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Ante- And Perinatal Risk Factors And Neuropsychological Outcome: Exploration Of The Role Of Multiple Birth And Acid-Base Status In Preterm Born Preschoolers

Jamie Piercy
Wayne State University, fj0485@wayne.edu

ANTE- AND PERINATAL RISK FACTORS AND NEUROPSYCHOLOGICAL OUTCOME: EXPLORATION OF THE ROLE OF MULTIPLE BIRTH AND ACID-BASE STATUS IN PRETERM BORN PRESCHOOLERS

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JAMIE CHRISTINE PIERCY

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CHAPTER 1: INTRODUCTION

Introduction to Preterm Birth

Fifteen million babies are born premature (before 37-weeks gestation) worldwide every year (Blencowe et al., 2012). According to the CDC (Ferre et al., 2016), in the USA, 9.5% of neonates are born preterm. Approximately 10% of these are products of twin gestation. Delivery before 37 weeks occurs in more than 50% of all twin pregnancies compared to in 6% of all singleton pregnancies (Ozturk & Templeton, 2002; Martin, Hamilton, & Osterman, 2012). Furthermore, approximately 15% of twins are born very or extremely preterm (Hediger et al., 2005), highlighting the high-risk nature of multiple gestations.

Advances in perinatal care, including improvements in ventilation, infection prevention, and the use of surfactant therapy since the 1990s, have resulted in an improved survival rate of preterm born children (Chang et al., 2013). For example, in industrialized countries, half of babies under 25 weeks now survive (Petrou et al., 2005). However, despite and perhaps because of these advances, accompanying improved survival rates is an increased risk for structural brain abnormalities, neurological deficits, visual disorders, intellectual disabilities, and learning impairment (Dammann & Leviton, 2006; Moster, Lie, & Markestad, 2008). In other words, those who would have otherwise not survived without advances in perinatal care are now surviving, but often with the burden of developmental deficits or disabilities. It should be noted that deviations from a typical developmental trajectory are attributable to ante- peri- or neonatal adversity. Specifically, medical risk factors or complications that precede, accompany, or follow preterm birth (Bejar et al., 1990; Hack et al., 2009; Lopriore et al., 2006; Taylor et al., 1985). Hypoxia-ischemia is an important perinatal risk factor. This risk factor has been documented in term-born infants, though has not been a focus in the preterm literature (Logitharajah, Rutherford, & Cowan,

2009).

In this extensive multi-component project, I propose to study the influence of two disparate biological risk factors on the neuropsychological outcome of preterm-born preschoolers. The first risk factor, *multiple birth*, presumably exerts its negative influence during gestation, whereas the second risk factor, *peripartum hypoxia*, exerts its adverse effects during birth and delivery. The literature about multiple birth and peripartum hypoxia, two topics that have been understudied in the preterm population beyond infancy and toddlerhood, will be presented sequentially, with each section concluding with comments addressing methodological shortcomings. Unlike the existing research, the current study will investigate long term outcomes extending to the preschool age, thus substantially broadening the scope of the currently available literature on the neuropsychological sequelae of the risk factors of interest.

Preterm Birth and Twin Gestation

The rate of twin pregnancies has increased substantially in recent decades, rising 70% since the 1980s (Datar & Jacknowitz, 2009). This growth is in part attributed to the increase in artificial reproductive techniques (ARTs; Cheong & Doyle, 2012) utilization to address challenges to natural conception, including increased maternal age and infertility. Approximately 50% of twin births occur before 37-weeks gestation (Martin, Hamilton, & Osterman, 2012). Eighty percent of such births are characterized by antenatal and neonatal complications (Norwitz, Edusa, & Park, 2005). These include preeclampsia (hypertension and high protein levels in the urine), chorioamnionitis (inflammation of the placenta) and neonatal infections (Norwitz, Edusa, & Park, 2005). Twins also have significantly lower birthweight and increased perinatal mortality rate seven times higher than their singleton counterparts (Martin et al., 2006, Giuffré, Piro, & Corsello, 2012; Hack et al., 2008). In addition to the complications related to prematurity, twins are characterized

by biological risks unique to multiple gestation such as uterine crowding, disorders associated with monochorionic placenta, and significant birthweight discordance coupled with intrauterine growth (Einaudi et al., 2008; Giuffré et al., 2012; Garite et al., 2004).

Per the American College of Obstetricians and Gynecologists, intrauterine growth restriction in twins is diagnosed when there is a difference, or discordance, between the fetal weight of twin A and B that is greater than 20% (1998). Severe birth weight discordance (>25%) has been associated with increased risk of death, compared to birthweight concordant twins, as well as increased risk for birth weight < 10^{th} centile ("small for dates") in the smaller co-twin (Branum & Schoendrof, 2002). In the majority of cases with birth weight discordance, the smaller twin has an increased (60%) likelihood of being growth restricted (Blickstein & Kieth, 2003). Growth discordance has been recognized as an adaptational failure, or the inability of the uterine environment to meet the demands of multiple fetuses (Halling et al., 2005), which often results in intrauterine growth restriction in one or both of the fetuses. Specifically, 15% to 29% of co-twins are discordant in birth weight (Cheung, Bocking, & Dasilva, 1995; Ross, Krauss, & Perlman, 2012), a risk factor for perinatal morbidity (Pollack & Divon, 1992). Not only higher rates of death, but also fetal anomalies, longer hospital stays, as well as intellectual delays have been demonstrated in discordant birthweight twins (Amaru et al., 2004; Branum & Schoendorf, 2002; Blickstein & Kieth, 2003).

Research investigating the neuropsychological functioning of preterm born twins and singletons been limited primarily to infancy, using infant developmental indexes as dependent measures (Eras et al., 2013; Wadhawan et al., 2009; Kyriakidou, Karagianni, & Iliodromiti, 2013; Manuck, Sheng, Yoder, & Varner, 2014; Gnanedran et al., 2014). There are only three available studies using cohorts born in a modern NICU and focusing on preschoolers (Raz et al., 2016;

Bodeau-Livinec et al., 2013; Einaudi et al., 2008). All three of these studies reported significant group differences, with poorer performance in twins, on various neuropsychological measures. Only one study (Raz et al., 2016) focused on broad neuropsychological outcome (attention, language, visuospatial, visual-motor) domains. This study described twin disadvantage in the language and visual processing domains

Relative to the number of investigations comparing twins and singletons (Table 1), few studies examined differences within the population of twins born preterm, with methodologies varying from intra-pair comparisons (e.g., weight discordant co-twins; first and second born) to inter-pair comparisons (e.g., monochorionic vs dichorionic sets, or weight discordant vs. weight concordant sets). Most within-pair comparisons focused on birth weight discordance (Steingass et al., 2013; Halling et al., 2014; Adegbite et al., 2003; Goyen, Veddovi, & Lui, 2003; Ross, Krause, & Perlman, 2012) and between-pair comparisons on monochronicity (Steingass et al., 2013; Adegbite et al., 2003; Kawurama et al., 2015) to define risk. With the exception of two studies (Steingass et al., 2013; Gonzalez-Mesa, Cazorla-Granandos, & Gonzalez-Valenzuela, 2016), other important intra-pair differences between twins, such as perinatal risk factors, were not considered in these studies. In addition, studies addressing the issue of intra-pair discrepancy in risk did not investigate co-twin outcome differences in important neuropsychological and motor domains. A case in point are the studies of weight discordance, by far the most commonly explored, which have been limited primarily to infancy developmental measures (Goyen, Veddovi, & Lui, 2003; Gnanedran et al., 2014; Halling et al., 2015; Kawamura et al., 2015; Adegbite et al., 2003; Steingass et al., 2013).

Comparison of Preterm Twin and Singletons Neuropsychological Outcome: Systematic Review.

