	*df*	*p*	ΔR^2
Stationary	Initial BD[c, d]	94	2.00	1, 87.00	.049	.032	85	1.68	1, 78.00	.097	.028
Locomotion	Initial BD[c, d]	93	0.74	1, 77.46	.460		84	0.08	1, 75.03	.938	
Object Manipulation	Initial BD[c, d]	93	1.59	1, 86.00	.116		84	0.64	1, 75.72	.523	

[a]Peabody Developmental Motor Scales – Second Edition (Folio & Fewell, 2000)

[b]All analyses included gestational age, standardized birthweight, total antenatal complications, sex, and socioeconomic status as covariates.

[c] Neonatal arterial or capillary blood base deficit obtained within the first three hours of life.

[d] One case was noted to be a multivariate outlier (determined with Mahalanobis Distance; critical value, $\chi2$= 20.52) across the three measured outcomes in the total sample (observed values for Stationary, $\chi2$= 23.97; Locomotion, $\chi2$= 23.73; Object Manipulation, $\chi2$= 23.73; all $p < .001$) and in the reduced sample (observed values for Stationary, $\chi2$= 24.38; Locomotion, $\chi2$= 24.17; Object Manipulation, $\chi2$= 24.17; all $p < .001$). When the outlier was included in the total sample, the relationships between initial BD and Locomotion ($t[87] = 0.40$, $p = .690$) and Object Manipulation ($t[87] = 1.08$, $p = .281$) scores remained nonsignificant. The relationship between initial BD and Stationary scores was no longer significant ($t[88] = 1.61$, $p = .112$). When the outlier was included in the reduced sample, the relationship between initial BD and all three measured outcomes remained nonsignificant (Stationary: ($t[79] = 1.32$, $p = .190$), Locomotion: ($t[78] = -0.28$, $p = .783$), Object Manipulation: ($t[75] = 0.07$, $p = .946$)).

[e] Outcome data missing for subtests in the total sample ($N = 98$) and non-neurological subsample ($N = 88$):
Stationary: 3 cases from the total sample (3.1%) and 2 cases from the non-neurological subsample (2.3%).
Locomotion: 4 cases from the total sample (4.1%) and 3 cases from the non-neurological subsample (3.4%).
Object Manipulation: 4 cases from the total sample (4.1%) and 3 cases from the non-neurological subsample (3.4%).

Table 22

Summary of linear mixed model analyses of the relationships between initial neonatal pCO_2 and preschool motor and language measures

			Total Sample[f]					Non-Neurological Subsample[f]			
Index	Source	*N*	*t*	*df*	*p*	ΔR^2	*N*	*t*	*df*	*p*	ΔR^2
Motor											
PDMS-2[a] Gross Motor Quotient	Initial pCO_2[c]	94	0.62	1, 83.80	.436		85	0.87	1, 77.00	.354	
	Gestational Age		1.05	1, 78.63	.299			-0.07	1, 69.21	.941	
	Standardized BW		1.39	1, 86.00	.169			1.23	1, 77.00	.224	
	Antenatal		-1.22	1, 82.66	.228			0.13	1, 69.80	.895	
	Sex (F > M)		2.68	1, 86.00	.009	.003		3.27	1, 77.00	.002	.027
	Socioeconomic Status		-0.13	1, 74.24	.896			0.90	1, 62.77	.373	
	Sex*Initial pCO_2		-2.79	1, 86.00	.006	.086		-3.56	1, 77.00	<.001	.143
PDMS-2[a] Fine Motor Quotient	Initial pCO_2[c]	96	-0.10	1, 89.00	.923		86	0.98	1, 78.00	.324	
	Gestational Age		1.15	1, 89.00	.252			0.46	1, 78.00	.648	
	Standardized BW		1.04	1, 89.00	.303			0.78	1, 78.00	.439	
	Antenatal		-0.59	1, 89.00	.558			-0.34	1, 78.00	.737	
	Sex (F > M)		-3.84	1, 89.00	<.001	.133		1.24	1, 78.00	.217	
	Socioeconomic Status		2.83	1, 89.00	.006	.078		3.34	1, 78.00	.001	.115
	Sex*Initial pCO_2		-	-	-			-2.11	1, 78.00	.038	.049
Language											
CELF-P2[b] Core Language Index	Initial pCO_2[c, e]	81	0.38	1, 70.00	.706		74	0.42	1, 63.00	.678	
	Gestational Age		0.18	1, 55.51	.860			0.38	1, 48.71	.707	
	Standardized BW		0.21	1, 70.00	.832			0.15	1, 63.00	.882	
	Antenatal		-1.17	1, 46.36	.247			-0.92	1, 45.99	.365	
	Sex (F > M)		-0.25	1, 67.51	.807			-0.24	1, 58.71	.809	
	Socioeconomic Status		2.81	1, 45.41	.007	.133		2.65	1, 42.22	.011	.137
	Oromotor Sequences[d]		-5.30	4, 57.65	<.001	.344		-4.36	4, 55.19	<.001	.319
CELF-P2[b] Expressive Language Index	Initial pCO_2[c, e]	79	-0.09	1, 68.00	.931		72	0.20	1, 61.00	.842	
	Gestational Age		0.82	1, 56.19	.413			1.08	1, 51.57	.287	
	Standardized BW		-0.42	1, 68.00	.677			-0.61	1, 61.00	.546	
	Antenatal		-1.44	1, 49.12	.157			-1.26	1, 51.77	.215	
	Sex (F > M)		-0.91	1, 64.38	.365			-0.86	1, 55.44	.396	
	Socioeconomic Status		2.25	1, 48.34	.029	.090		2.36	1, 47.37	.022	.106
	Oromotor Sequences[d]		-5.64	4, 59.50	<.001	.385		-4.62	4, 58.91	<.001	.367
CELF-P2[b] Receptive Language Index	Initial pCO_2[c]	91	-0.66	1, 84.00	.514		83	-0.48	1, 76.00	.634	
	Gestational Age		0.66	1, 72.47	.511			1.23	1, 62.48	.224	
	Standardized BW		0.15	1, 84.00	.882			-0.16	1, 76.00	.876	
	Antenatal		-1.29	1, 67.41	.201			-1.50	1, 60.53	.139	
	Sex (F > M)		-2.01	1, 70.77	.049	.057		-1.79	1, 62.38	.078	.050
	Socioeconomic Status		3.44	1, 64.85	.001	.133		3.36	1, 55.73	.001	.141

[a]Peabody Developmental Motor Scales – Second Edition (Folio & Fewell, 2000)
[b]Clinical Evaluation of Language Fundamentals – Preschool Second Edition (CELF-P2; Wiig et al., 2004)
[c] Infant arterial or capillary blood partial pressure of carbon dioxide obtained within the first three hours of life
[d] NEPSY Second Edition (NEPSY-2; Korkman, Kirk, & Kemp, 1997)
[e] When Oromotor Sequences score was not included as a covariate in analyses with CLI or ELI as the outcome variable, the relationships between initial pCO_2 and CLI and ELI remained nonsignificant in the total (CLI: $t[84] = 0.10$, $p = .919$, ELI: $t[81] = -0.16$, $p = .872$) and reduced sample (CLI: $t[76] = 0.71$, $p = .865$, ELI: $t[73] = 0.10$, $p = .925$).
[f] Outcome data missing for subtest in the total sample ($N = 98$) and non-neurological subsample ($N = 88$):

GMQ: 4 cases from the total sample (4.1%) and 3 cases from the non-neurological subsample (3.4%).

FMQ: 2 cases from the total sample (2.0%) and 2 cases from the non-neurological subsample (2.3%).

CLI: 7 cases from the total sample (7.1%) and 5 cases from the non-neurological subsample (5.7%). 16 cases (16.3%) had missing data from the Oromotor Sequences subtest in the total sample, and 13 cases (14.8%) in the non-neurological subsample.

ELI: 10 cases from the total sample (10.2%) and 8 cases from the non-neurological subsample (9.1%). 16 (16.3%) cases had missing data from the Oromotor Sequences subtest in the total sample, and 13 cases (14.8%) in the non-neurological subsample.

RLI: 7 cases from the total sample (7.1%) and 5 cases from the non-neurological subsample (5.7%).

Table 23

Summary of linear mixed model analyses of the relationships between initial neonatal pO_2 and preschool motor and language measures

			Total Sample[g]					Non-Neurological Subsample[g]			
Index	Source	*N*	*t*	*df*	*p*	ΔR^2	*N*	*t*	*df*	*p*	ΔR^2
Motor											
PDMS-2[a] Gross Motor Quotient	Initial pO_2[c, e]	92	0.24	1, 85.00	.811		83	0.03	1, 76.00	.979	
	Gestational Age		1.15	1, 76.40	.254			0.19	1, 66.34	.852	
	Standardized BW		1.47	1, 85.00	.147			1.29	1, 76.00	.201	
	Antenatal		-1.25	1, 85.00	.215			0.09	1, 74.13	.930	
	Sex (F > M)		-0.58	1, 54.12	.562			-1.51	1, 58.01	.137	
	Socioeconomic Status		-0.31	1, 74.14	.756			0.58	1, 62.82	.564	
PDMS-2[a] Fine Motor Quotient	Initial pO_2[c, e]	92	-1.08	1, 87.00	.283		84	-1.22	1, 77.00	.228	
	Gestational Age		0.98	1, 87.00	.328			0.47	1, 77.00	.639	
	Standardized BW		1.00	1, 87.00	.320			0.82	1, 77.00	.417	
	Antenatal		-0.46	1, 87.00	.648			-0.06	1, 77.00	.951	
	Sex (F > M)		-3.88	1, 87.00	<.001	.138		-4.56	1, 77.00	<.001	.198
	Socioeconomic Status		2.42	1, 87.00	.017	.060		2.61	1, 77.00	.011	.075
Language											
CELF-P2[b] Core Language Index	Initial pO_2[c, e, f]	78	-1.33	1, 68.00	.188		71	-1.46	1, 61.00	.149	
	Gestational Age		0.04	1, 48.32	.968			0.24	1, 42.06	.809	
	Standardized BW		0.30	1, 68.00	.765			0.57	1, 61.00	.573	
	Antenatal		-0.91	1, 44.24	.366			-0.29	1, 43.29	.775	
	Sex (F > M)		0.07	1, 68.00	.941			0.33	1, 61.00	.743	
	Socioeconomic Status		1.85	1, 45.43	.071	.061		1.36	1, 42.70	.180	
	Oromotor Sequences[d]		-4.90	4, 60.03	<.001	.362		-4.13	4, 55.60	<.001	.357
CELF-P2[b] Expressive Language Index	Initial pO_2[c, e, f]	76	-0.06	1, 66.00	.952		69	-0.15	1, 59.00	.883	
	Gestational Age		0.67	1, 50.33	.509			0.97	1, 44.10	.337	
	Standardized BW		-0.23	1, 66.00	.822			-0.15	1, 59.00	.882	
	Antenatal		-1.01	1, 50.54	.320			-0.64	1, 52.09	.525	
	Sex (F > M)		-0.69	1, 65.27	.491			-0.43	1, 58.09	.667	
	Socioeconomic Status		1.65	1, 50.85	.105			1.58	1, 48.89	.121	
	Oromotor Sequences[d]		-5.15	4, 61.31	<.001	.363		-4.34	4, 57.56	<.001	.359
CELF-P2[b] Receptive Language Index	Initial pO_2[c, e]	89	-1.43	1, 82.00	.157		81	-1.25	1, 72.22	.215	
	Gestational Age		0.18	1, 72.95	.859			0.76	1, 58.23	.450	
	Standardized BW		0.10	1, 82.00	.919			-0.15	1, 74.00	.885	
	Antenatal		-0.69	1, 74.31	.493			-0.83	1, 63.62	.407	
	Sex (F > M)		-1.94	1, 78.85	.055	.051		-1.57	1, 63.67	.121	
	Socioeconomic Status		2.72	1, 69.00	.008	.092		2.59	1, 53.62	.012	.095

[a]Peabody Developmental Motor Scales – Second Edition (Folio & Fewell, 2000)

[b]Clinical Evaluation of Language Fundamentals – Preschool Second Edition (CELF-P2; Wiig et al., 2004)

[c] Infant arterial or adjusted capillary blood partial pressure of oxygen obtained within the first three hours of life;

capillary values adjusted using Brodkorb et al. (2022) conversion formula.

[d] NEPSY Second Edition (NEPSY-2; Korkman, Kirk, & Kemp, 1997)

[e] Two cases were noted to be multivariate outliers (determined with Mahalanobis Distance; critical value, $\chi2= 20.52$) when GMQ, FMQ, and RLI were outcome variables in the total (observed values for GMQ, $\chi2= 32.56$, $\chi2= 55.66$; FMQ, $\chi2= 33.43$, $\chi2= 56.41$; RLI, $\chi2= 32.19$, $\chi2= 53.60$; all $p < .001$) and reduced (observed values for GMQ, $\chi2= 30.69$, $\chi2= 50.46$; FMQ, $\chi2= 31.17$, $\chi2= 51.01$; RLI, $\chi2= 30.11$, $\chi2= 49.30$; all $p < .001$) sample. Three cases were noted to be multivariate outliers (determined with Mahalanobis Distance; critical value, $\chi2= 24.32$) when CLI and ELI were outcome variables in the total (observed values for CLI, $\chi2= 57.32$, $\chi2= 48.95$, $\chi2= 26.81$; ELI, $\chi2= 56.27$, $\chi2= 47.74$, $\chi2= 26.16$; all $p < .001$) and reduced (observed values for CLI, $\chi2= 53.21$, $\chi2= 44.85$, $\chi2= 26.84$; ELI, $\chi2= 51.97$, $\chi2= 43.63$, $\chi2= 26.25$; all $p < .001$) sample. When the outliers were included in the total sample, the relationship between initial pO_2 and GMQ, FMQ, and ELI remained nonsignificant, (GMQ: (t[55] = 1.03, p = .307), FMQ: (t[89] = -0.25, p = .806), ELI: (t[68] = -1.42, p = .161). The relationships between initial pO_2 CLI and RLI reached statistical significance in the total sample (CLI: (t[70] = -2.64, p = .010, RLI: (t[84] = -2.30, p = .024)). When the outliers were included in the reduced sample, the relationship between initial pO_2 and GMQ, FMQ, and ELI remained nonsignificant as well, (GMQ: (t[62] = 0.86, p = .391), FMQ: (t[79] = -0.36, p = .717), ELI: (t[61] = -1.25, p = .217). The relationship between initial pO_2 and CLI was also significant in the reduced sample (t[63] = -2.63, p = .011), and the relationship between initial pO_2 and RLI trended in the similar observed direction, (t[73] = -1.98, p = .052).

[f] When Oromotor Sequences score was not included as a covariate in analyses with CLI or ELI as the outcome variable, the relationships between initial pO_2 and CLI and ELI remained nonsignificant in the total (CLI: t[82] = -0.86, p = .393, ELI: t[79] = -0.10, p = .921) and reduced sample (CLI: t[74] = -0.77, p = .444, ELI: t[71] = 0.08, p = .933).

[g] Outcome data missing for subtest in the total sample (N = 98) and non-neurological subsample (N = 88):

GMQ: 4 cases from the total sample (4.1%) and 3 cases from the non-neurological subsample (3.4%).

FMQ: 2 cases from the total sample (2.0%) and 2 cases from the non-neurological subsample (2.3%).