General Scope of Studies: As demonstrated in Table 1, ten twin-singleton comparisons were conducted since 2001. From a design standpoint, eight of the studies reviewed (Raz et al., 2016; Bodeau-Livinec et al., 2013; Wadhawan et al., 2009; Eras et al., 2013; Manuck, Sheng, Yoder, & Varner, 2014; Hajnal et al., 2005, Einaudi et al., 2008; Gnanedran et al., 2014) compared cohorts of twins and singletons born within a given time frame, typically attempting to statistically adjust for multiple potential confounds. Two other studies (Asztalos, Barrett, Lacy, & Luther, 2001; Kyriakidou, Karagianni, & Iliodromiti, 2013) individually matched each twin to a same gender and gestational age singleton, in contrast with comparing twin births with singleton births and possibly adjusting statistically for potential confounds. Taking sex into consideration in study design and/or statistical analysis is particularly important here, because in the preterm population, there are often differences between males and females, with males typically having poorer outcomes (Raz et al., 2015). Additionally, there is extreme variability within the preterm population in terms of SES, gestational age, and the number or type of perinatal complications. In order to isolate the effects of multiplicity on developmental outcome, it is important to adjust for the potentially confounding influences of these variables on neuropsychological outcome.

As noted earlier and shown in Table 1, seven studies focused exclusively on infants and toddlers (Asztalos, Barrett, Lacy, & Luther, 2001; Kyriakidou, Karagianni, & Iliodromiti, 2013; Eras et al., 2013; Kyriakidou, Karagianni, & Iliodromiti, 2013; Hajnal et al., 2005: Manuck, Sheng, Yoder, & Varner, 2014; Gnanedran et al., 2014); however, only three investigations, all documenting twin-singleton differences, focused on the preschool and school age (Raz et al., 2016; Einaudi et al., 2008; Bodeau-Livinec et al., 2013). As the long-term implications of twin gestation in the preterm population are unclear, further investigation beyond infancy is warranted.

Methodological Considerations in the Comparison of Preterm Twin and Singletons:

Beyond the aforementioned general methodological considerations, there are several specific methodological shortcomings in surfactant era studies of developmental outcome in preterm twins, as described below.

***Limitations in the coverage of neuropsychological outcome domains*.** As shown in Table 1, of the studies reviewed focusing on differences between twins and singletons, besides evaluation of medical or neurological abnormalities, all ten limited neuropsychological outcome measures to the cognitive domain. As demonstrated in Table 1, 7 of 10 studies reviewed focused on infancy and reported performance on the Bayley or Griffiths Developmental indices, Hence, the studies provided only a limited long-term perspective and did not include additional measures of expressive or receptive language, memory, or motor skills.

Dichotomization of outcome data. As described above, three of the ten twin outcome studies used binary classification of outcome data to classify cases into those with and without cognitive deficit (Asztalos, Barrett, Lacy, & Luther, 2001; Manuck, Sheng, Yoder, & Varner, 2014; Wadhawan et al., 2009). The dichotomization of this continuous measure (typically based on a cutoff of two SD's below the mean) likely resulted in loss of information, casting doubt in particular on studies with negative findings (Asztalos, Barrett, Lacy, & Luther, 2001; Manuck, Sheng, Yoder, & Varner, 2014; Gnanedran et al., 2014).

Insufficient Exclusionary Criteria. A few of the studies reviewed failed to take into consideration cerebral involvement (IVH, PVL, hydrocephalus), neurological handicaps (CP), or sensory impairments (uncorrected visual and hearing deficits). For instance, a number of studies did not exclude neurological disorders (Eras et al., 2013; Manuck, Sheng, Yoder, & Varner, 2014; Hajnal et al., 2005; Kyriakidou, Karagiani, & Iliodromiti, 2013; Wadhawan et al., 2009;

Gnanedran et al., 2014). Importantly, those who chose to include children with neurological disorders failed to adjust for the independent effects of these disorders in their statistical analyses, thus potentially confounding the effect of twin birth.

Failure to adjust for socioeconomic status. Eight of ten of the studies reviewed in Table 1 failed to account for socioeconomic status within their sample (Manuck, Sheng, Yoder, & Varner, 2014; Eras et al., 2013; Wadhawan et al., 2009; Hajnal et al., 2005; Asztalos, Barrett, Lacy, & Luther, 2001; Kyriakidou, Karagianni, & Iliodromiti, 2013; Einaudi et al., 2008; Gnanedran et al., 2014). This background factor must be taken into account because has a substantial impact on the outcome of full as well as preterm-birth children (Hajnal et al., 2005; Mikkola et al., 2005; Hack et al., 1991). Additionally, SES may interact with gestational age to influence outcome. Specifically, multiplicative effects have been demonstrated in this body of research, with low SES and prematurity enhancing the risk of developmental delay (Potijk, Kerstjens, Bos, Reijneveld, & de Winter, 2013).

Failure to adjust for sex. As seen in Table 1, two of ten studies (Kyriakidou, Karagianni, & Iliodromiti, 2013; Asztalos, Barrett, Lacy, & Luther, 2001) matched their premature-twin participants to control preterm-singletons on sex as well as gestational age. However, one study failed to match for gender (Wadhawan et al., 2009), and five failed to adjust for sex (Eras et al., 2013; Wadhawan et al., 2009; Hajnal et al., 2005; Einaudi et al., 2008; Kyriakidou, Karagianni, & Iliodromiti, 2013). As sex effects have been demonstrated in the body of literature on preterm birth (Peters, Heitzer, Piercy, & Raz, 2014; Wolke et al., 2008; Sansavini et al., 2006) it is necessary to account for the variance attributable to this sociobiological factor.

Failure to consider background perinatal risk-factors. As demonstrated in Table 1, six out of ten studies that compared preterm twins to preterm singletons did not statistically adjust or

match for gestational age, for the medical status of the infant (perinatal complications), or for birthweight deviation from gestational age norms, i.e., adequacy of intrauterine growth (Eras et al., 2013; Wadhawn et al., 2009; Hajnal et al., 2005; Asztalos, Barrett, Lacy, & Luther, 2001; Einaudi et al., 2008; Kyriakidou, Karagianni, & Iliodromiti, 2013).

Use of birth-weight instead of gestational age cut-off. As shown in Table 1, two of the ten reviewed studies (Wadhawan et al., 2009; Hajnal et al., 2004) exclusively used birth weight cutoffs instead of gestational age cutoff. This practice leads to overrepresentation of twins born SGA, resulting from artificial truncation of the birth-weight range in preterm cohorts.

Risk Factors Influencing Neuropsychological Outcome *within* the preterm twin population: Systematic Review.

***General scope of studies*.** Of the eight available studies that investigated biological factors influencing developmental outcome within twin cohorts following preterm delivery (Table 2), five studies focused on infancy and early childhood development at 20 to 48 months (Steingass et al., 2013; Adegbite et al., 2003; Kawamura et al., 2015; Halling et al., 2015; Gnanedran et al., 2014). Of these five studies, three (Halling et al., 2015; Steingass et al., 2013l Gnanedran et al., 2014) utilized the Bayley Scales of Infant Development to assess infant cognitive outcomes (Gnanderan and colleagues used second edition; Halling and colleagues used third edition). Three studies utilized the Griffiths Mental Developmental Scales (Goyen, Veddovi, & Lui, 2003; Gnanedran et al., 2014; Adegbite et al., 2003).

Three studies focused on early preschool years (Goyen, Veddovi, & Lui, 2003; Ross, Krause, & Perlman, 2012; Kawurama et al., 2015), whereas one study focused on early childhood (age 6; Gonzalez-Mesa, Cazorla-Granandos, & Gonzalez-Valenzuela, 2016).

As outlined in Table 2, only one of the eight studies examined outcomes beyond infancy and early preschool age *(*Gonzalez-Mesa, Cazorla-Granandos, & Gonzalez-Valenzuela, 2016*)*. This study focused on the influence of perinatal and obstetric variables on school development and intelligence in early elementary years.

In terms of the findings, as shown in Table 3, three studies investigating birthweight discordance documented poorer outcome in the lower weight co-twin (Halling et al. 2015; Ross, Krause, & Perlman, 2012; Goyen, Veddovi, & Lui, 2003). Whereas the first study focused primarily on infancy, the other two studied preschool age. Of the two studies focusing on birth order effects, one (Gonzalez-Mesa, Cazorla-Granandos, & Gonzalez-Valenzuela, 2016) found lower scores in second-twin males across domains, however the other infant study (Gnanedran et al., 2014) found no significant differences. Of the two studies that focused on placentation, one infant study (Kawurama et al., 2015) found no differences between monoamnionic and diamnionic infant twins; the other (Adegbite et al., 2003) found higher rates of cerebral palsy in monochorionic twins. Lastly, the remaining study found higher rates of discordant risk (i.e., abnormal cerebral ultrasound) in twin pairs with neurodevelopmental impairment.

Methodological Considerations in Intra-Twin Comparisons: As Table 2 shows, the eight studies described above varied along multiple methodological dimensions including sample characteristics, exclusionary criteria, and degree of controlling or adjusting for confounding variables as described below.

***Sample characteristics*.** The eight studies listed in Table 2 varied in the degree of prematurity or birthweight thresholds of the target group or sample. Two out of eight studies included twins born < 36-37 weeks gestation (Gonzalez-Mesa, Cazorla-Granandos, & Gonzalez-Valenzuela, 2016; Ross, Krause, & Perlman, 2003), whereas two other studies focused on very

preterm born children (<29 weeks, Gnanedran et al., 2014; 24-34 weeks, Adegbite et al., 2003). Three studies focused on very low birth weight samples (<1500 grams; Steingass et al., 2013; Kawurama et al., 2015; Goyen, Veddovi, & Lui, 2003). In studies investigating birth weight discordance, three studies targeted co-twins with ≥15% discordance (Steingass et al., 2013; Goyen, Veddovi, & Lui, 2003; Ross, Krause, & Perlman, 2012), and two studies included twins with birthweight discordance > 20% (Adegbite et al., 2003; Halling et al., 2015).

Risk factor of interest. As mentioned above, of the eight studies addressing the relationships between biological risk factors and neuropsychological outcome within twin cohorts (Table 2), the predictor of interest varied. The majority of studies (five investigations) focused on the risk associated with discordant birth weights (Ross, Krause & Perlman, 2012; Goyen, Veddovi, & Lui, 2003; Halling et al., 2015; Adegbite et al., 2003: Steingass et al., 2013). Of these, three studies (Steingass et al., 2013; Goyen, Veddovi, & Lui, 2003; Ross, Krause, & Perlman, 2012) utilized a threshold of >15% birthweight discordance, and two studies (Halling et al., 2015; Adegbite et al., 2003) compared twins with greater than 20% discordance. Three studies (Kawurama et al., 2015; Adegbite et al., 2003; Steingass et al., 2013) investigated differences between the outcomes of monochrionic compared to dichorionic twin-pairs, and two studies (Gnanedran et al., 2014; Gonzalez-Mesa, Cazorla-Granandos, & Gonzalez-Valenzuela) focused on risk associated with the co-twins birth order. Lastly, two studies investigated intra-pair differences based on presence of obstetric variables and neonatal risk (Steingass et al., 2013; Gonzalez-Mesa, Cazorla-Granandos, & Gonzalez-Valenzuela; 2016). These studies compared the relationship between specific risk factors between co-twins and later outcomes.

Failure to consider perinatal background risk-factors. Twins share many elements of the intra-uterine and postnatal environments; however, the degree of neonatal risk varies within twin

pairs and should be accounted for in order to avoid confounding the influence of the risk factor of interest on twin outcome with other adverse influences. However, two of the studies did not account (either match for or covary) for gestational age (Kawurama et al., 2015; Adegbite et al., 2003), whereas others (Ross, Krause, & Perlman, 2012; Goyen, Veddovi, & Lui, 2003; Halling et al., 2015; Kawurama et al., 2015; Adegbite et al., 2003) did not take number of complications or risk factors into consideration.

Use of birth-weight instead of gestational age cut-off. As shown in Table 2, three of the eight reviewed studies (Steingass et al 2013; Kawurma et al., 2015; Goyen, Veddovi, & Lui, 2003) used birth weight cutoffs thus limiting the generalizability of the findings.

Arterial Cord pH and Neonatal Outcome

The umbilical cord is a conduit between the developing fetus and the placenta. It contains one umbilical vein, which supplies the fetus with oxygenated nutrient rich blood from the placenta, and two arteries, which pump deoxygenated, nutrient-depleted blood back to the placenta (Wang & Zhao, 2010). Compared to umbilical arterial blood gas values, umbilical vein blood gas values more closely resemble the blood gas values of the mother's arterial blood. This is because the umbilical vein carries oxygenated blood from the mother. In contrast, the venous cord blood reflects the combined effect of maternal acid-base status and placental function, arterial cord blood reflects fetal acid-base status (Thorp et al., 1996).

Umbilical cord pH is a biochemical indicator of perinatal acidosis, or fetal academia, a correlate of hypoxia, or oxygen deprivation (Beard, Morris, & Clayton, 1967). In recent decades, there has been considerable study of the relationships between cord pH values as an objective measure of peripartum asphyxial insult and subsequent neonatal outcome (Victory, 2004). Whereas the venous cord pH values reflect the utero-placental blood circulation, the arterial cord

pH values reflects the fetal-placental blood circulation (Wang & Zhao, 2010). Thus, acid base parameters, including pH and base excess (BE) should be measured in umbilical cord arterial blood to assess neonatal hypoxia. The umbilical *artery* (not vein) cord blood reflects the fetal acid-basis of the infant at birth, with abnormalities in the umbilical cord arterial acid-based status suggests potential intrapartum hypoxic events (Acker, 2013). Nonetheless, it should be noted that because the fetus receives oxygenated blood through the uteroplacental circulation, fetal acid-base status, or fetal academia, is related to maternal or antepartum risk factors that increase the risk for preterm birth, including abruption, prolonged labor, chorioamnionitis, and delivery of multiples (Acker, 2013).

Severe cord blood acidemia, or perinatal metabolic acidosis (acid in the tissues), is indicated by umbilical cord pH below a value of 7.0 and base deficit greater than or equal to 12mmol/L (Jonsson, Norden-Lindeberg, & Hansson, 2009). Fetal asphyxia is related to both respiratory and metabolic acidosis. Respiratory acidosis pertains to impaired gas exchange (in response to elevated carbon dioxide levels), whereas metabolic acidosis is caused by anaerobic metabolism, such as excessive formation of metabolic acids in the body (Ross, 2002). When fetal cells are not receiving adequate oxygen, they revert to anaerobic metabolism, which produces acidic byproducts (lactic acid) and results in acidosis. Perinatal acidosis is associated with increased incidence of intrapartum hypoxia, as well as subsequent morbidity and mortality (D'Alton et al., 2004; Randolph, 2014). The International Cerebral Palsy Task Force has supported the aforementioned pH level cutoffs (<7.0) and has deemed a sufficiently low pH as necessary criteria to attribute intrapartum acidemia as the cause of cerebral palsy (Yeh et al., 2012; MacLennan, 2003). The severe acidemia threshold (pH <7.0) is accepted as indicating increased risk, yet as shown in Malin's quantitative integration, and in Table 3 which includes more recent

investigations, research studies varied considerably, with acidosis cutoffs ranging from pH = 7.00 – 7.20.

Importantly, however, perinatal risk increases with worsening acidemia, as such, the recognition of this continuum of risk (i.e., a dose-response relationship) may help identify newborns at risk for cerebral palsy and associated long term neurological events (D'Alton et al., 2004; Victory et al., 2003; Socol, 1994). Most studies utilize the umbilical cord artery as the source of pH, though one study has found comparable outcomes using arterial and venous pH in the preterm population (Victory et al., 2003); supporting the use of pH or base excess from either the umbilical artery or vein. Practically, however, the sampling of blood from the umbilical cord artery is more challenging than sampling of blood from the umbilical vein because the umbilical veins are more accessible; thus, obtaining samples from both sources is recommended, as they can be distinguished based on their pH, which will always be lower in the artery (Acker, 2013). In other words, obtaining blood from both sources is recommended to ascertain or verify based on pH discrepancy (lower in artery) that the technician indeed sampled blood from the artery and not from the vein which more clearly visible).

The results of an extensive meta-analysis (Malin, 2004), have shown that in term and preterm-born infants, a low umbilical cord pH value at birth ranging from 7.0 – 7.2 (cutoffs for severe and mild acidosis, respectively) amongst various investigations is associated with adverse short term outcome (i.e., increased incidence of neonatal neurological morbidity, operationalized as a composite of seizures, hypoxic-ischemic encephalopathy, intraventricular hemorrhage and periventricular leukomalacia). When compared to term infants, there is a limited number of studies examining the relationship between umbilical artery pH and outcomes in children born preterm, recent studies (published following the Malin meta-analysis) continue to demonstrate relationships

between metabolic acidemia and increased risk in infants born premature (Randolph et al., 2014; Morgan, 2016). Importantly, though Malin and colleagues were able to use quantitative integration to demonstrate the link between low cord pH and cerebral palsy, due to the dearth of long term outcome studies they were unable to demonstrate a relationship with preschool neuropsychological functioning and beyond. Importantly, the studies reviewed by Malin used arterial pH as the sole medical indicator of perinatal asphyxia, without requiring the use of base excess (BE) to distinguish between metabolic and respiratory acidosis at birth.