CLI: 7 cases from the total sample (7.1%) and 5 cases from the non-neurological subsample (5.7%). 16 cases (16.3%) had missing data from the Oromotor Sequences subtest in the total sample, and 13 cases (14.8%) in the non-neurological subsample.

ELI: 10 cases from the total sample (10.2%) and 8 cases from the non-neurological subsample (9.1%). 16 (16.3%) cases had missing data from the Oromotor Sequences subtest in the total sample, and 13 cases (14.8%) in the non-neurological subsample.

RLI: 7 cases from the total sample (7.1%) and 5 cases from the non-neurological subsample (5.7%).

Table 24

Summary of linear mixed model analyses of the relationships between lowest pH value obtained in the first week of life (3 completed hours of life through 7 completed days of life) and preschool motor and language measures

			Total Sample[f]					Non-Neurological Subsample[f]			
Index	Source	*N*	*t*	*df*	*p*	ΔR^2	*N*	*t*	*df*	*p*	ΔR^2
Motor											
PDMS-2[a] Gross Motor Quotient	Lowest pH[c]	111	0.34	1, 73.89	.732		101	-0.66	1, 72.85	.511	
	Gestational Age		1.14	1, 104.00	.257			0.52	1, 93.11	.607	
	Standardized BW		2.45	1, 104.00	.016	.047		2.35	1, 94.00	.021	.049
	Antenatal		-0.80	1, 103.69	.429			0.30	1, 89.75	.764	
	Sex (F > M)		-0.59	1, 87.40	.560			-1.67	1, 84.39	.099	.037
	Socioeconomic Status		-0.64	1, 94.13	.527			0.21	1, 81.68	.837	
PDMS-2[a] Fine Motor Quotient	Lowest pH[c]	114	-0.37	1, 107.00	.714		103	-0.97	1, 96.00	.335	
	Gestational Age		1.85	1, 107.00	.068	.029		1.79	1, 96.00	.077	.030
	Standardized BW		1.87	1, 107.00	.065	.030		1.55	1, 96.00	.125	
	Antenatal		-0.50	1, 107.00	.620			-0.44	1, 96.00	.660	
	Sex (F > M)		-3.38	1, 107.00	.001	.091		-4.33	1, 96.00	<.001	.154
	Socioeconomic Status		2.16	1, 107.00	.033	.039		2.78	1, 96.00	.007	.070
Language											
CELF-P2[b] Core Language Index	Lowest pH[c, e]	95	0.79	1, 84.00	.433		87	0.32	1, 76.00	.752	
	Gestational Age		0.34	1, 77.49	.734			0.80	1, 69.30	.429	
	Standardized BW		0.52	1, 84.00	.602			0.36	1, 76.00	.718	
	Antenatal		-0.58	1, 66.70	.567			-0.51	1, 61.84	.610	
	Sex (F > M)		-0.63	1, 84.00	.528			-0.77	1, 76.00	.444	
	Socioeconomic Status		2.13	1, 65.42	.037	.051		2.18	1, 58.18	.034	.060
	Oromotor Sequences[d]		-5.13	1, 78.08	<.001	.255		-4.24	1, 70.49	<.001	.247
CELF-P2[b] Expressive Language Index	Lowest pH[c, e]	93	0.83	1, 82.00	.409		85	0.15	1, 74.00	.883	
	Gestational Age		0.38	1, 79.66	.705			1.01	1, 72.21	.318	
	Standardized BW		0.03	1, 82.00	.976			-0.32	1, 74.00	.749	
	Antenatal		-1.29	1, 72.15	.202			-1.32	1, 67.86	.192	
	Sex (F > M)		-1.54	1, 82.00	.126			-1.63	1, 74.00	.108	
	Socioeconomic Status		2.26	1, 71.03	.027	.060		2.58	1, 64.53	.012	.083
	Oromotor Sequences[d]		-6.10	1, 81.29	<.001	.347		-5.11	1, 74.00	<.001	.348
CELF-P2[b] Receptive Language Index	Lowest pH[c]	108	0.45	1, 92.32	.656		99	0.44	1, 80.60	.660	
	Gestational Age		0.19	1, 99.87	.852			0.76	1, 89.34	.449	
	Standardized BW		0.88	1, 101.00	.379			0.53	1, 92.00	.595	
	Antenatal		-1.36	1, 94.38	.178			-1.60	1, 85.14	.113	
	Sex (F > M)		-1.97	1, 99.21	.051	.040		-1.73	1, 87.38	.087	.032
	Socioeconomic Status		2.96	1, 89.33	.004	.086		2.95	1, 79.25	.004	.093

[a]Peabody Developmental Motor Scales – Second Edition (Folio & Fewell, 2000)

[b]Clinical Evaluation of Language Fundamentals – Preschool Second Edition (CELF-P2; Wiig et al., 2004)

[c] Lowest infant arterial or capillary blood pH obtained within the first seven days of life
[d] NEPSY Second Edition (NEPSY-2; Korkman, Kirk, & Kemp, 1997)
[e] When Oromotor Sequences score was not included as a covariate in analyses with CLI or ELI as the outcome variable, the relationships between lowest pH and CLI and ELI remained nonsignificant in the total (CLI: $t[101] = -0.18$, $p = .856$, ELI: $t[78] = -0.71$, $p = .483$) and reduced sample (CLI: $t[92] = -0.35$, $p = .729$, ELI: $t[69] = -0.92$, $p = .360$).
[f] Outcome data missing for subtest in the total sample ($N = 116$) and non-neurological subsample ($N = 105$):

GMQ: 5 cases from the total sample (4.3%) and 4 cases from the non-neurological subsample (3.8%).

FMQ: 2 cases from the total sample (1.7%) and 2 cases from the non-neurological subsample (1.9%).

CLI: 8 cases from the total sample (6.9%) and 6 cases from the non-neurological subsample (5.7%). 20 cases (17.2%) had missing data from the Oromotor Sequences subtest in the total sample, and 17 cases (16.2%) in the non-neurological subsample.

ELI: 11 cases from the total sample (9.5%) and 9 cases from the non-neurological subsample (8.6%). 20 (17.2%) cases had missing data from the Oromotor Sequences subtest in the total sample, and 17 cases (16.2%) in the non-neurological subsample.

RLI: 8 cases from the total sample (6.9%) and 6 cases from the non-neurological subsample (5.7%).

Table 25a

Summary of linear mixed model analyses of the relationships between lowest base deficit value obtained in the first week of life (3 completed hours of life through 7 completed days of life) and preschool motor and language measures

		Total Sample[g]					Non-Neurological Subsample[g]				
Index	Source	*N*	*t*	*df*	*p*	ΔR^2	*N*	*t*	*df*	*p*	ΔR^2
Motor											
PDMS-2[a] Gross Motor Quotient	Lowest BD[c, e]	110	-0.71	1, 71.37	.483		100	-1.33	1, 71.45	.189	
	Gestational Age		1.50	1, 103.00	.136			1.00	1, 93.00	.320	
	Standardized BW		2.56	1, 103.00	.012	.053		2.34	1, 93.00	.022	.051
	Antenatal		-0.79	1, 103.00	.433			0.33	1, 90.39	.739	
	Sex (F > M)		-0.48	1, 85.94	.630			-1.55	1, 83.66	.126	
	Socioeconomic Status		-0.76	1, 92.89	.447			0.23	1, 81.59	.821	
PDMS-2[a] Fine Motor Quotient	Lowest BD[c, e]	113	-0.97	1, 106.00	.332		102	-1.46	1, 95.00	.148	
	Gestational Age		1.99	1, 106.00	.049	.034		2.05	1, 95.00	.043	.040
	Standardized BW		1.89	1, 106.00	.061	.031		1.52	1, 95.00	.132	
	Antenatal		-0.58	1, 106.00	.562			-0.49	1, 95.00	.629	
	Sex (F > M)		-3.23	1, 106.00	.002	.084		-4.15	1, 95.00	<.001	.144
	Socioeconomic Status		2.06	1, 106.00	.041	.037		2.76	1, 95.00	.007	.070
Language											
CELF-P2[b] Core Language Index	Lowest BD[c, f]	95	1.04	1, 84.00	.303		87	0.46	1, 76.00	.646	
	Gestational Age		0.05	1, 84.00	.962			0.58	1, 76.00	.562	
	Standardized BW		0.55	1, 84.00	.582			0.36	1, 76.00	.719	
	Antenatal		-0.49	1, 70.82	.625			-0.48	1, 65.06	.636	
	Sex (F > M)		-0.73	1, 84.00	.468			-0.82	1, 76.00	.413	
	Socioeconomic Status		2.10	1, 68.08	.039	.043		2.17	1, 60.25	.034	.023
	Oromotor Sequences[d]		-5.16	1, 80.78	<.001	.256		-4.25	1, 73.74	<.001	.239
CELF-P2[b] Expressive Language Index	Lowest BD[c, f]	93	0.29	1, 82.00	.771		85	-0.63	1, 74.00	.531	
	Gestational Age		0.47	1, 82.00	.640			1.26	1, 74.00	.213	
	Standardized BW		0.13	1, 82.00	.898			-0.28	1, 74.00	.781	
	Antenatal		-1.22	1, 75.24	.226			-1.34	1, 71.25	.185	
	Sex (F > M)		-1.63	1, 82.00	.108			-1.63	1, 74.00	.107	
	Socioeconomic Status		2.25	1, 72.24	.027	.059		2.61	1, 66.17	.011	.057
	Oromotor Sequences[d]		-5.99	1, 82.00	<.001	.323		-5.01	1, 74.00	<.001	.299
CELF-P2[b] Receptive Language Index	Lowest BD[c, e]	107	1.84	1, 79.66	.069	.006	98	1.59	1, 68.60	.116	
	Gestational Age		-0.90	1, 100.00	.371			-0.21	1, 91.00	.834	
	Standardized BW		0.62	1, 100.00	.535			0.32	1, 91.00	.749	
	Antenatal		-1.75	1, 96.48	.083	.033		-1.98	1, 87.38	.051	.044
	Sex (F > M)		-1.84	1, 91.89	.069	.030		-1.57	1, 80.53	.120	
	Socioeconomic Status		2.55	1, 88.57	.013	.068		2.47	1, 79.42	.016	.070

[a]Peabody Developmental Motor Scales – Second Edition (Folio & Fewell, 2000)

[b]Clinical Evaluation of Language Fundamentals – Preschool Second Edition (CELF-P2; Wiig et al., 2004)

[c] Lowest infant arterial or capillary blood base deficit obtained within the first seven days of life

[d] NEPSY Second Edition (NEPSY-2; Korkman, Kirk, & Kemp, 1997)

[e] One case was noted to be a multivariate outlier (determined with Mahalanobis Distance; critical value, $\chi 2 = 20.52$) when GMQ, FMQ, and RLI were outcome variables in the total (observed values for GMQ, $\chi 2 = 21.37$; FMQ, $\chi 2 = 21.16$; RLI, $\chi 2 = 21.14$; all $p < .001$) and reduced (observed values for GMQ, $\chi 2 = 21.95$; FMQ, $\chi 2 = 21.45$; RLI, $\chi 2 = 21.54$; all $p < .001$) sample. When the outlier was included in the total sample, the relationships between lowest BD and GMQ and FMQ remained nonsignificant (GMQ: ($t[80] = -0.90$, $p = .372$), FMQ: ($t[107] = -1.22$, $p = .226$), and the relationship between lowest BD and RLI was no longer significant, ($t[90] = 1.04$, $p = .302$). When the outlier was included in the reduced sample, the relationships between lowest BD and all three measured outcomes remained nonsignificant (GMQ: ($t[81] = -1.36$, $p = .179$), FMQ: ($t[96] = -1.60$, $p = .113$), RLI: ($t[80] = 0.75$, $p = .454$).

[f] When Oromotor Sequences score was not included as a covariate in analyses with CLI or ELI as the outcome variable, the relationships between lowest BD and CLI and ELI remained nonsignificant in the total (CLI: $t[100] = 1.02$, $p = .312$, ELI: $t[75] = 0.16$, $p = .874$) and reduced sample (CLI: $t[91] = 0.64$, $p = .522$, ELI: $t[67] = -0.38$, $p = .704$).

[g] Outcome data missing for subtest in the total sample ($N = 116$) and non-neurological subsample ($N = 105$):

GMQ: 5 cases from the total sample (4.3%) and 4 cases from the non-neurological subsample (3.8%).

FMQ: 2 cases from the total sample (1.7%) and 2 cases from the non-neurological subsample (1.9%).

CLI: 8 cases from the total sample (6.9%) and 6 cases from the non-neurological subsample (5.7%). 20 cases (17.2%) had missing data from the Oromotor Sequences subtest in the total sample, and 17 cases (16.2%) in the non-neurological subsample.

ELI: 11 cases from the total sample (9.5%) and 9 cases from the non-neurological subsample (8.6%). 20 (17.2%) cases had missing data from the Oromotor Sequences subtest in the total sample, and 17 cases (16.2%) in the non-neurological subsample.

RLI: 8 cases from the total sample (6.9%) and 6 cases from the non-neurological subsample (5.7%).

Table 25b

Summary of linear mixed model analyses of the relationships between lowest base deficit value obtained in the first week of life (3 completed hours of life through 7 completed days of life) and preschool receptive language subtest scores

		Total Sample[e]					Non-Neurological Subsample[e]			
Subtest[a, b]	Source	*N*	*t*	*df*	*p*	ΔR^2	*N*	*t*	*df*	*p*
Sentence Structure	Lowest BD[c, d]	109	1.19	1, 102.00	.237		100	1.30	1, 93.00	.198
Concepts & Following Directions	Lowest BD[c, d]	107	2.04	1, 67.87	.045	.010	98	1.67	1, 58.22	.100
Basic Concepts	Lowest BD[c]	109	1.93	1, 51.55	.059	.012	100	1.63	1, 45.94	.111

[a]Clinical Evaluation of Language Fundamentals – Preschool Second Edition (CELF-P2; Wiig et al., 2004)

[b]All analyses included gestational age, standardized birthweight, total antenatal complications, sex, and socioeconomic status as covariates.

[c] Lowest infant arterial or capillary blood base deficit obtained within the first seven days of life

[d] One case was noted to be a multivariate outlier (determined with Mahalanobis Distance; critical value, $\chi2= 20.52$) for all three measured outcomes in the total (observed values for Sentence Structure, $\chi2= 21.44$; CFD, $\chi2= 21.14$; Basic Concepts, $\chi2= 21.44$; all $p < .001$) and reduced (observed values for Sentence Structure, $\chi2= 21.84$; CFD, $\chi2= 21.54$; Basic Concepts, $\chi2= 21.84$; all $p < .001$) sample. When the outlier was included, the relationship between lowest BD and Sentence Structure score remained nonsignificant in the total sample ($t[103] = 0.78$, $p = .438$), and the relationships between lowest BD and CFD and Basic Concepts scores were no longer significant in the total sample (CFD: ($t[78] = 1.32$, $p = .190$), Basic Concepts: ($t[60] = 1.27$, $p = .211$). When the outlier was included in the reduced sample, the relationships between lowest BD and all three measured outcomes remained nonsignificant (Sentence Structure: ($t[94] = 0.83$, $p = .409$), CFD: ($t[69] = 0.96$, $p = .342$), Basic Concepts: ($t[55] = 0.91$, $p = .365$).

[e] Outcome data missing for subtests in the total sample ($N = 116$) and non-neurological subsample ($N = 105$):

Sentence Structure: 6 cases from the total sample (5.2%) and 4 cases from the non-neurological subsample (3.8%).

Concepts & Following Directions: 8 cases from the total sample (6.9%) and 6 cases from the non-neurological subsample (5.7%).

Basic Concepts: 6 cases from the total sample (5.2%) and 4 cases from the non-neurological subsample (3.8%).

Table 26

Summary of linear mixed model analyses of the relationships between highest pCO_2 value obtained in the first week of life (3 completed hours of life through 7 completed days of life) and preschool motor and language measures

		Total Sample[f]					Non-Neurological Subsample[f]				
Index	Source	*N*	*t*	*df*	*p*	ΔR^2	*N*	*t*	*df*	*p*	ΔR^2
Motor											
PDMS-2[a] Gross Motor Quotient	Highest pCO_2[c]	111	-0.72	1, 47.14	.473		101	0.22	1, 47.75	.824	
	Gestational Age		1.24	1, 100.75	.218			0.32	1, 87.93	.754	
	Standardized BW		2.40	1, 104.00	.018	.045		2.29	1, 94.00	.024	.047
	Antenatal		-0.84	1, 103.65	.402			0.27	1, 89.79	.792	
	Sex (F > M)		-0.50	1, 85.70	.616			-1.62	1, 83.37	.108	
	Socioeconomic Status		-0.62	1, 94.47	.539			0.20	1, 81.78	.841	
PDMS-2[a] Fine Motor Quotient	Highest pCO_2[c]	113	0.04	1, 106.00	.970		102	0.49	1, 95.00	.626	
	Gestational Age		1.98	1, 106.00	.051	.033		1.71	1, 95.00	.090	.028
	Standardized BW		1.91	1, 106.00	.059	.031		1.56	1, 95.00	.121	
	Antenatal		-0.56	1, 106.00	.576			-0.49	1, 95.00	.624	
	Sex (F > M)		-3.44	1, 106.00	<.001	.095		-4.33	1, 95.00	<.001	.155
	Socioeconomic Status		2.00	1, 106.00	.049	.034		2.57	1, 95.00	.012	.061
Language											
CELF-P2[b] Core Language Index	Highest pCO_2[c, e]	95	-0.6	1, 80.29	.550		87	-0.28	1, 66.26	.780	
	Gestational Age		0.60	1, 72.63	.553			0.92	1, 62.97	.360	
	Standardized BW		0.58	1, 84.00	.566			0.38	1, 76.00	.704	
	Antenatal		-0.60	1, 63.43	.552			-0.53	1, 58.51	.600	
	Sex (F > M)		-0.59	1, 84.00	.556			-0.75	1, 76.00	.456	
	Socioeconomic Status		2.14	1, 62.65	.037	.052		2.20	1, 54.73	.032	.062
	Oromotor Sequences[d]		-5.10	1, 75.13	<.001	.262		-4.24	1, 67.21	<.001	.257
CELF-P2[b] Expressive Language Index	Highest pCO_2[c, e]	93	-1.05	1, 80.78	.298		85	-0.61	1, 66.57	.541	
	Gestational Age		0.61	1, 76.10	.547			1.08	1, 67.40	.282	
	Standardized BW		0.04	1, 82.00	.970			-0.32	1, 74.00	.750	
	Antenatal		-1.36	1, 69.26	.177			-1.38	1, 64.36	.174	
	Sex (F > M)		-1.41	1, 82.00	.161			-1.50	1, 74.00	.137	
	Socioeconomic Status		2.27	1, 68.96	.026	.058		2.59	1, 61.15	.012	.082
	Oromotor Sequences[d]		-6.16	1, 79.37	<.001	.360		-5.20	1, 71.68	<.001	.364
CELF-P2[b] Receptive Language Index	Highest pCO_2[c]	107	-0.48	1, 63.89	.633		98	-0.65	1, 55.20	.519	
	Gestational Age		0.29	1, 95.05	.770			0.89	1, 84.01	.374	
	Standardized BW		0.88	1, 100.00	.382			0.53	1, 91.00	.598	
	Antenatal		-1.36	1, 92.96	.176			-1.64	1, 83.73	.104	
	Sex (F > M)		-1.90	1, 97.93	.061	.037		-1.64	1, 86.85	.104	
	Socioeconomic Status		2.92	1, 88.20	.004	.084		2.90	1, 77.88	.005	.090

[a]Peabody Developmental Motor Scales – Second Edition (Folio & Fewell, 2000)

[b]Clinical Evaluation of Language Fundamentals – Preschool Second Edition (CELF-P2; Wiig et al., 2004)

[c] Highest infant arterial or capillary blood partial pressure of carbon dioxide obtained within the first seven days of life.

[d] NEPSY Second Edition (NEPSY-2; Korkman, Kirk, & Kemp, 1997)

[e] When Oromotor Sequences score was not included as a covariate in analyses with CLI or ELI as the outcome variable, the relationships between highest pCO_2 and CLI and ELI remained nonsignificant in the total (CLI: $t[75] = -0.54$, $p = .593$, ELI: $t[42] = 0.73$, $p = .469$) and reduced sample (CLI: $t[67] = -0.49$, $p = .629$, ELI: $t[39] = 0.69$, $p = .497$).

[f] Outcome data missing for subtest in the total sample ($N = 115$) and non-neurological subsample ($N = 104$):

GMQ: 4 cases from the total sample (3.5%) and 3 cases from the non-neurological subsample (2.9%).

FMQ: 2 cases from the total sample (1.7%) and 2 cases from the non-neurological subsample (1.9%).

CLI: 8 cases from the total sample (7.0%) and 6 cases from the non-neurological subsample (5.8%). 19 cases (16.5%) had missing data from the Oromotor Sequences subtest in the total sample, and 16 cases (15.4%) in the non-neurological subsample.

ELI: 11 cases from the total sample (9.6%) and 9 cases from the non-neurological subsample (8.7%). 19 (16.5%) cases had missing data from the Oromotor Sequences subtest in the total sample, and 16 cases (15.4%) in the non-neurological subsample.

RLI: 8 cases from the total sample (7.0%) and 6 cases from the non-neurological subsample (5.8%).

Table 27a

Summary of linear mixed model analyses of the relationships between lowest pO_2 value obtained in the first week of life (3 completed hours of life through 7 completed days of life) and preschool motor and language measures

			Total Sample[g]					Non-Neurological Subsample[g]			
Index	Source	*N*	*t*	*df*	*p*	ΔR^2	*N*	*t*	*df*	*p*	ΔR^2
Motor											
PDMS-2[a] Gross Motor Quotient	Lowest pO_2[c, e]	110	0.39	1, 92.35	.700		100	-0.62	1, 90.06	.537	
	Gestational Age		1.61	1, 101.62	.111			0.86	1, 90.35	.393	
	Standardized BW		2.63	1, 103.00	.010	.057		2.52	1, 93.00	.013	.055
	Antenatal		-0.27	1, 101.44	.787			1.05	1, 88.41	.296	
	Sex (F > M)		-0.30	1, 91.27	.767			-1.48	1, 90.88	.141	
	Socioeconomic Status		-0.34	1, 92.62	.735			0.68	1, 82.09	.499	
PDMS-2[a] Fine Motor Quotient	Lowest pO_2[c, e]	113	-0.53	1, 106.00	.601		102	-1.06	1, 95.00	.292	
	Gestational Age		2.41	1, 106.00	.018	.049		2.28	1, 95.00	.025	.049
	Standardized BW		2.00	1, 106.00	.049	.034		1.57	1, 95.00	.120	
	Antenatal		0.05	1, 106.00	.962			0.18	1, 95.00	.855	
	Sex (F > M)		-3.24	1, 106.00	.002	.085		-4.28	1, 95.00	<.001	.152
	Socioeconomic Status		2.56	1, 106.00	.012	.055		3.32	1, 95.00	.001	.097
Language											
CELF-P2[b] Core Language Index	Lowest pO_2[c, f]	95	-0.35	1, 84.00	.727		87	-0.77	1, 76.00	.447	
	Gestational Age		0.72	1, 77.12	.471			1.07	1, 69.23	.289	
	Standardized BW		0.67	1, 84.00	.503			0.39	1, 76.00	.698	
	Antenatal		-0.48	1, 69.67	.636			-0.41	1, 65.88	.685	
	Sex (F > M)		-0.72	1, 84.00	.473			-0.88	1, 76.00	.384	
	Socioeconomic Status		2.12	1, 67.71	.038	.043		2.26	1, 63.03	.027	.023
	Oromotor Sequences[d]		-5.00	1, 78.13	<.001	.256		-4.20	1, 71.86	<.001	.239
CELF-P2[b] Expressive Language Index	Lowest pO_2[c, f]	93	0.03	1, 82.00	.976		85	-0.76	1, 74.00	.451	
	Gestational Age		0.65	1, 78.79	.515			1.20	1, 71.08	.234	
	Standardized BW		0.15	82.00	.879			-0.30	1, 74.00	.767	
	Antenatal		-1.23	1, 73.56	.222			-1.24	1, 70.02	.220	
	Sex (F > M)		-1.61	1, 82.00	.111			-1.69	1, 74.00	.095	.026
	Socioeconomic Status		2.24	1, 71.39	.028	.059		2.62	1, 66.62	.011	.057
	Oromotor Sequences[d]		-5.98	1, 80.43	<.001	.323		-5.08	1, 74.00	<.001	.299
CELF-P2[b] Receptive Language Index	Lowest pO_2[c, e]	107	-0.52	1, 100.93	.605		98	-0.78	1, 90.82	.438	
	Gestational Age		0.57	1, 98.01	.573			1.2	1, 88.87	.232	
	Standardized BW		1.05	1, 101.00	.296			0.69	1, 92.00	.494	
	Antenatal		-1.26	1, 93.64	.212			-1.47	1, 85.32	.145	
	Sex (F > M)		-2.06	1, 101.00	.042	.043		-1.88	1, 91.34	.064	.039
	Socioeconomic Status		2.94	1, 89.20	.004	.085		3	1, 80.66	.004	.095

[a]Peabody Developmental Motor Scales – Second Edition (Folio & Fewell, 2000)

[b]Clinical Evaluation of Language Fundamentals – Preschool Second Edition (CELF-P2; Wiig et al., 2004)

[c] Lowest infant arterial or adjusted capillary blood partial pressure of oxygen obtained within the first seven days of life; capillary values adjusted used Brodkorb et al. (2022) conversion formula.
[d] NEPSY Second Edition (NEPSY-2; Korkman, Kirk, & Kemp, 1997)
[e] One case was noted to be a multivariate outlier (determined with Mahalanobis Distance; critical value, $\chi 2 = 20.52$) when GMQ, FMQ, and RLI were outcome variables in the total (observed values for GMQ, $\chi 2 = 22.55$; FMQ, $\chi 2 = 21.43$; RLI, $\chi 2 = 21.19$; all $p < .001$) and reduced (observed values for GMQ, $\chi 2 = 21685$; FMQ, $\chi 2 = 20.66$; RLI, $\chi 2 = 20.56$; all $p < .001$) sample. When the outlier was included in the total sample, the relationship between lowest pO_2 and all three measured outcomes remained nonsignificant (GMQ: ($t[92] = -0.36$, $p = .721$), FMQ: ($t[107] = -1.29$, $p = .200$), RLI: ($t[100] = -0.52$, $p = .605$). When the outlier was included in the reduced sample, the relationship between lowest pO_2 and GMQ and RLI remained nonsignificant (GMQ: ($t[90] = -1.42$, $p = .158$), RLI: ($t[90] = 0.-0.78$, $p = .438$). The relationship between lowest pO_2 and FMQ approached statistical significance ($t[96] = -1.87$, $p = .064$).
[f] When Oromotor Sequences score was not included as a covariate in analyses with CLI or ELI as the outcome variable, the relationships between lowest pO_2 and CLI and ELI remained nonsignificant in the total (CLI: $t[101] = -1.33$, $p = .185$, ELI: $t[83] = -1.47$, $p = .145$) sample, but trended towards significance in the reduced sample (CLI: $t[92] = -1.73$, $p = .088$, ELI: $t[75] = -1.98$, $p = .052$).
[g] Outcome data missing for subtest in the total sample ($N = 116$) and non-neurological subsample ($N = 105$):

GMQ: 5 cases from the total sample (4.3%) and 4 cases from the non-neurological subsample (3.8%).

FMQ: 2 cases from the total sample (1.7%) and 2 cases from the non-neurological subsample (1.9%).

CLI: 8 cases from the total sample (6.9%) and 6 cases from the non-neurological subsample (5.7%). 20 cases (17.2%) had missing data from the Oromotor Sequences subtest in the total sample, and 17 cases (16.2%) in the non-neurological subsample.

ELI: 11 cases from the total sample (9.5%) and 9 cases from the non-neurological subsample (8.6%). 20 (17.2%) cases had missing data from the Oromotor Sequences subtest in the total sample, and 17 cases (16.2%) in the non-neurological subsample.

RLI: 8 cases from the total sample (6.9%) and 6 cases from the non-neurological subsample (5.7%).

Table 27b

Summary of linear mixed model re-analysis of the relationships between lowest pO_2 value obtained in the first week of life (3 completed hours of life through 7 completed days of life) and preschool language measures following removal of a single covariate

Language		Total Sample[d]				Non-Neurological Subsample[d]				
Index[a,b]	Source	*N*	*t*	*df*	*p*	*N*	*t*	*df*	*p*	ΔR^2
Core Language	Lowest pO_2 [c]	108	-1.33	1, 101.00	.185	99	-1.73	1, 92.00	.088	.024
Expressive Language	Lowest pO_2 [c]	105	-1.47	1, 18300	.145	96	-1.98	1, 75.00	.052	.025

Note. Re-analysis of language outcomes without the Oromotor Sequences score as a covariate.

[a] Clinical Evaluation of Language Fundamentals – Preschool Second Edition (CELF-P2; Wiig et al., 2004)

[b] All analyses included gestational age, standardized birthweight, total antenatal complications, sex, and socioeconomic status as covariates.

[c] Lowest infant arterial or adjusted capillary blood partial pressure of oxygen obtained within the first seven days of life; capillary values adjusted used Brodkorb et al. (2022) conversion formula.

[d] Outcome data missing for subtests in the total sample ($N = 116$) and non-neurological subsample ($N = 105$):
CLI: 8 cases from the total sample (6.9%) and 6 cases from the non-neurological subsample (5.7%).
ELI: 11 cases from the total sample (9.5%) and 9 cases from the non-neurological subsample (8.6%).