According to Low (2004) the relative importance of peripartum acidosis for long-term outcome prediction in the preterm infant is less clear than their full-term counterparts (Randolph et al., 2014). Low investigated asphyxia in a sample of preterm born children, comparing asphyxia in those delivered prior to the onset of labor (antepartum) and those after the onset of labor (intrapartum). Based on the increased rate of pregnancy complications during gestation in preterm infants, including antepartum complications such as growth restriction, Low concluded that increased rates of asphyxia in preterm neonates may be attributable to the antepartum, rather than the peripartum, period as in their term-born counterparts. Importantly, the early complications occurring in pregnancies that result in preterm delivery may account for the compromised maternal-placental blood exchange, which leads to the increased prevalence of peripartum asphyxia in the immature, compared to the term or near-term, infant (Low, 2004).

Results of experimental animal (fetal lamb) models (Gunn, 2001) have suggested that the preterm infant may be uniquely able to survive prolonged periods of hypoxia-ischemia compared to their term or near-term counterparts. In this animal model of fetal asphyxia, Gunn and colleagues inflicted asphyxiation on the fetal lamb following 100-day gestation (out of 152 days needed for completed gestation) via 30-minute umbilical cord occlusion. These authors suggest the premature

fetus is able to survive more prolonged periods of severe asphyxia (30 minutes) than their term counterparts (10-12 minutes). This phenomenon of relative resistance to asphyxia injury observed in the fetal lamb is attributed to high cardiac and neural compensation, in part due to a compensatory mechanism with increased blood flow the heart, brain, and adrenal gland (Perlman & Risser, 1993; Goldstein et al., 1995; Low, 2004). Importantly, though these reserves presumably allow survival following longer periods of uterine asphyxia in the preterm infant with maintained systemic blood pressure (Perlman & Risser, 1993), longer periods of occlusion continue to be associated with an increased risk of grey and white matter injury (Gunn, 2001).

In my view, the findings from the quantitative integration by Malin et al. (2004) are inconsistent with the notion of resilience in preterm-born infant to peripartum hypoxia as demonstrated in the animal research (Gunn et al., 2001). Malin and colleagues demonstrated increased risk for neonatal neurological complications in preterm-born infants with low cord blood pH, as well as increased risk for cerebral palsy. As noted above, the long term neuropsychological outcome for this population, however, remains unclear because of the extremely limited body of research on the topic (see Table 3 for study details).

Arterial Cord pH in Preterm-Born Children and Neuropsychological Outcome: Systematic Review.

General scope of studies. Of the 7 available studies that investigated developmental outcome following preterm delivery, with arterial cord pH used as an index of intrapartum hypoxia (Table 3), 6 studies focused on infancy (12 to 18 months) (Randolph et al., 2014; Beeby et al., 2994; Lavrijsen et al., 2003; Huseman et al., 2011; Mittendorf et al., 2008; Kato et al., 1996). Of these six studies, two (Randolph et al., 2014; Mittendorf et al., 2008) utilized the Bayley Scales of Infant Development to assess infant cognitive (Randolph et al., 2014) and motor (Randolph et al.,

2013; Mittendorf et al., 2008) outcomes. One study used the second edition of the Bayley (Mittendorf et al., 2008), whereas the other used either the second or third edition (Randolph et al., 2014). Three studies utilized the Griffiths Mental Developmental Scales (Lavrijsen et al., 2003; Beeby et al., 1993; Huseman et al., 2011). As outlined in Table 3, only one of the seven studies (Mikkelson et al., 2017) examined outcomes beyond infancy. This study focused exclusively on the behavioral sequelae of perinatal hypoxia. A binary index (qualifying for ICD 10 ADHD diagnosis, between the ages of five and 16) was used as an outcome measure.

Methodological considerations. As Table 3 shows the seven studies described above varied along multiple methodological dimensions including sample characteristics, exclusionary criteria, and degree of controlling or adjusting for confounding variables as described below.

***Sample characteristics*.** The seven studies varied in the degree of prematurity of the target group or sample. Six of the seven studies focused on the very preterm or very low birth weight (Lavrijsen et al, 2004; Beeby et al,. 1994; Kato et al., 1996; Huseman et al., 2011; Mittendorf et al., 2008; Mikkelsen et al., 2017) category, and one focused on the extremely low birthweight category (Randolph et al., 2014). Importantly, the current study is not using a birthweight cut off, and will be including subjects born before 34 weeks. As such, this study will include a wider range of gestational ages, and thus will increase the generalizability of the findings within the preterm population.

Exclusionary criteria. Of the seven studies, four excluded children with congenital/chromosomal anomalies or severe malformations (Randolph et al., 2014; Lavrijsen et al., 2004; Beeby et al., 1994; Kato et al., 1996)), whereas the remaining three (Mikkelsen et al., 2017; Mittendorf et al., 2008; Huseman et al., 2011) did not mention exclusion of participants with congenital/chromosomal anomalies or severe malformations. Two studies excluded multiples

(Kato et al., 1996; Mikkelsen et al., 2017) which typically constitute approximately 25-40% of the preterm-newborn population served by the modern neonatal intensive care units (White, 2011), thus severely limiting the generalizability of these studies to preterm singleton births. One investigation excluded children with unclear gestational age, missing data, and out born infants (Mikkelsen et al., 2017). Mittendorf and colleagues (2008) excluded children with maternal infection, preeclampsia, antenatal steroid use, and infants who required reassuring fetal assessments. It should be noted, as in the case of twins, that these exclusions severely limit the generalizability of the findings, as maternal infections, preeclampsia and antenatal steroids characterize a significant proportion of preterm births. In particular, preeclampsia is one of the most common medical disorders associated with preterm delivery (Sibai, 2006). In brief, though some exclusions (e.g., chromosomal anomalies, malformations, etc.) are essential, other exclusions severely limit generalization of findings.

Acidosis as binary vs. continuous variable. Three of seven available studies (Lavrijsen et al., 2004; Beeby et al., 1994; Kato et al., 1996) compared groups above and below specified threshold values (i.e., dichotomized the sample). Four additional studies (Mikkelsen et al., 2017; Huseman et al., 2011; Mittendorf et al., 2008; Randolph et al., 2014) compared groups above and below a pH threshold, yet also included statistical analyses treating pH as a continuous, rather than dichotomous, variable. Clearly, treating pH exclusively as a dichotomous variable may result in loss of information in the study of the relationships between acidosis and neuropsychological outcome.

Acidemia thresholds. In selecting the study group, three of seven studies utilized an umbilical cord pH of less than 7.0 to ascertain severe acidosis (Randoloph et al., 2013; Lavrijsen et al., 2004; Huseman et al., 2011). Two of these studies also included a base excess threshold to

ascertain metabolic acidosis; less than -12mEg/L (Randolph et al., 2014), and less than -16 (Huseman et al., 2011). The remaining studies used pH values less than 7.10 (Beeby et al., 1994), 7.15 (Mikkelsen et al., 2017), and 7.20 (Mittendorf et al., 2008; Kato et al., 1996) as thresholds for group classification (i.e., acidotic vs. non-acidotic). In brief, whereas some studies use a severe acidosis cutoff and even coupled this cutoff with an additional BE cutoff, others used mild acidosis as a cutoff to define their target group. As noted above, it would appear that an arbitrary binary split of pH value, at any level, would restrict the statistical power needed for exploration of relationships with outcome variables.

Hypotheses and Rationale

As noted earlier, this proposal focuses on two risk factors associated with prematurity. Specifically, this project will explore an antenatal factor, multiple gestation, and a peripartum factor, arterial umbillical pH, a measure of acid-base status. The section below enumerates two hypotheses addressing the statistical effects of multiple birth, and one hypothesis addressing the effects of acid-base status on neuropsychological outcome, in preterm-born children.