APPENDIX B

Figure 1
Flow diagram of recruitment process

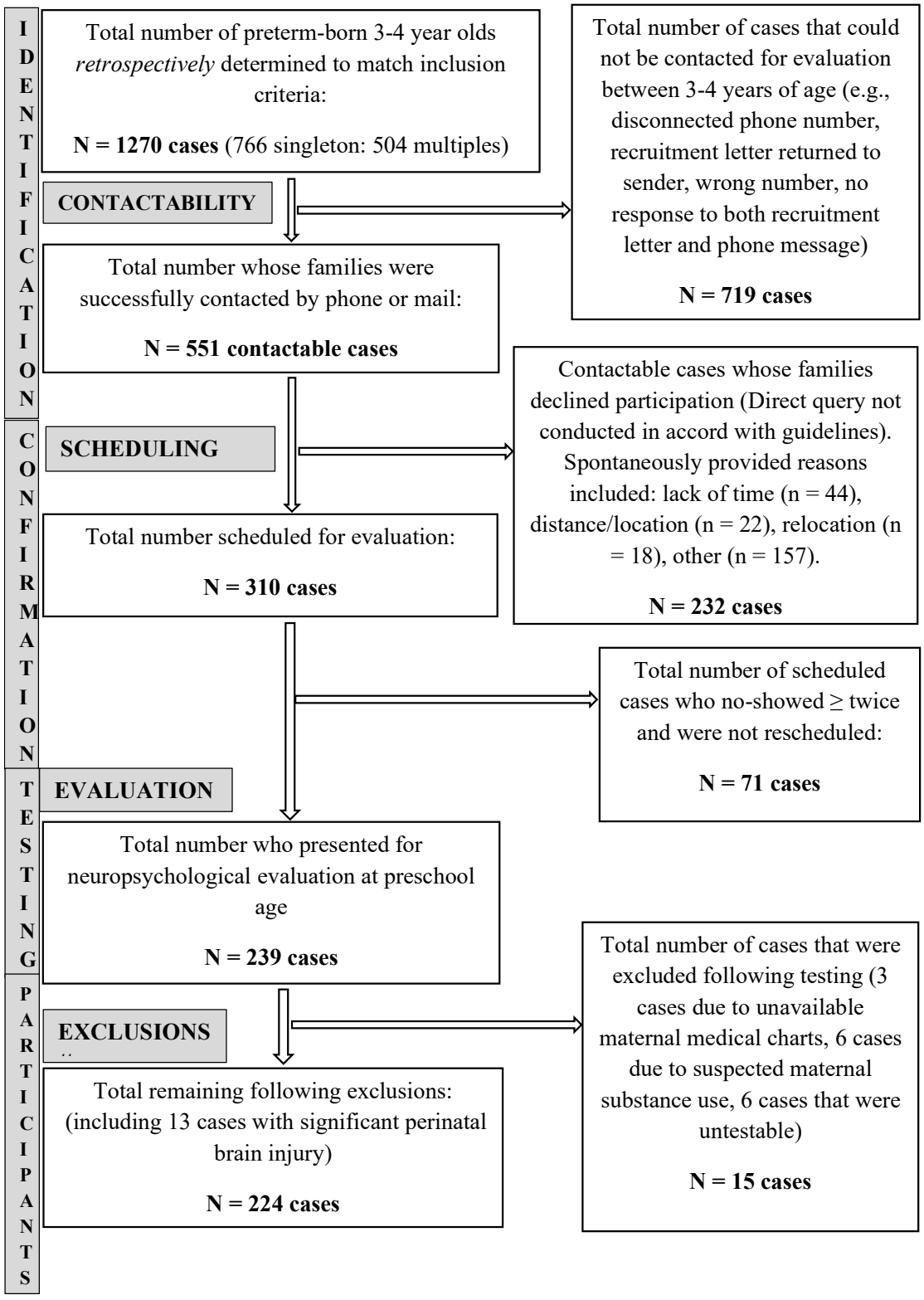
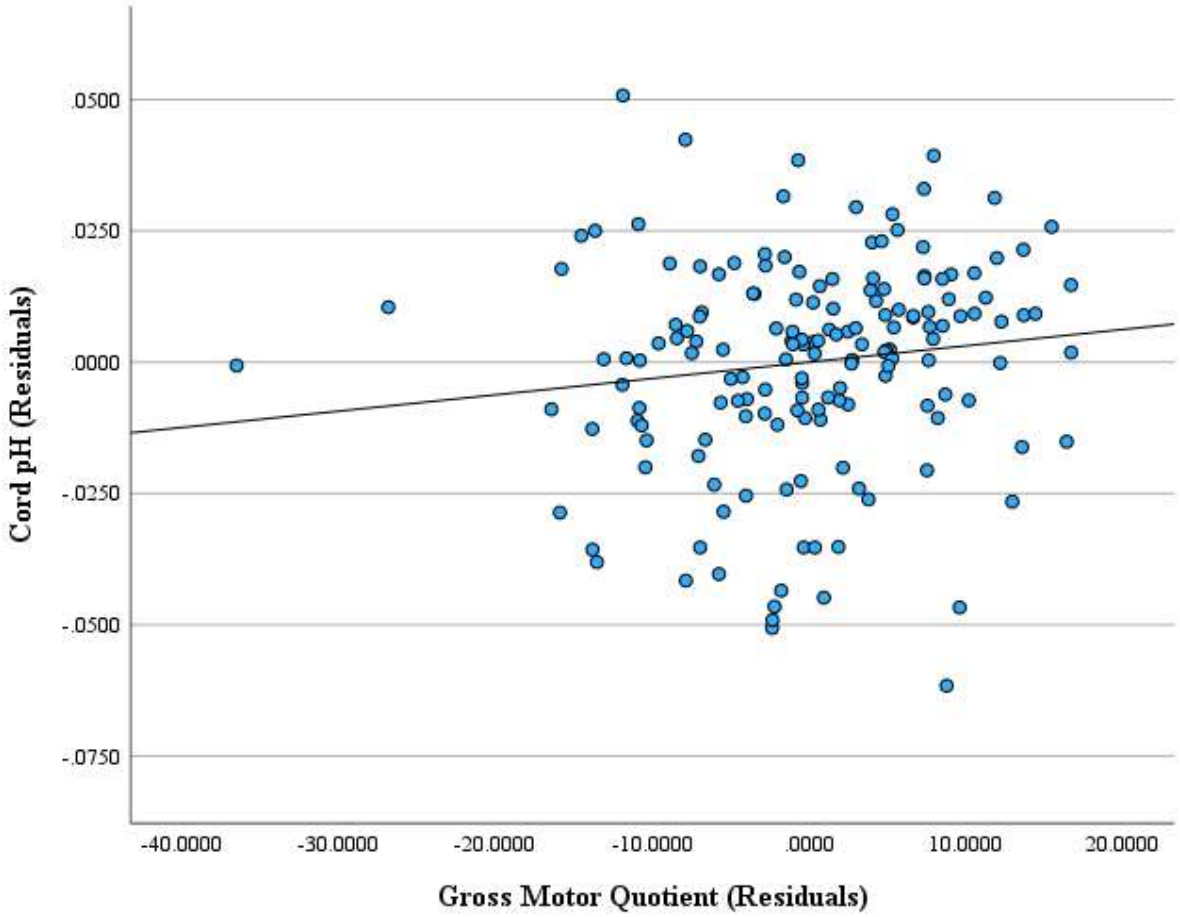
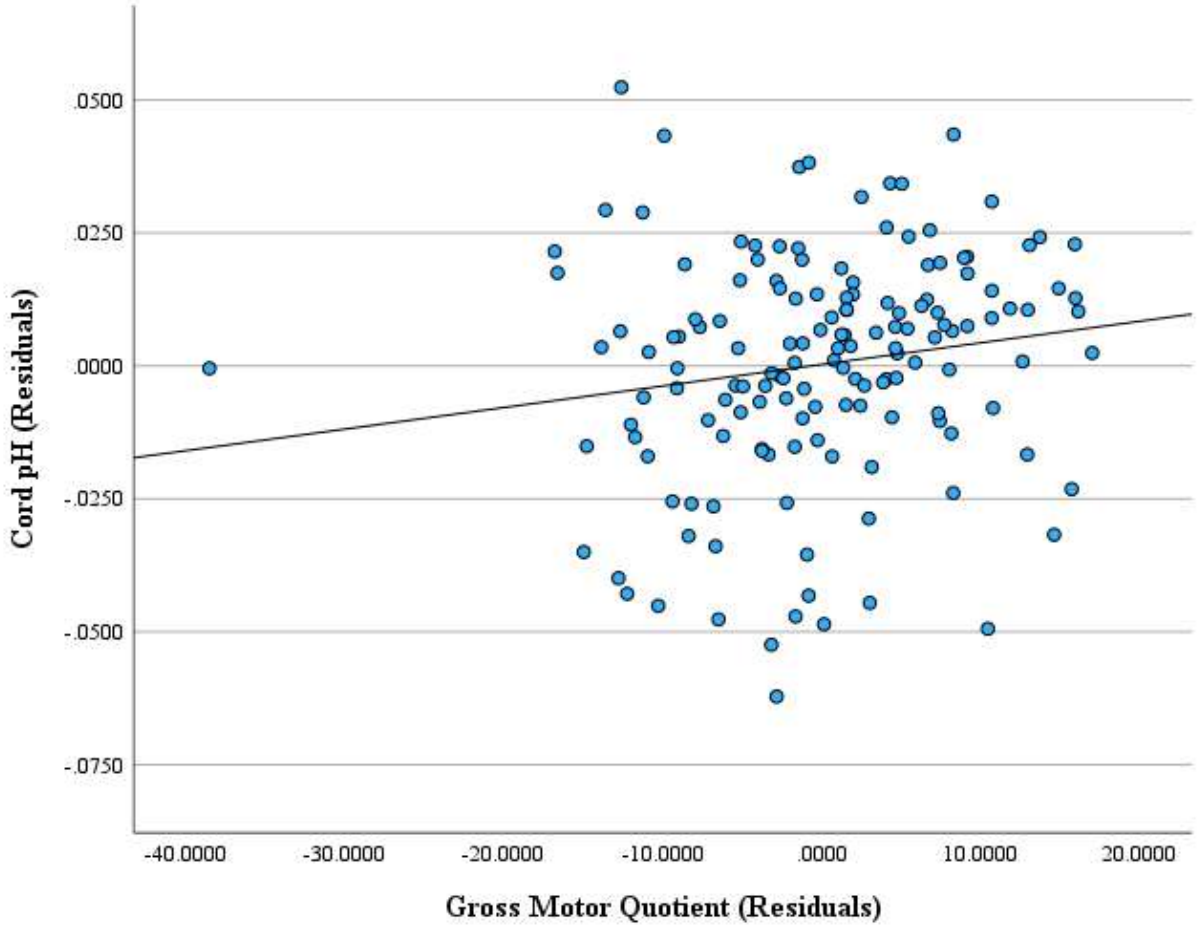


Figure 2
Umbilical cord pH values regressed on GMQ, adjusted for covariates, in the total sample



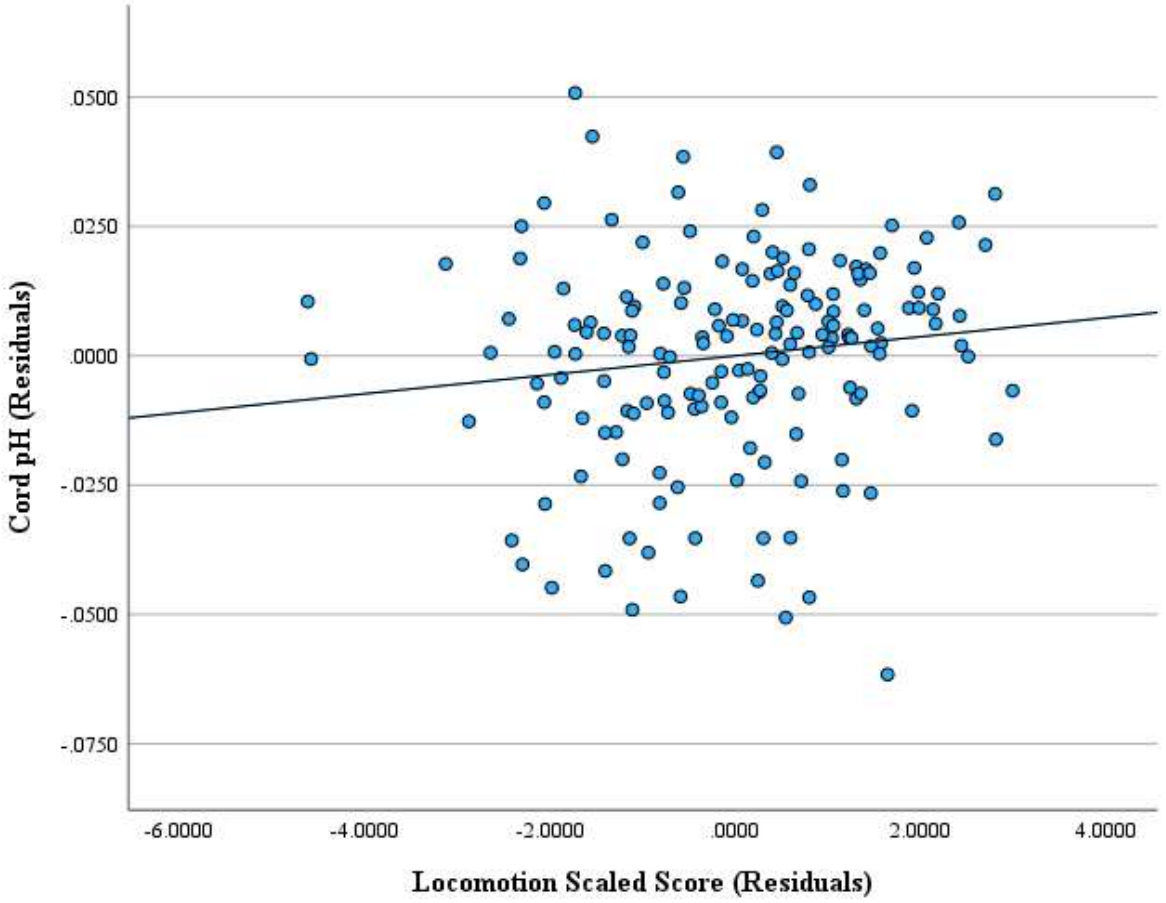
Note: Adjusted for sociodemographic (socioeconomic status, sex) and perinatal (gestational age, standardized birthweight, antenatal complications) variables with multiple status (i.e., family membership) treated as random factor.

Figure 3
Umbilical cord pH values regressed on GMQ, adjusted for covariates, in the reduced sample



Note: Adjusted for sociodemographic (socioeconomic status, sex) and perinatal (gestational age, standardized birthweight, antenatal complications) variables with multiple status (i.e., family membership) treated as random factor.

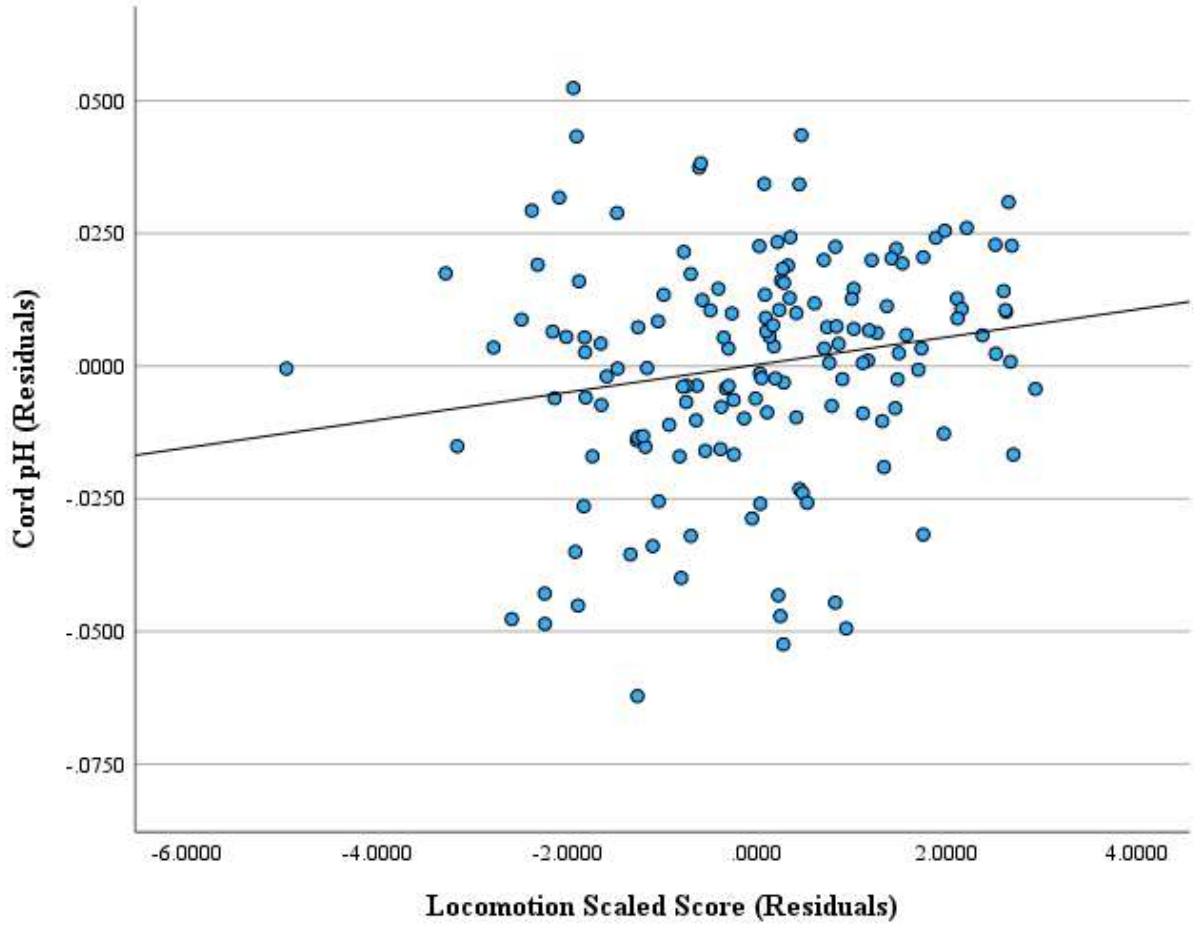
Figure 4
Umbilical cord pH values regressed on Locomotion scaled scores, adjusted for covariates, in the total sample



Note: Adjusted for sociodemographic (socioeconomic status, sex) and perinatal (gestational age, standardized birthweight, antenatal complications) variables with multiple status (i.e., family membership) treated as random factor.

Figure 5

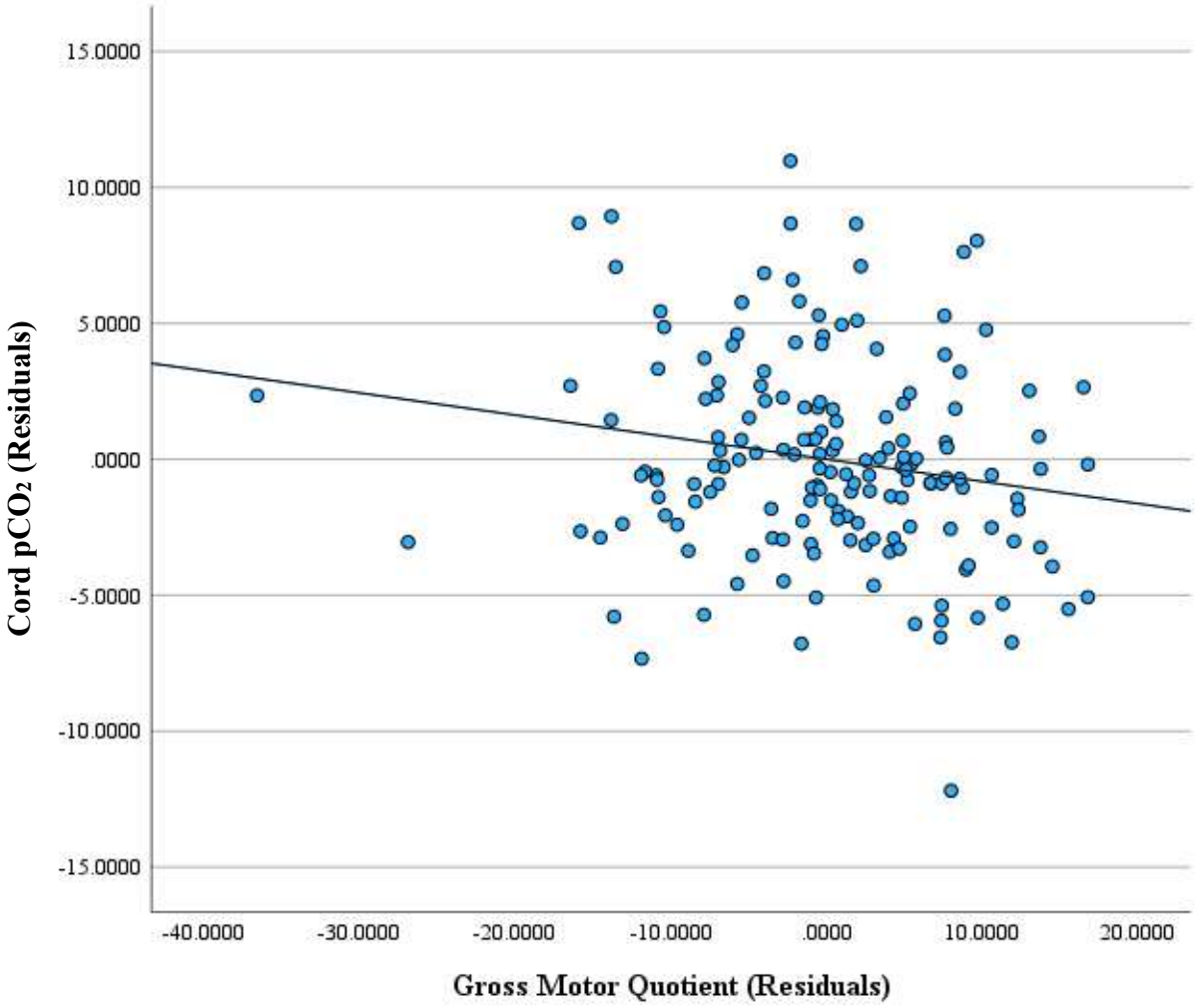
Umbilical cord pH values regressed on Locomotion scaled scores, adjusted for covariates, in the reduced sample



Note: Adjusted for sociodemographic (socioeconomic status, sex) and perinatal (gestational age, standardized birthweight, antenatal complications) variables with multiple status (i.e., family membership) treated as random factor.

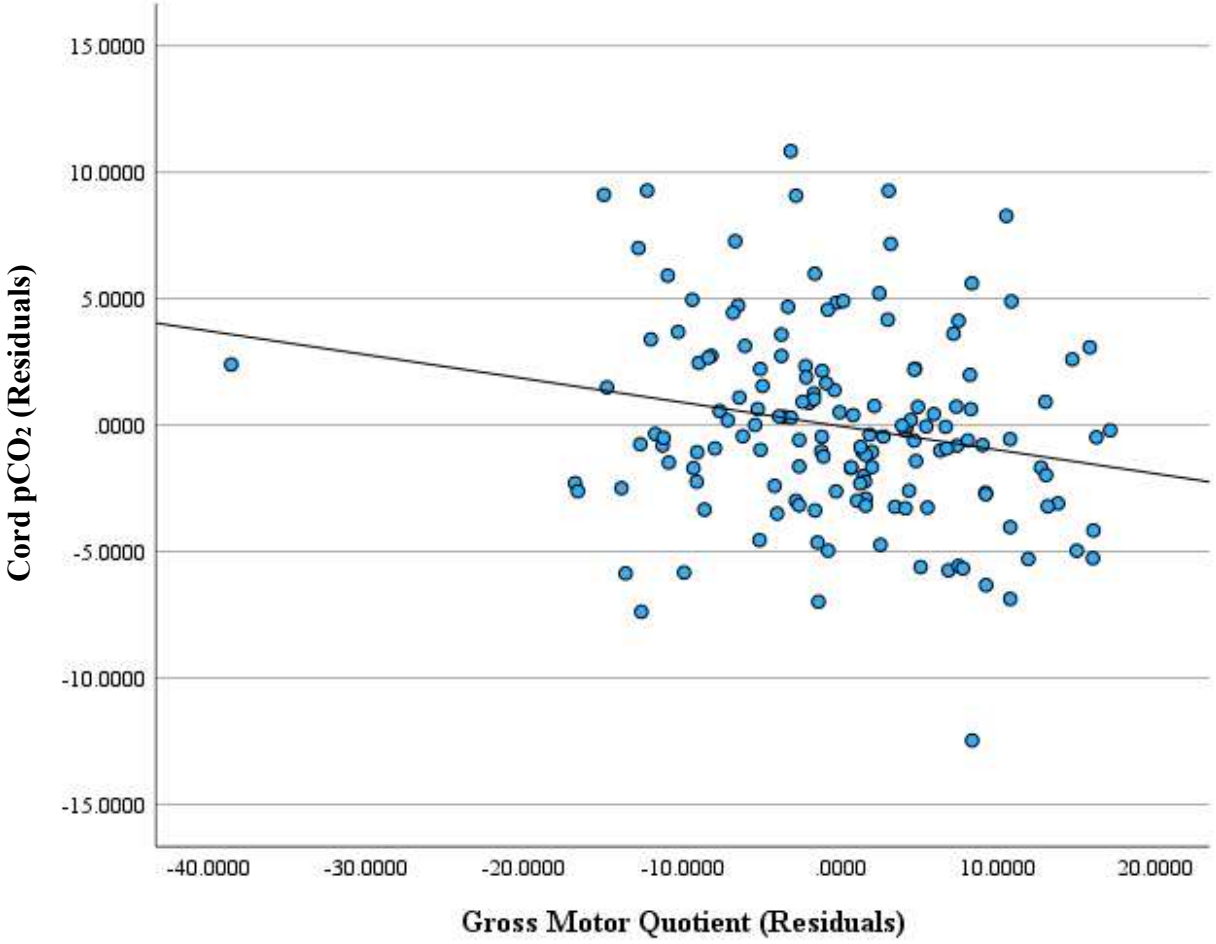
Figure 6

Umbilical cord pCO_2 values regressed on GMQ, adjusted for covariates, in the total sample



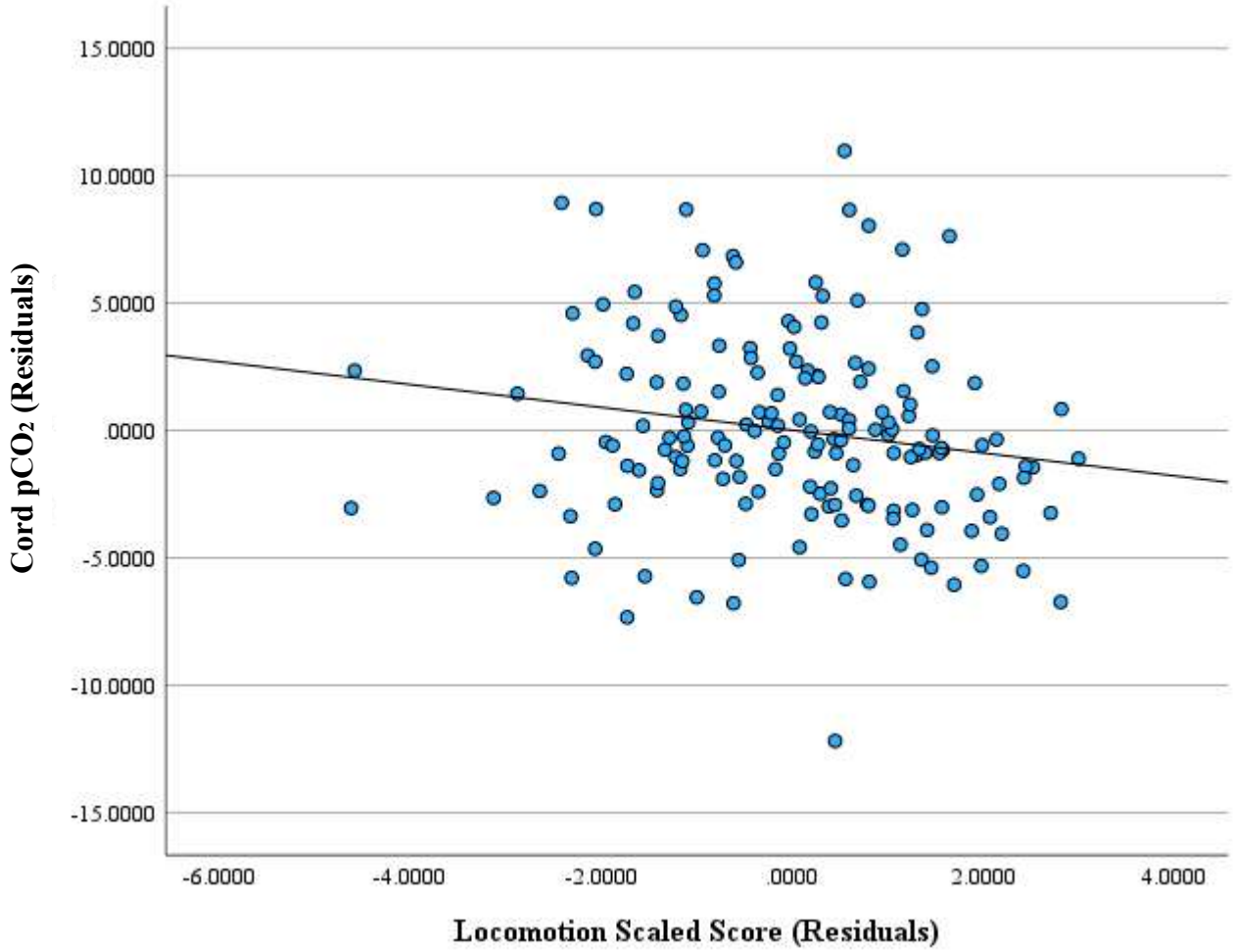
Note: Adjusted for sociodemographic (socioeconomic status, sex) and perinatal (gestational age, standardized birthweight, antenatal complications) variables with multiple status (i.e., family membership) treated as random factor.

Figure 7
Umbilical cord pCO_2 values regressed on GMQ, adjusted for covariates, in the reduced sample



Note: Adjusted for sociodemographic (socioeconomic status, sex) and perinatal (gestational age, standardized birthweight, antenatal complications) variables with multiple status (i.e., family membership) treated as random factor.