1a. Hypothesis: *It is hypothesized that preterm (<34 weeks) preschoolers who are products of twin gestation will obtain lower scores on measures of cognitive, language, and motor abilities compared to preterm singletons, after taking into consideration variance accounted for by sociodemographic and perinatal factors.*

Rationale:

As described above, the rates of twin births have substantially increased in the last four decades, in part due to increased use of increased maternal age at birth and assisted reproductive technology. At the same time, and particularly since the early 90's, there have been several improvements in the neonatal intensive care unit, including use of prenatal steroids, prenatal

antibiotics, endotracheal intubation, resuscitation in delivery room, and the development of surfactant therapy (Patel et al., 2015). In addition to the aforementioned advents, universal resuscitation methods were applied to the care of infants born at the border of viability in WBH NICU since the 1990's (Batton et al., 2011). Increasingly thereafter, and particularly since the arrival of the new millennium, the use of universal resuscitation in many NICUs around the US has led to higher survival rates of children at the threshold of viability.

Twin gestations involve greater perinatal risks than singleton pregnancies (Boulet et al., 2008), with higher rates (11%; Martin et al., 2013) of very preterm births (<32 weeks), intrauterine growth restriction, and mortality (Martin et al., 2006). In addition, there are unique risks to twins related to growth rates, such as intrauterine crowding and twin-to-twin transfusion syndrome, frequently resulting in birthweight discordance within twin pairs (Cheung, Bocking, & Dalsiva 1995). Birthweight discordance has been purported to negatively influence neurodevelopment (Halling et al., 2014).

Not surprisingly, twins are also at higher risk than singletons for neurodevelopmental impairment that has been demonstrated to persist throughout early childhood. Twins have demonstrated poorer performance, when compared to singletons, in the visual processing, language, and intellectual domains (Voracek & Haubner, 2008; Raz et al., 2016). Yet there is dearth of research investigating the long-term neurodevelopmental outcomes of twin gestation, with only 3 of 10 extant studies devoted to preschool/school age children (see Table 1). Furthermore, there is paucity of research describing outcome of twin gestation in the new millennium, a period characterized by the aforementioned improvements in the NICU. As described in the literature review above (Introduction, page), only four of the studies included in Table 1 focused on preschool/school age in cohorts served by the NICU in the new millennium.

In addition to the rationale elaborated above, this study is expected to add to the body of literature on the topic of interest as 9 of the 10 reviewed studies (Table 1) were limited to comparisons of cognitive abilities of twins versus singletons. Other neuropsychological functional domains were not investigated. In brief, there is a dearth of information regarding intelligence and its components, language, and motor skills of twins in the preschool age. Thus, this study will further explore the neuropsychological outcome of preterm twins compared with the outcome of preterm singletons at early preschool age across these neuropsychological domains. In a previous investigation conducted with the current cohort of preterm preschoolers (Piercy et al., in preparation) significant differences between twins and singletons in language and motor outcome were discovered. However in that investigation, conducted with 22 twin-pairs, no intra-twin comparisons were conducted. In the current study I will increase the power significantly, with an anticipated total of 35 sets (37% increase) of pairs.

1b: Hypothesis: *It is hypothesized that neuropsychological outcome differences will be found within twin pairs based on within pair discrepancy in level of risk. Specifically, it is hypothesized that the co-twin at higher risk (i.e., lower birth weight, and/or greater number of perinatal complications) will obtain lower scores on measures of cognitive, language, and motor abilities compared to their lower risk co-twin.*

Rationale:

Intrauterine growth restriction, very low birthweight, and discordant birthweight are common in twins and have a significant impact on preterm-twins' later developmental outcomes (Ross, Krauss, & Perlman, 2012; Goyen, Veddovi,& Lui, 2003; Halling et al., 2015). Despite the shared uterine and postnatal environments, differences within twin pairs in morbidity and neurodevelopmental outcomes have been demonstrated (Steingass et al., 2013). More specifically,

birthweight discordance of 20% of more in either mono- or dichorionic twin pairs has been reported to result in a developmental disadvantage and neurodevelopmental impairment of the smaller twin (Halling et al., 2015; Ross, Kraus, & Perlman, 2012, see Table 2).

In the available literature, the study of risk within-twin pairs focused on several dimensions of twin-specific early biological risk, including birthweight discordance and birth order, both examined within pairs, and chorionicity, which may only be examined between pairs. As discussed above (Table 2), several of the studies reviewed (Ross, Krause & Perlman, 2012; Goyen, Veddovi, & Lui, 2003; Halling et al., 2015; Adegbite et al., 2003: Steingass et al., 2013) investigated a cohort of twins with discordant (greater than 15% difference) birthweights within pairs. Other studies listed in Table 2 (Kawurama et al., 2015; Adegbite et al., 2003; Steingass et al., 2013) investigated differences between the outcomes of monochrionic and dichorionic twin pairs, whereas a single study (Gnanedran et al., 2014) examined outcome differences between first and second born multiples. Only one study compared twins based on presence of various neonatal risks (i.e., small for gestational age, abnormal cranial ultrasound, sepsis/NEC, bronchopulmonary dysplasia) factors (Steingass et al., 2013).

As a result of investigation into birthweight discordance and outcome, a recent study by Halling and colleagues (2015) demonstrated the relative importance of prematurity (below 33 weeks) over and above the impact of birthweight discordance in a twin sample. Whereas 61 sets of premature twins participated in that study, term-born twins with discordant and concordant birth weights were also included. It is noteworthy that the authors reported worse performance in the smaller co-twin across domains and across gestational age, with adverse impacts of discordance occurring in multiples born below 33-weeks gestation. However, in this proposed study, the impact of birthweight discordance will be explored exclusively within the population of twins born before

34 weeks. Comparisons will be conducted in effort to elucidate the impact of birthweight discordance (i.e., between higher and lower weight co-twins) on neuropsychological outcomes.

Increased risk of adverse neurodevelopmental outcome was also identified in the study by Adegbite and colleagues (2003), where they compared preterm born monochorionic and dichorionic twins, with and without birth weight discordance. Although their study did not investigate intra-pair differences, they found higher rates of neurodevelopmental impairment (DQ <70) in the birth weight discordant MC and DC twin groups compared to the birth weight concordant MC and DC groups. In accord with the results reported by Halling and Adegbite, Steingass and colleagues found higher rates of neurodevelopmental impairment and cerebral palsy in in a sample of low birth weight (<1500 grams) toddlers within co-twin pairs who had discordant neonatal risk compared to twins concordant for risk. The investigators examined specific risk factors and identified each of the 88 twin sets as either concordant for a risk factor, discordant for a risk factor, or not characterized by the risk factor. This research group found relationships between discordant neonatal cerebral ultrasound (normal vs. abnormal) and either cerebral palsy or neurodevelopmental impairment at 20 months (i.e., higher rates of neurodevelopmental impairment and cerebral palsy in the co-twin with abnormal ultrasound). However, their study did not include twins weighing above 1500 grams, thus limiting the generalizability of the results.

Summary of Rationale

It is important to note that, of the studies reviewed, none extended beyond infancy and toddlerhood (max age 3 years, see Table 2). The current study will extend the current literature by focusing on preschool outcomes. In addition, the reviewed studies included only measures of cognitive outcome, cerebral palsy, or sensory impairment, and thus did not explore important neuropsychological (e.g., attention, visuospatial, visual-motor control) or motor domains (see

Table 4 for developmental outcome measures). Finally, whereas most studies considered birth weight discordance, only one reviewed study considered discordance for other perinatal indices of risk. In the current study, I propose to investigate differences between twin pairs in terms of degree of ante- and neonatal risk. In order to evaluate risk within twin pairs, the number of complications experienced by each child will be counted and subsequently compared within twin pairs (e.g., assigned as the twin with higher or lower number of complications).

2. Hypothesis: *It is hypothesized that hypoxic risk associated with birth and delivery, as indexed by arterial cord pH, will explain a unique portion of neuropsychological outcome variance in a preterm-born sample of preschoolers. Specifically, I expect arterial cord pH to explain preschool outcomes in this at-risk population, over and above the variance already accounted for by sociodemographic factors, as well as antenatal and neonatal risk factors.*

Rationale:

Umbilical cord pH is a biochemical index frequently used to evaluate intra-, or peripartum asphyxia, or asphyxia occurring during birth and delivery (D'Alton et al., 2014). As mentioned in the Introduction, low arterial cord pH (< 7; MacLennon, 2003; Morgan et al., 2016; D'Alton et al., 2014) is associated with increased risk of childhood mortality (Randolph et al., 2014), morbidity (van de Berg, 1996; Low, Panagiotopoulous, & Derrick, 2005; Victory et al., 2003), and cerebral palsy (Malin et al., 2004). Intrapartum asphyxia indexed by low arterial umbilical pH and metabolic acidosis (base deficit > 12; Morgan et al., 2014; D'Alton et al., 2014) amplifies the risk already associated with prematurity. As described above, the majority of studies exploring fetal or perinatal asphyxia are focused on perinatal medical outcome, or infancy outcome measures (see Table 3).

As shown in Table 3, and described in the review of intrapartum hypoxia/umbilical cord pH, 4 of 8 studies exploring the relationship between umbilical arterial pH and developmental outcome in preterm children found significant associations between lower arterial umbilical cord pH and adverse outcomes, including death (Randolph et al., 2014), neurodevelopmental impairment (Kato et al., 1996; Randolph et al., 2014), ADHD (Mikkelson et al., 2017), and higher rates of developmental delay than their non-acidotic (pH >7.0) counterparts (Lavrijsen et al., 2005). The remaining 4 studies found no long-term difference in development. Taken together, the extant literature is sparse with mixed results, and limited to infancy developmental screeners. The current study will focus on preschool outcome. Importantly, only 1 of the 8 studies reviewed examined long term outcome, and this was specific to the diagnosis of ADHD.

Four of the 8 available studies (Baenziger et al., 1999; Lavrijsen et al., 2005; Beeby et al., 1994; Kato et al., 1996) examined pH solely as a dichotomous variable (low pH vs normal pH), in accord with various medical conventions of arbitrary binary splits between normal and pathological pH (D'Alton et al., 2014). Three of the four remaining studies examined outcomes using umbilical arterial pH as both a dichotomous and continuous variable (Mikkelson et al., 2017; Huseman et al., 2011; Mittendorf et al., 2008). One study (Randolph et al., 2014) examined pH and base excess as continuous variables. Importantly, across the reviewed studies the threshold for pathological pH varied, with studies using pH <7.0 (Baenziger et al., 1999; Lavrijsen et al., 2005; Huseman et al., 2011), <7.1 (Beeby et al., 1994), and <7.2 (Mittendorf et al., 2008; Kato et al., 1996). In the current study, I will be treating acidemia (pH values) as a continuum, as such, anticipating greater sensitivity to statistical effects of acidemia on neuropsychological performance in the preschool age.

As demonstrated in Table 3, the available studies did not examine a variety of

neuropsychological domains. Of the 8 studies outlined, all used developmental scales for infants. (Bayley Scales of Infant Development, Griffiths Developmental Scale) and none of the studies utilized language or motor outcome measures. Only one study (Beeby et al., 1994) took perinatal neurological injury (e.g., IVH) into consideration. In the current study, a broad array of neuropsychological outcome measures will investigate cognitive, language, and motor outcomes in the preschool age.

CHAPTER 2. METHOD

Participants

Overall follow-up study

Two hundred and six subjects were recruited as part of a larger investigation titled Neuropsychological Outcome in Preschool and School Aged Children with Perinatal Complications and with Various Degrees of Exposure to Prenatal Steroids, approved by both William Beaumont Hospital (WBH) and Wayne State University (WSU) internal review boards. The parents of preterm-born preschoolers who were born and treated in the Neonatal Intensive Care Unit (NICU) at William Beaumont Hospital (Royal Oak, Michigan) were contacted to determine interest in participating in a follow-up neuropsychological evaluation of their children at three years of age. The children were evaluated between May 2011 and March 2018. The inclusion and exclusion criteria for the study are provided below.

Inclusion Criteria. We included children who were born before 34 completed gestational weeks and treated in the NICU between September 2007 and March 2014. The children's age ranged from three to four years (adjusted for prematurity) at the time of evaluation.

Exclusion Criteria. Infants were excluded from the cohort considered for follow-up under the following circumstances: presence of major congenital anomalies or chromosomal disorders, neonatal meningitis, or need for mechanical ventilation following discharge from the NICU. Infants were also excluded if they were born in another hospital and transported to WBH.

Recruitment. From the NICU cohort matching our inclusion and exclusion criteria (N = 848), 55% of the families could be contacted. Of these families, 41% (N = 155) were not interested in participation for multiple reasons (too busy, too far away, or did not want to travel to Detroit).

Families of 56 cases (7% of those contacted) were scheduled yet did not arrive for testing. The 207 available participants constituted 55% of contactable families and 25% of the total relevant cohort.

General Sample characteristics. Neuropsychological outcome data was available for 197 children recruited for the study. Five children with suspected antepartum exposure to drugs were excluded. One case was excluded as the child did not participate in the assessment or complete background history forms. Three children with cerebral palsy (spastic diplegia) and nine children with moderate-to- severe intracranial hemorrhage were included in the current study as they were able to complete at least partial testing. The statistical analyses were performed first with, and then without, these nine cases with neurological injury (labeled here as the "neurological subgroup").

Subsample used to investigate hypotheses associated with cord pH. As outlined in Figure 1, 207 children presented for evaluation for the study. Five cases with suspected drug abuse underwent testing but were excluded from statistical analyses. For the current study, children of triplet pregnancies (n = 9) were tested and later excluded from analyses. Of the remaining 193 children, 151 had arterial umbilical cord pH recorded at delivery (see flow-chart in Figure 1). These 151 cases did not differ from the 42 cases in terms of hospital stay, number of complications, gestational age, or birthweight. Tables 8-11 display data for the whole subsample of 151 cases, including thirteen cases with history of neural injury, the "neurological group" (six CP and seven severe ICH cases).

The demographic and socio-familial characteristics of the 151 cases with available cord pH are presented in Table 9. This sample was comprised of 45% males and included 65 children from twin gestation. Demographically, this sample was comprised of children from predominantly white, middle class families, with Average maternal IQ (Mean IQ =100.401 ± 12.37). The antenatal, perinatal, and neonatal complications for all 151 cases are depicted in Table 10. As

described in Table 10, the average gestational age for this sample was 30.6 weeks (± 2.64), with an average birthweight of 1503 grams (± 481.35). Neonatal risk factors experienced by this sample are also summarized in Table 10. Lastly, diagnostic and intervention procedures are depicted in Table 11. The majority of this sample (78%) was born via caesarean section, and nearly all (89%) mothers were administered steroids antenatally. Specific to this portion of the study, the variables associated with acid-base status based on umbilical cord arterial and venous blood samples are listed in Table 8. As may be expected, the average arterial cord pH (7.29 ± 0.07) was lower than the average venous cord pH (7.33 ± 0.07). As shown in Table 8, there were more cases with arterial cord pH than venous cord pH samples available.

Subsample used to compare twins and singletons. As demonstrated in Figure 1, 207 children presented for evaluation for the study. Five cases with suspected drug abuse underwent testing but were excluded from statistical analyses. For the current study, children of triplet pregnancies (n = 9) were tested and later excluded from analyses. Participants were divided into two groups based on type of gestation (singleton or twins). Altogether 83 multiples were available for this study. There were 38 sets of twins (9 male-male, 17 female-female, 12 male-female). Within the multiple group, in two sets of twins the co-twin was not tested as they were unable to cope with task demands due to severe functional impairment (one co-twin had cerebral palsy, while the other had cerebral palsy and periventricular leukomalacia). Seven children within the multiple gestation group (2 males and 5 females) did not have a co-twin available to test as they deceased prior to the current study (i.e., in utero or shortly following delivery). In total, for nine twins their outcome data for a co-twin was lacking. Altogether 109 singletons, and 83 children of twin gestation participated in this portion of the study.

The demographic and socio-familial characteristics of each group are presented in Table 5. As the table shows, the two groups were roughly comparable, with two exceptions. Significant group differences were observed in the level of paternal education (t (1, 188) = -2.152, p = .033), with fathers of multiples having more years of education than fathers of singletons. The adjusted age at testing was also slightly, though significantly, higher for children in the multiple group (t (1, 189) = -2.699, p = .008).