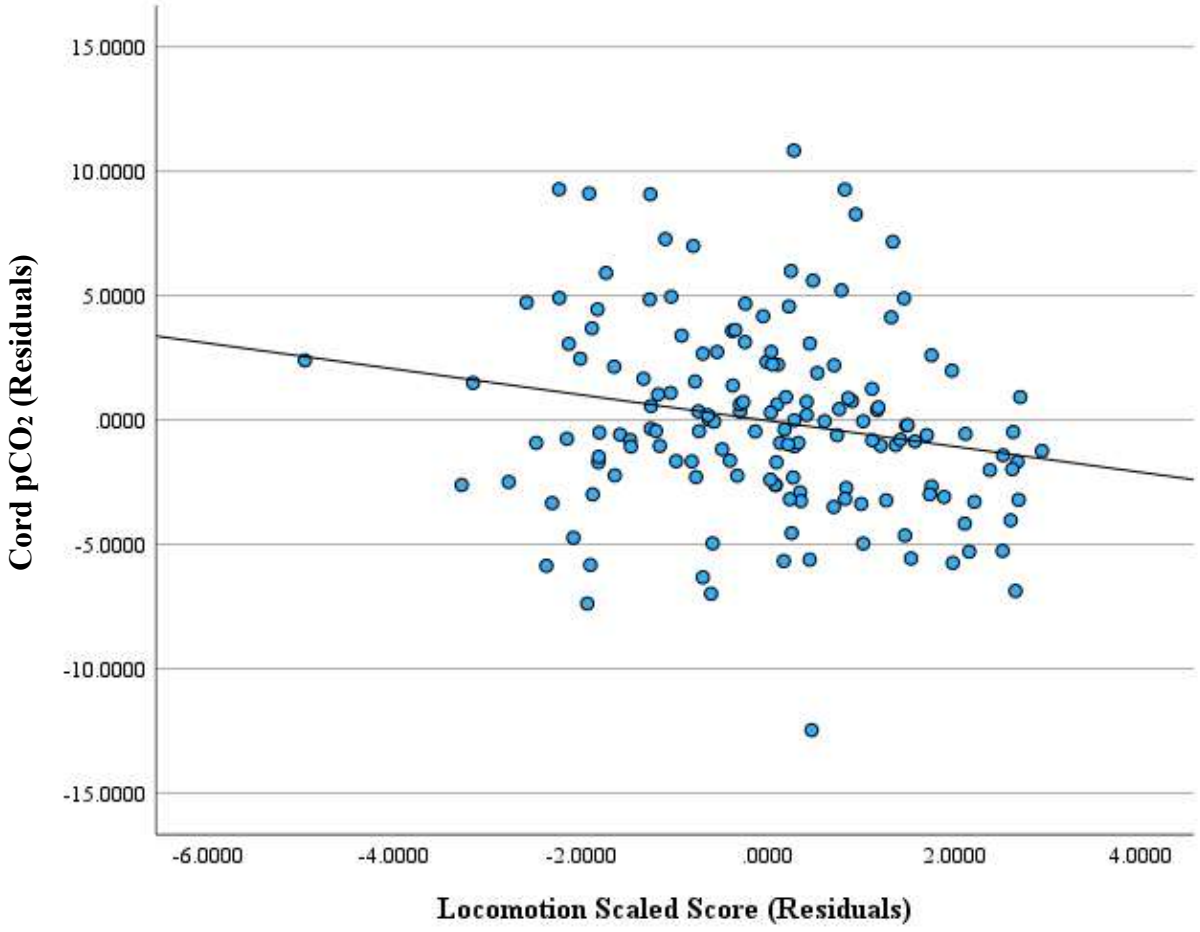
Figure 8
Umbilical cord pCO_2 values regressed on Locomotion scaled scores, adjusted for covariates, in the total sample



Note: Adjusted for sociodemographic (socioeconomic status, sex) and perinatal (gestational age, standardized birthweight, antenatal complications) variables with multiple status (i.e., family membership) treated as random factor.

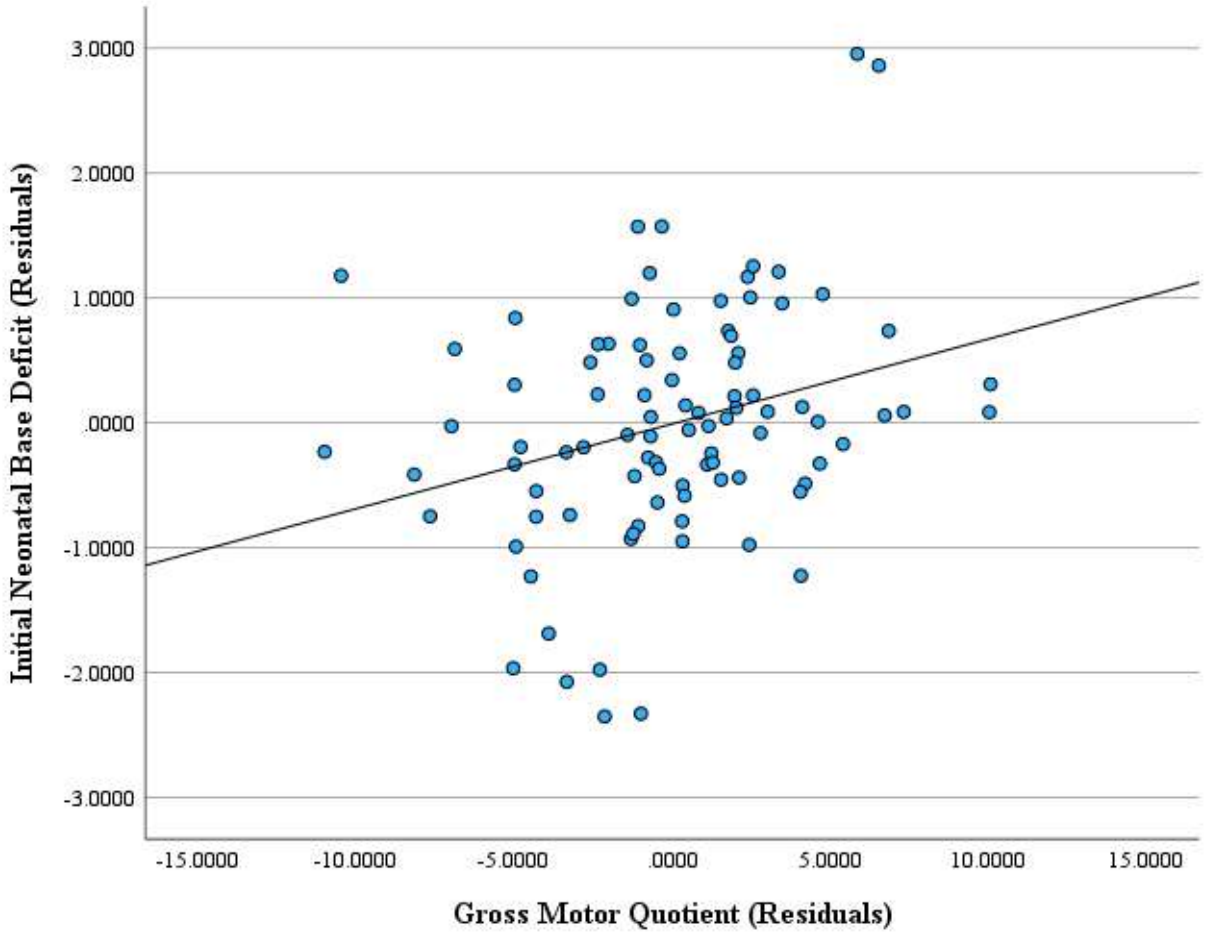
Figure 9

Umbilical cord pCO_2 values regressed on Locomotion scaled scores, adjusted for covariates, in the reduced sample



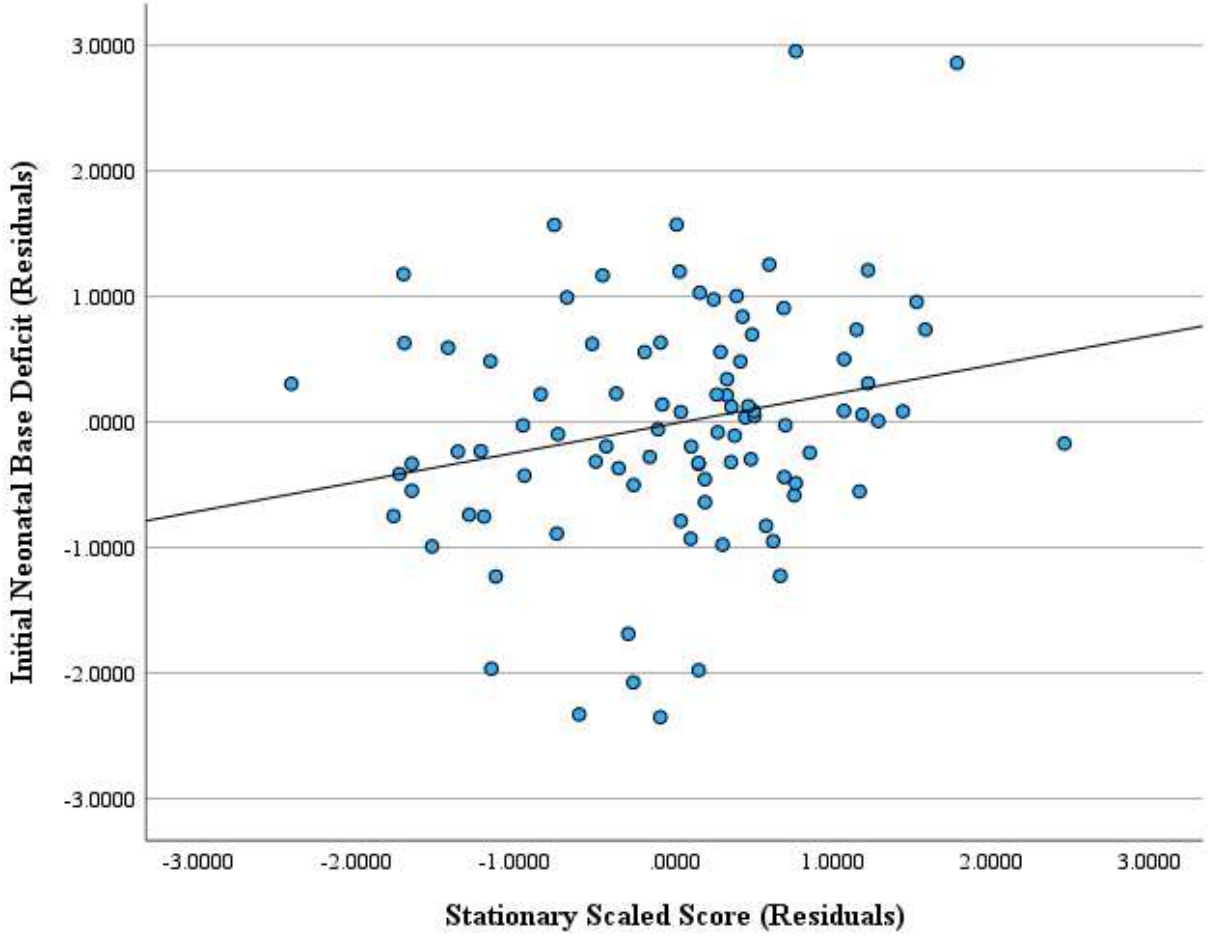
Note: Adjusted for sociodemographic (socioeconomic status, sex) and perinatal (gestational age, standardized birthweight, antenatal complications) variables with multiple status (i.e., family membership) treated as random factor.

Figure 10
Initial neonatal base deficit values regressed on GMQ, adjusted for covariates, in the total sample



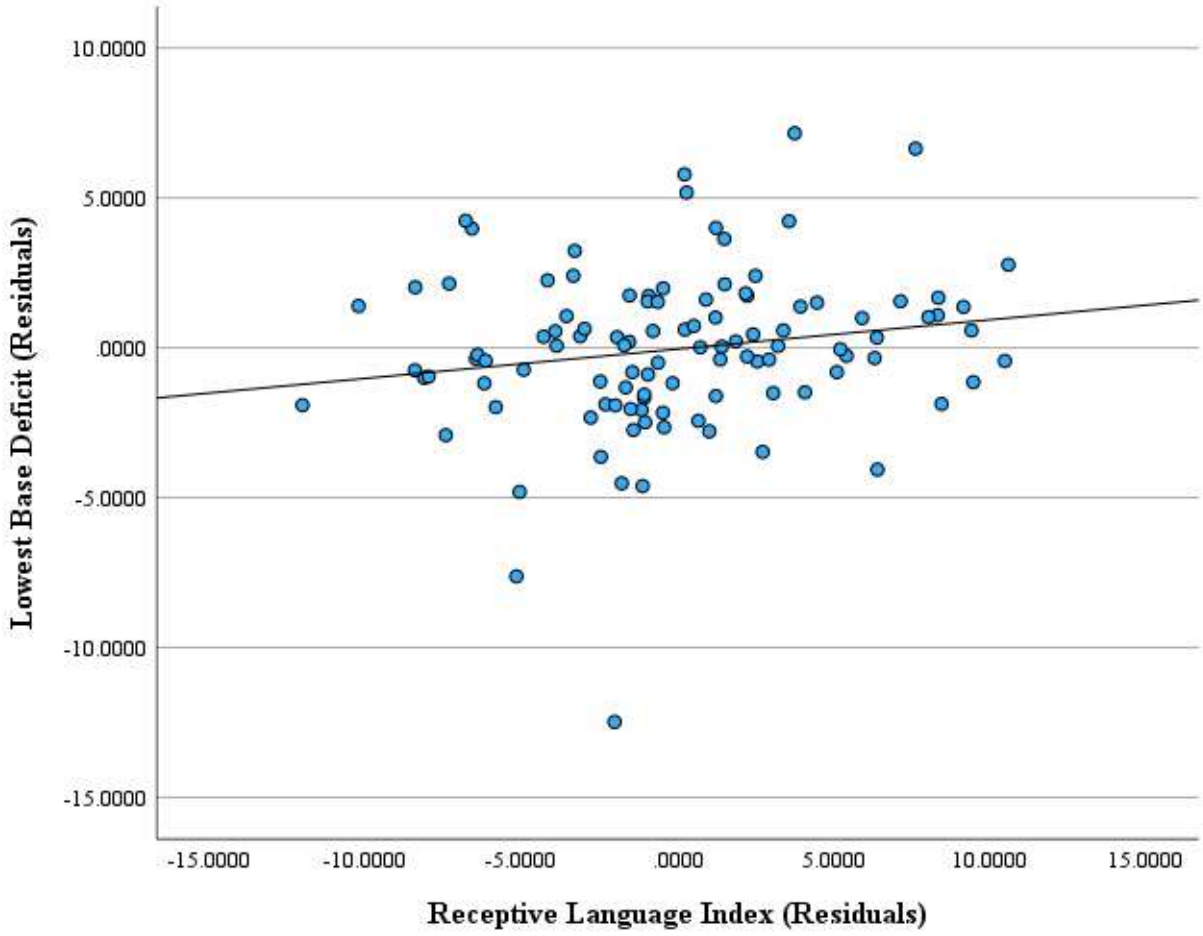
Note: Adjusted for sociodemographic (socioeconomic status, sex) and perinatal (gestational age, standardized birthweight, antenatal complications) variables with multiple status (i.e., family membership) treated as random factor.