The antenatal, perinatal, and neonatal complications by type of gestation are described in Table 5. As the table shows, the groups did not differ in the total number of antenatal comps (t (1, 148.86) = 1.50, p = .135). However, the singleton group demonstrated a higher rate of three complications that typically lead to preterm birth, including placental abruption ((χ^2(1, N = 191) = 5.770, p = .016), histological chorioamnionitis (χ^2(1, N = 171) = 4.073, p = .044) and prolonged rupture of membranes ((χ^2(1, N = 188) = 9.316, p = .002). In contrast, higher rates of hyperthyroid was observed in the twin group ((χ^2(1, N = 191) = 7.69, p = .006). There were significantly higher rates of diabetes in the twins group (χ^2(1, N = 191) = 4.941, p = .026).

The groups did not differ significantly in perinatal status with the exception of higher occurrence of nuchal cord (χ^2(1, N = 191) = 3.864, p = .049) in singletons.

As shown in Table 6, the groups did not differ significantly in overall neonatal risk as indexed by the total neonatal complications score. There were significant group differences in the prevalence of retinopathy of prematurity ((χ^2(1, N = 192) = 6.320, p = .012) and sepsis ((χ^2(1, N = 192) = 5.155, p = .023), with higher rates of ROP and sepsis observed in the singletons group.

In terms of antenatal and neonatal diagnostic and intervention procedures (see Table 7), twin births were characterized by higher frequency of artificial reproductive techniques utilization (χ^2(3, N = 184) = 51.710, p < .001). As may be expected, the twins also had significantly higher

rates of birth by caesarean section (χ^2 (1, N = 192) = 13.690, $p < .001$). No other group differences were observed.

Overall, the groups were similar in total antenatal, perinatal, and neonatal complications as indicated by the ante- peri- and neonatal complication summary scores. However, the total number of complications (comprised of the sum of ante-, peri- and neonatal complications), was trending toward group differences (t (1, 190) = 2.153, p = .084), with the total complications summary score being greater in singletons.

Neuropsychological Assessment

General considerations. Each child was evaluated over 1 to 3 sessions depending upon the child's ability to maintain attention and focus during the assessment. The examiners were five clinical neuropsychology graduate students (four females, one male) trained extensively in developmental neuropsychological assessment. To prevent bias in administration and scoring, the graduate students were kept unaware of the child's medical history with the exception of the general knowledge of preterm birth status. The graduate students were supervised by a licensed psychologist weekly throughout the duration of the study. All testing and perinatal background data are obtained in compliance with the regulations of the Human Investigation committees of Wayne State University and William Beaumont Hospital, Royal Oak.

Prior to evaluation, the parents signed an informed consent form verifying that they understood the nature of the assessment and agreed to the outlined terms. During the evaluation, the parents completed a background questionnaire regarding their child's medical and developmental history. Following feedback, each parent was mailed a typed copy of a report sharing the results of their child's evaluation, including recommendations for further testing as needed.

Intellectual ability. Intellectual functioning was evaluated using the Wechsler Preschool and Primary Scale of Intelligence-Third Edition (WPPSI-III; Wechsler, 2002) or Wechsler Preschool and Primary Scale of Intelligence – Fourth Edition (WPPSI-IV; Wechsler, 2012). Reliability and validity properties can be found in Table 4. One subtest from the verbal subscale (Information) and one subtest from the performance subscale (Block Design) was administered to each child to obtain an estimate of overall intellectual ability (FSIQ), verbal ability (VIQ) and visual-spatial ability (PIQ). These two subtests were selected because they have the highest correlations with PIQ and VIQ respectively (Wechsler, 2002, 2012).

Motor ability. Gross and fine motor functioning were evaluated using the Peabody Developmental Motor Scales—Second Edition (PDMS-2; Folio & Fewell, 2000). Reliability and validity properties can be found in Table 4. The Total Motor Quotient (TMQ) is a composite of five gross and fine motor subtest scores, representing overall motor performance. The Gross Motor Quotient (GMQ) is comprised of three subtests: Stationary, Locomotion, and Object Manipulation. The Stationary subtest assesses the child's ability to maintain his or her balance (e.g., walking on a line, standing on tiptoes, etc.). The Locomotion subtest examines a child's ability to move around the room (e.g., running, skipping, jumping, etc.). The Object Manipulation subtest includes throwing, catching, and kicking balls. The Fine Motor Quotient (FMQ) is comprised of the Grasping and Visual-Motor Integration subtests. The Grasping subtest assesses the child's ability to grasp objects (e.g., blocks, markers) and control finger movements. The Visual-Motor Integration subtest evaluates hand-eye coordination (e.g., building structures, manipulating buttons).

Language ability. The Expressive Clinical Evaluation of Language Fundamentals—Preschool, Second Edition (CELF-P2; Wiig, Secord, & Semel, 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 properties for three and four-year olds can be found in Table 4. 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 Score (CLS), a composite measure of overall language performance, is comprised of three subtests: Sentence Structure, Word Structure, and Expressive Vocabulary. Sentence Structure requires the child to select a picture from a choice of four that corresponds to an oral prompt (e.g., "The child is sleepy."). In Word Structure, the child is given a picture and a partial phrase and is asked to complete the phrase based on the cues given (e.g., "Here is one dog. Here are two _____" [dogs]). Expressive Vocabulary is a one-word naming task in which the child is shown a picture and is asked to name the object (e.g., flag) or action (e.g., riding) shown.

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. Concepts and Following Directions is a complex language comprehension task in which the child is shown a set of pictures in the stimulus book and is asked to point to specific objects in a certain order (i.e., "Point to the big dog then the small cat") after a prompt ("Go"). For Basic Concepts, the child is show is asked to point to a concept spoken by the examiner (e.g., "point to the one that is full"). The Expressive Language Index (ELI) is a measure of language production, and it is comprised of Word Structure, Expressive Vocabulary, and Recalling Sentences. In the Recalling Sentences subtest, the examiner presents a sentence (of increasing length and complexity) and then asks the child to immediately repeat the sentence verbatim (e.g., say "The kindergartener cannot cross the street by himself").

Lastly, one subtest of the NEPSY-II (Korkman et al., 2007) was used to measure language skills: Word Generation. This subtest measured the child's ability to provide responses within a semantic category (e.g. things you can eat/drink, animals) within a 60 second time limit.

CHAPTER 3: RESULTS

Statistical Analyses

General statistical considerations: Mixed model multiple regression analyses was used to analyze the data for Hypothesis 1a (Table 12) and Hypothesis 2 (Table 16). To capture (i.e., take into consideration) the shared variance within each of the 38 pairs of co-twins, linear mixed effects model analyses were used with twin status as a random effect. In this model, the individual twins within each set were treated as replications with a common set-identifier. In contrast, singleton children or twins without an evaluated co-twin (i.e., fetal demise) did not have a replication and were considered a random block with size = 1 with their own unique identifier. This model allowed both twins and singletons to be used in the same analysis without either violating independence assumptions or discarding information about twin sets with the use of only one co-twin in analysis. For Hypothesis 1a, where the comparison between the groups of singletons and multiples was the focus of interest, singleton vs. twin birth (a dichotomous variable) was the predictor of interest (as well as a fixed effect).

For Hypothesis 1a and Hypothesis 2, the linear mixed models included an appropriate variable of interest (i.e., twin status, arterial cord pH, respectively) as well as sociodemographic and medical covariates. The two demographic variables were sex and SES (indexed by maternal and paternal education and occupation according to Hollingshead's four-factor index (Hollingshead, 1975). The three medical (perinatal) variables were gestational age (a continuous variable) and the intrauterine growth z-score (or birthweight SD), operationalized as the deviation of an infant's birth weight from the sex-specific mean weight for his/her gestational age, as specified by the reference norms published by Kramer and colleagues on a similar cohort (2001). The total number of complications, calculated as a sum of ante-, peri-, and neonatal risks (detailed in Table 6 and 10 footnote s) was also included as a covariate. The dependent (outcome) variables

across all three hypotheses included: intellectual, language, and motor indices as described in the neuropsychological assessment section above.