Figure 11
Initial neonatal base deficit values regressed on Stationary scale scores, adjusted for covariates, in the total sample



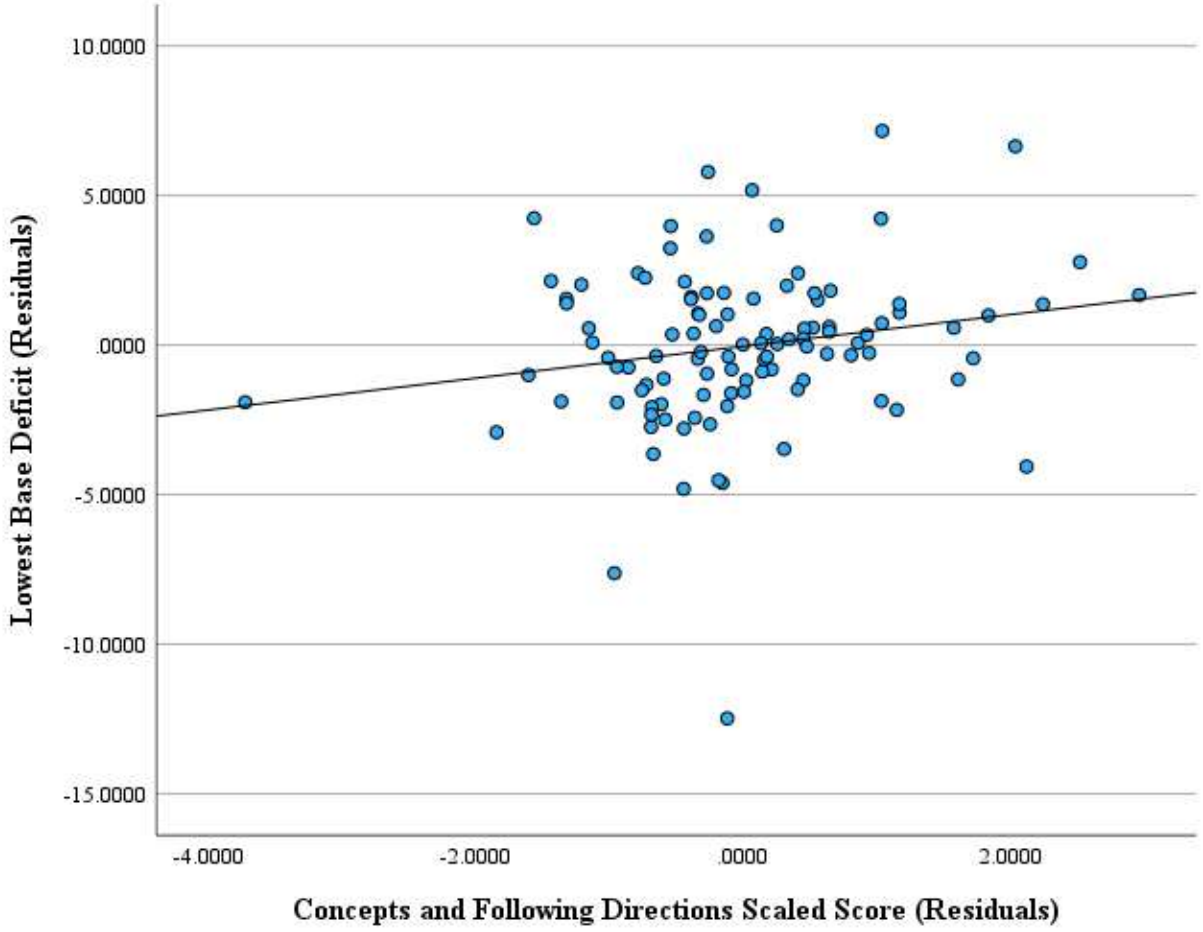
Note: Adjusted for sociodemographic (socioeconomic status, sex) and perinatal (gestational age, standardized birthweight, antenatal complications) variables with multiple status (i.e., family membership) treated as random factor.

Figure 12
Lowest base deficit values regressed on RLI, adjusted for covariates, in the total sample



Note: Adjusted for sociodemographic (socioeconomic status, sex) and perinatal (gestational age, standardized birthweight, antenatal complications) variables with multiple status (i.e., family membership) treated as random factor.

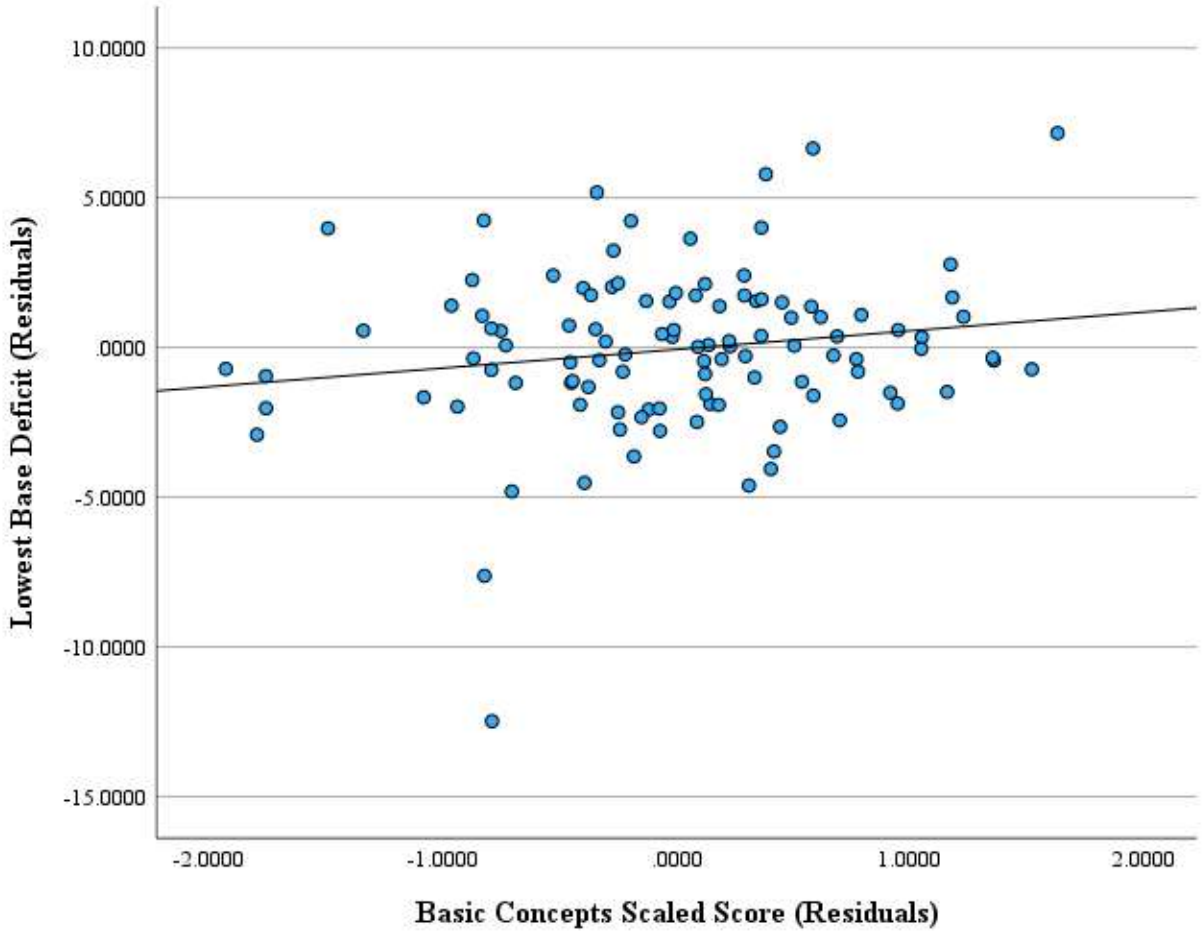
Figure 13
Lowest base deficit values regressed on Concepts and Following Directions scale scores, adjusted for covariates, in the total sample



Note: Adjusted for sociodemographic (socioeconomic status, sex) and perinatal (gestational age, standardized birthweight, antenatal complications) variables with multiple status (i.e., family membership) treated as random factor.

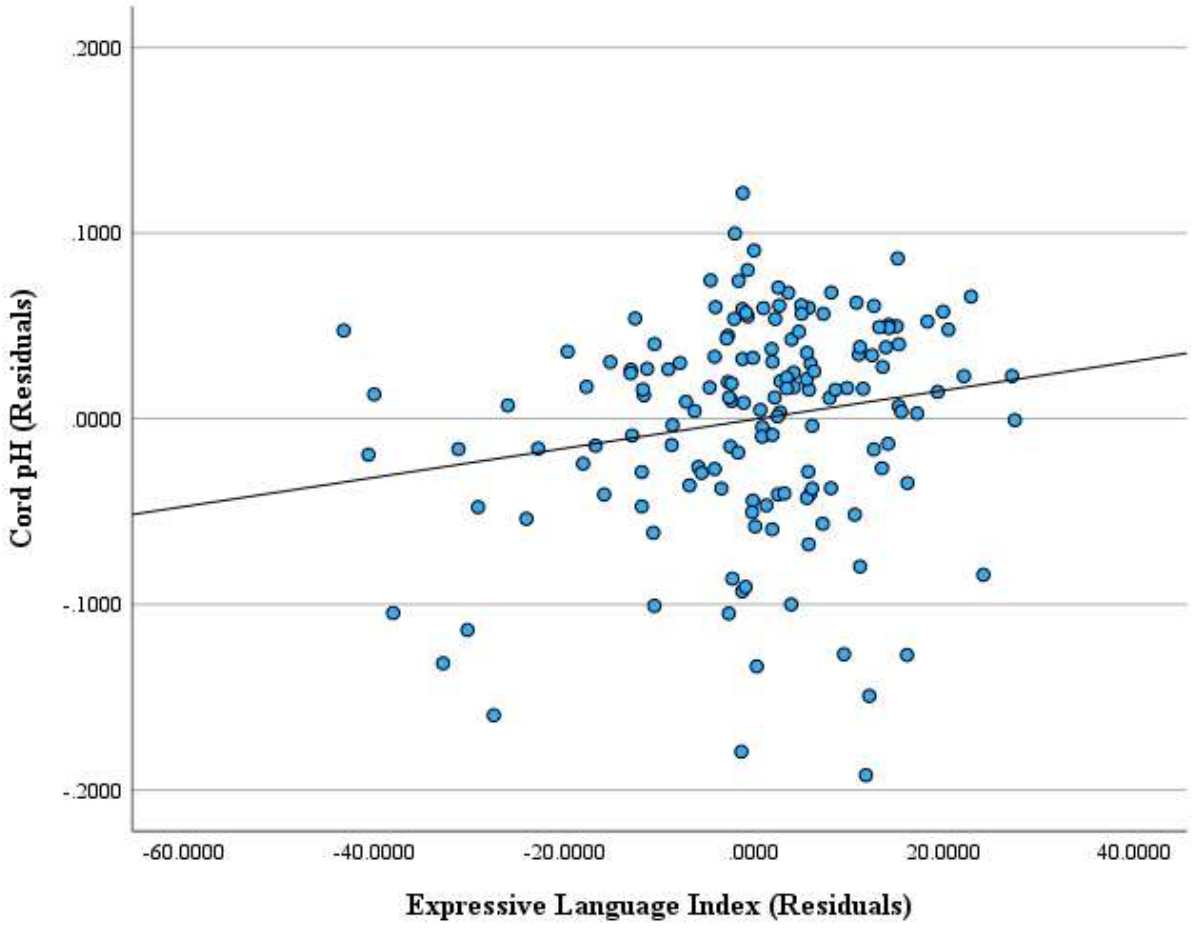
Figure 14

Lowest base deficit values regressed on Basic Concepts scale scores, adjusted for covariates, in the total sample



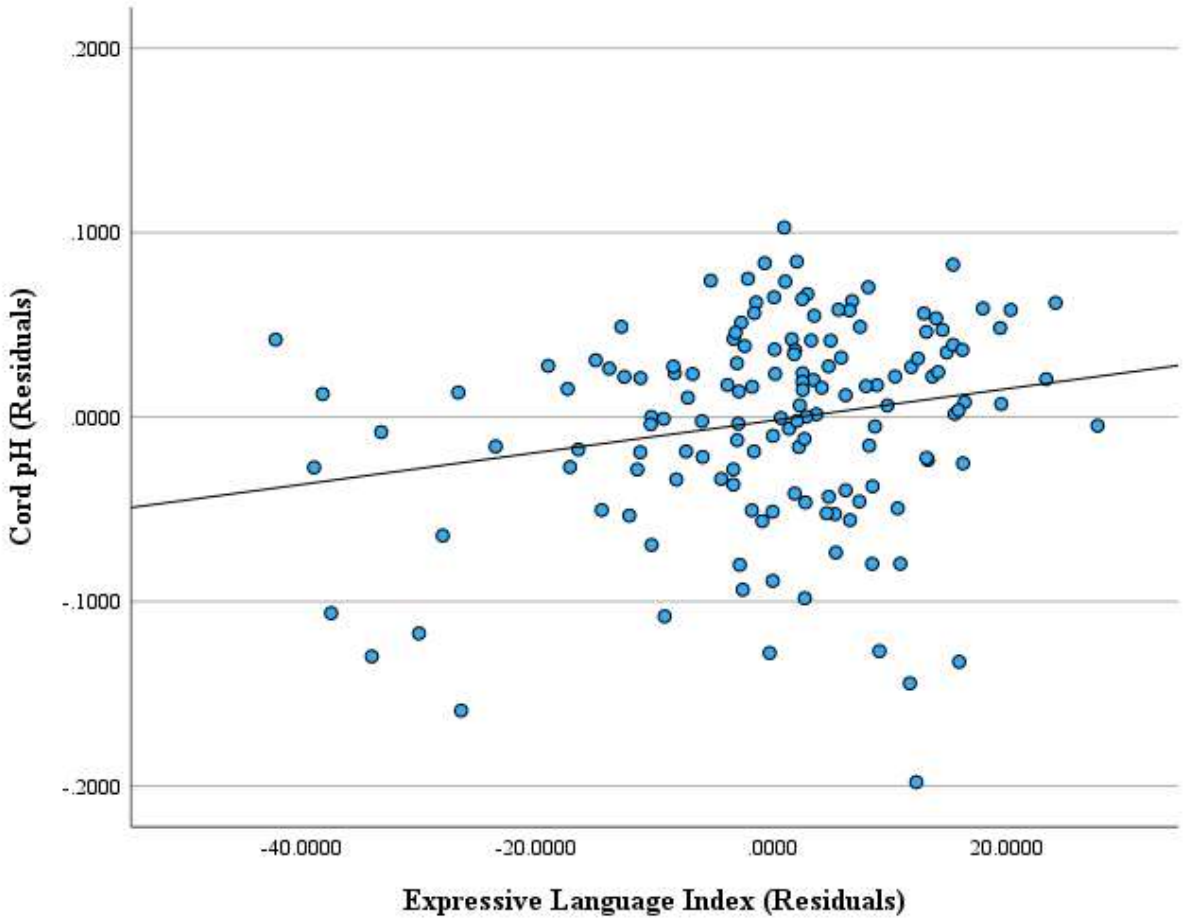
Note: Adjusted for sociodemographic (socioeconomic status, sex) and perinatal (gestational age, standardized birthweight, antenatal complications) variables with multiple status (i.e., family membership) treated as random factor.

Figure 15
Umbilical cord pH values regressed on ELI, adjusted for covariates, in the total sample



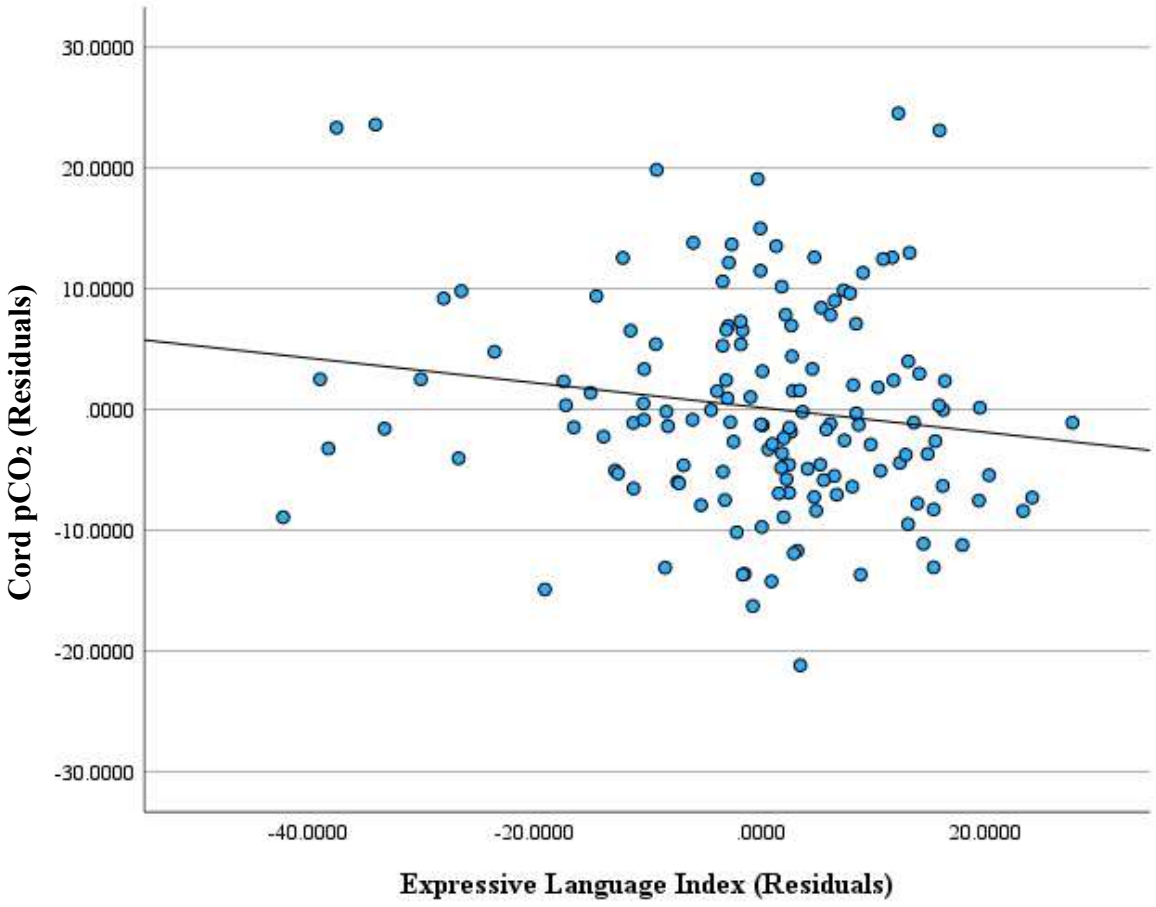
Note: Adjusted for sociodemographic (socioeconomic status, sex) and perinatal (gestational age, standardized birthweight, antenatal complications) variables with multiple status (i.e., family membership) treated as random factor.

Figure 16
Umbilical cord pH values regressed on ELI, adjusted for covariates, in the reduced sample



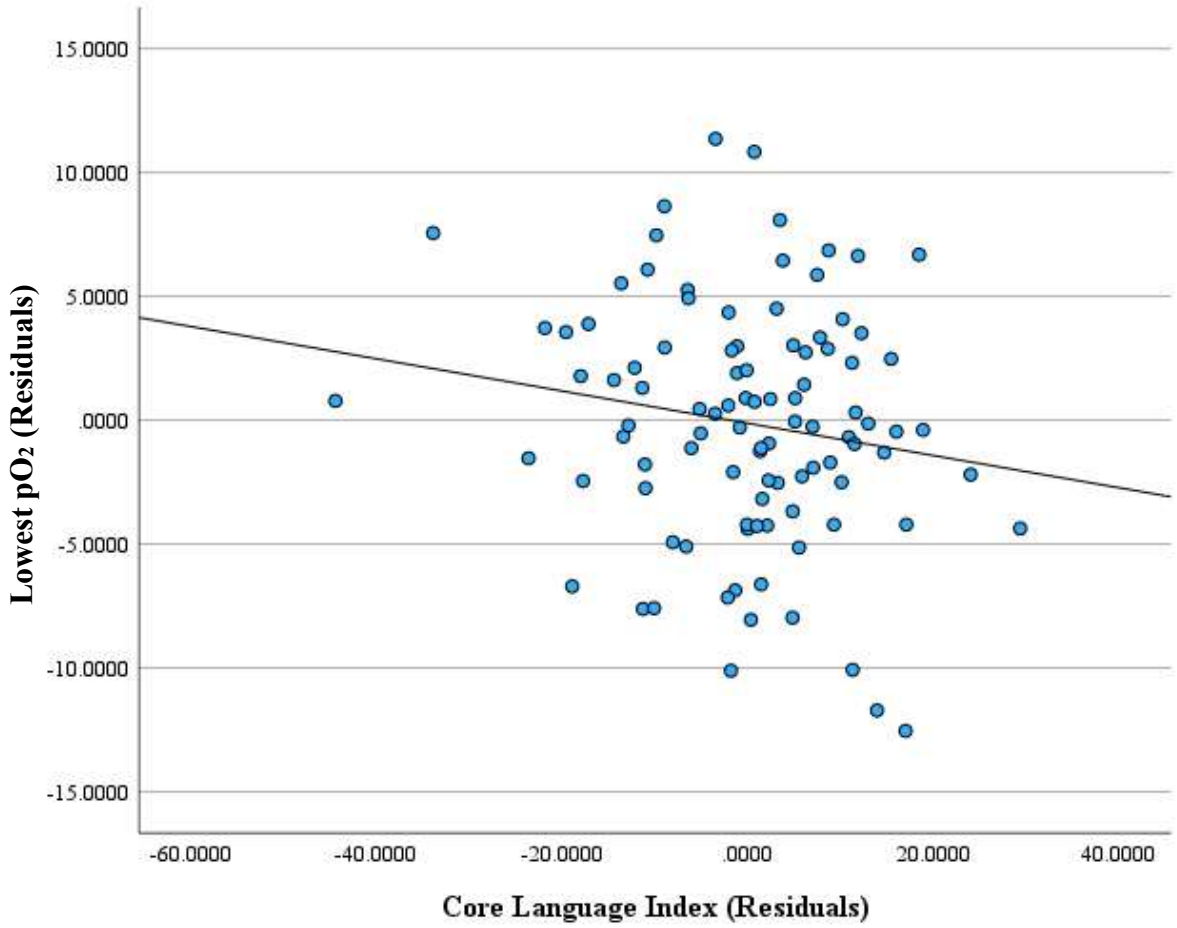
Note: Adjusted for sociodemographic (socioeconomic status, sex) and perinatal (gestational age, standardized birthweight, antenatal complications) variables with multiple status (i.e., family membership) treated as random factor.

Figure 17
Umbilical cord pCO_2 values regressed on ELI, adjusted for covariates, in the reduced sample



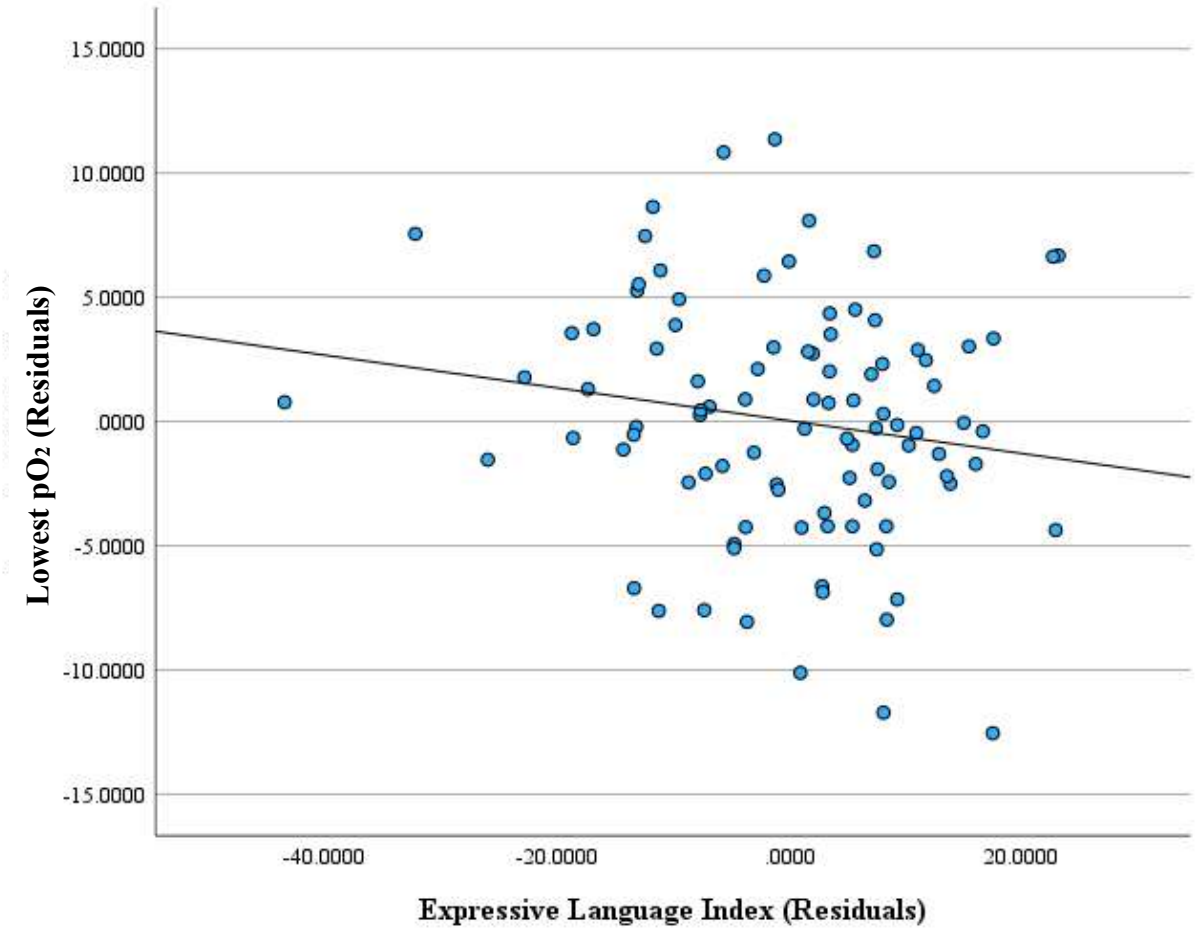
Note: Adjusted for sociodemographic (socioeconomic status, sex) and perinatal (gestational age, standardized birthweight, antenatal complications) variables with multiple status (i.e., family membership) treated as random factor.

Figure 18
Lowest pO_2 values regressed on CLI, adjusted for covariates, in the reduced sample



Note: Adjusted for sociodemographic (socioeconomic status, sex) and perinatal (gestational age, standardized birthweight, antenatal complications) variables with multiple status (i.e., family membership) treated as random factor.

Figure 19
Lowest pO_2 values regressed on ELI, adjusted for covariates, in the reduced sample



Note: Adjusted for sociodemographic (socioeconomic status, sex) and perinatal (gestational age, standardized birthweight, antenatal complications) variables with multiple status (i.e., family membership) treated as random factor.

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ABSTRACT

ASSOCIATIONS OF BLOOD GAS AND ACID-BASE VALUES WITH MOTOR AND LANGUAGE OUTCOMES IN PRETERM-BORN PRESCHOOLERS

by

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Hypoxia and ischemia are of the most common causes of acquired brain injury in preterm infants and often results in damage to the periventricular areas of the preterm brain. Several biochemical indices are commonly associated with hypoxic-ischemic injury, including blood pH, base deficit (BD), oxygen, and carbon dioxide (pCO_2). The aim of this study was to examine the contribution of early biochemical indexes of hypoxic-ischemic risk, particularly blood gas measures and acid-base balance measures, to neuropsychological outcome in preterm preschool-age children. I was particularly interested in the link between measures obtained either at birth, immediately after birth, or within the first week of life and motor and language functioning at preschool age.

Preterm children were assessed at 3-4 years of age, with 88 to 163 of the evaluated children qualifying for this investigation. Umbilical cord and neonatal blood-gas and acid-base measurements were collected retrospectively from medical records. The biochemical measures were the predictors of interest. Socioeconomic status, sex, sum of antenatal complications, and standardized birthweight served as covariates in linear mixed models. The dependent variables

were motor (gross and fine) and language (expressive and receptive) performance scores based on the Peabody Developmental Motor Scales – 2nd Edition and Clinical Evaluation of Language Fundamentals – Preschool, 2nd Edition. Children with a history of moderate to severe intracranial pathology or cerebral palsy were excluded.

The results showed that lower cord pH (p = .038) and higher cord pCO_2 (p = .029) values were associated with lower gross motor, but not fine motor, skills in a sample of high-risk preschoolers. None of the associations between blood-gas or acid-base values and language outcomes were significant when an oral-motor subtest score was included as a covariate to exclude the motor component underpinning expressive language. In contrast, without this covariate, lower cord pH (p = .027) was associated with lower expressive language performance. These discrepant results suggest that the oromotor skills involved in expressive language may be the primary mechanism driving the observed relationship between early blood biochemical indices of risk and expressive language. Together, these findings suggest that perinatal indices of severity of acidosis and hypercapnia are linearly associated with preschool-age gross motor and expressive language functioning in a preterm-born sample.

AUTOBIOGRAPHICAL STATEMENT

Christina was raised in Harrison Township, Michigan. She moved to Kalamazoo, Michigan, following high school to attend Kalamazoo College. There, she pursued a degree in psychology while playing for the women's soccer team. Christina was involved with various faculty-led research projects while at Kalamazoo College, and also participated in numerous independent projects at the University of Michigan. Through her combined experiences, she began to appreciate the nuances of brain vulnerability, as well as resiliency, and how specific biological risks may contribute to an individual's unique outcome. She graduated from Kalamazoo College in June 2018, with a Bachelor of Arts in Psychology.

Christina enrolled at Wayne State University in August 2018 to earn her doctoral degree in Clinical Psychology with a specific interest in Pediatric Neuropsychology. She has worked with Dr. Sarah Raz for the past five years, conducting research aimed at gaining a better understanding of the effects of premature birth on early development. In regards to clinical work, she has developed her skills at the Children's Hospital of Michigan, The Children's Center for Intellectual and Developmental Disabilities Services, and the University of Michigan Physical Medicine and Rehabilitation Neuropsychology service. Christina will complete her pre-doctoral internship at St. Jude Children's Research Hospital through the University of Tennessee Professional Psychology Internship Consortium (UTPPIC). After internship, Christina intends on obtaining a position as a post-doctoral fellow at an academic medical center, specializing in pediatric neuropsychology.