Finally, for Hypothesis 1b (Table 14 and 15), individual twins with missing co-twins were excluded to allow for investigation within the subsample of twin pairs. Within this subsample of 38 complete pairs, linear mixed effects model analyses were used with twin pair identification number (identical with "mother" or "family") as a random effect. For these analyses within the twin sample the pair random effect accounted for shared variance (correlations) between twins. For Hypothesis 1b, the comparison within twin pairs was the focus of interest. Discrepant risk, the predictor of interest, was indexed by an intra-pair difference in intrauterine growth (i.e., birthweight SD) in the first group of analyses (Table 14). In the second group of analyses, discrepant risk was captured by intra-pair differences in the total number of complications. Thus, intrauterine growth (twin pairs with birthweight discordance greater than .33 SD based on Kramer et al., 2001, gestational age-based reference norms) was defined as a minimum discrepancy. Altogether, 28 pairs had a discrepancy of ≥1/3 SD in birthweight and were therefore available for within-pair analysis. Differences in total complications (high risk twin with more complications =1, lower risk twin with fewer complications = 2) were set as fixed effects alongside sex. Pairs with equal number of complications were excluded from these analyses. In total, 27 pairs were included in the second group of analyses (see Table 15).

Hypothesis 1a: The relationships between twin gestation and neuropsychological outcome. Tables 12 and 13 present findings pertaining to Hypothesis 1a, for the 109 singletons and 83 children of twin birth. Prior to finalizing the models for analysis, sex by multiplicity interactions were examined for all outcomes. There were no significant interactions (p <.10 for all outcome variables). Therefore, the reduced model was used for all outcomes. As the table

shows, contrary to Hypothesis 1a, twin gestation was not associated with cognitive or motor performance. However, as the table shows, twin gestation was significantly associated with performance on NEPSY-2 Word Generation Subtest. Specifically, in contrast to the predicted direction, twins obtained *higher scores* than singletons on the NEPSY-2 Word Generation subtest [$t(1, 122.28) = 2.80$, $p = .006$ Table 12). As Table 12 (footnote b) reveals, this relationship remained significant following the exclusion of 13 "neurological" cases [$t(1, 107.23)$ 2.89 $p = .005$].

Hypothesis 1b: Within-twin pair discrepancies and neuropsychological outcomes. Table 14 and Table 15 depict the findings for Hypothesis 1b, an exploratory hypothesis investigating risk and neurodevelopmental outcome within twin pairs. The analyses explored neuropsychological outcome differences within-twin pairs, based on level of risk. Risk was determined based on either intrauterine growth discordance (intra-pair birthweight discrepancy >.33 SD) or as discordance for total complications.

As demonstrated in Table 14, in partial support of Hypothesis 1b, there were outcome differences between co-twins with discordant intrauterine growth. Consistent with Hypothesis 1b, there were significant differences between high and low risk twins with birthweight SD difference > .33 in both the cognitive and motor domains. As Table 14 shows, lower risk co-twins (higher intrauterine growth z score) obtained higher prorated FSIQ [t (1, 24.48) = 2.91, p = .008), primarily attributable to higher verbal intellectual performance [t (1, 23.15) = 2.34, p = .029 for Information subtest score). Consistently, lower risk co-twins also exhibited better Total Motor performance ($t(1, 26.99) = 2.40$, $p = .024$), primarily attributable to higher Gross Motor skills [t (1, 26.98) = 2.50, p = .024 for Gross Motor Index]. In contrast with Hypothesis 1b, however, (Table 15), there were no significant within-twin effects when risk discordance was determined on the basis of a difference

between co-twins in the total number of medical complications in the cognitive, language, or motor domains.

Hypothesis 2: The relationships between arterial cord pH and neuropsychological outcome. Table 16 presents findings pertaining to Hypothesis 2, investigating relationships between arterial cord pH and neuropsychological outcome in 151 preterm born preschoolers. No significant interactions were found on any outcome measure between sex and arterial cord pH, or multiplicity and arterial cord pH, and neuropsychological outcomes (p values ranged from .09 to .73). As such, the reduced model was used for all outcomes. As demonstrated in the table, consistent with Hypothesis 2, arterial cord pH explained a unique portion of the outcome variance across three separate domains: cognitive, language, and motor. Across domains, lower pH was invariably associated with poorer neuropsychological performance. As Table 16 shows, lower arterial pH was linked to poorer performances on the prorated FSIQ [$t(1, 145.90) = 2.06$, $p = .041$], primarily attributable to lower verbal intellectual performance [$t(1, 139.70) = 2.31$, $p = .022$ for Information subtest score]. Lower arterial cord pH was associated with poorer language skills [t (1, 131.79) = 2.06, $p = .041$ for Core Language Score]. This relationship was primarily explained by reduced expressive, but not receptive, [t (1, 128.17) = 2.81, $p = .006$ for Expressive Language Index] language skills. Lower arterial cord pH was also associated with reduced verbal fluency [$t(1, 128.60) = 2.01$, $p = .046$ for Word Generation]. Lastly, associations in the same direction were observed between arterial cord pH and Gross Motor performance [$t(1, 134.07) = 3.06$, $p = .003$].

Following exclusion of thirteen "neurological" cases the association between umbilical cord pH and the prorated FSIQ was reduced to a nonsignificant trend [$t(1, 134.45) = 1.88$, $p = .061$] (see Table 16, footnote b). This reduced effect, in turn, was likely influenced by the reduced

association between cord pH and verbal intellectual skills, as represented by the Information subtest [$t(127.65) = 1.83$, $p = .069$; see Table 16, footnote c). Similarly, when neurological cases were excluded and the version of WPPSI IQ test (third or fourth edition) was accounted for in the model, the relationship between arterial cord pH with both the prorated FSIQ and Information subtest was reduced to non-significant trends ($t(1, 134.76) = 1.92$, $p = .057$; $t(1, 128.704 = 1.88$, $p = .063$). However, as shown in the footnotes d-g of Table 16, following the exclusion of 13 "neurological" cases, the relationships between pH and outcomes in language (Core and Expressive Language indices, Word Generation subtest) and motor domains (Gross Motor) remained significant.

The relationships between socioeconomic status and neuropsychological outcome. As demonstrated in Table 12 and 16, as a covariate in the investigation of variables for specific hypotheses, significant associations were found between socioeconomic status (Hollingshead, 1975) and outcomes in the cognitive, language, and motor domains. In particular, children with higher socioeconomic status obtained higher scores on the WPPSI-III/IV Full Scale IQ, CELF-P2 Core, Receptive, and Expressive Language Indices, and PDMS-2 Fine Motor Quotient (see Table 12 and 15). These results remained significant following the exclusion of 13 neurological cases.

The relationships between sex and neuropsychological outcome. As demonstrated in Table 12 and 16, as a covariate in investigation of variables for specific hypotheses, significant associations were found between sex and outcomes across neuropsychological domains. Significant associations were found between sex and outcomes in the cognitive, language, and motor domains. More specifically, as demonstrated in Table 12 and 16, females outperformed their male counterparts and received higher standard scores on the WPPSI-III/IV Full Scale IQ,

CELF-P2 Core, Receptive, and Expressive Language Indices, and PDMS-2 Fine Motor Quotient. These results remained significant following the exclusion of 13 neurological cases.

CHAPTER 4. DISCUSSION

Overview of dissertation project

In this study I examined the developmental outcome contribution of early risk factors, the first antenatal (twin gestation), the second perinatal (degree of perinatal academia), in efforts to better understand neuropsychological outcomes in a sample of preterm born preschoolers.

My first hypothesis (Hypothesis 1a and b) focused on the outcome of multiple pregnancy (twins). The first component of my twin study (corresponding to Hypothesis 1a) was based on a sample of 192 children (83 twins and 109 singletons), with an average age of 44 months at evaluation. Here I examined outcome differences between twins and singletons that may be attributable to the type of gestation, predicting poorer performance in the higher-risk (i.e., twin) group. In the second, exploratory portion of my twin study (corresponding to Hypothesis 1b) I aimed to investigate differences within the twin group (n = 27 complete pairs of co-twins), specifically inquiring whether twins with higher level of risk (i.e., less optimal intrauterine growth as indexed by lower birth weight SD and higher number of perinatal complications) exhibited poorer performance across outcome domains than their lower risk co-twin.

To explore perinatal risk, I focused on a single variable of interest, arterial cord pH, to examine the relationships between perinatal hypoxia and neuropsychological performance (Hypothesis 2). To investigate whether lower (more acidic) arterial pH would be associated with poorer performance at preschool age. I used a subsample of 151 out of 192 preterm singletons and twins whose cord blood was analyzed and available for this investigation.

Discussion of findings from statistical analyses examining Hypothesis 1a:

My first hypothesis, that there would be poorer performance in twins than singletons across domains, was not supported. More specifically, as demonstrated in Table 12 and 13, there

were minimal differences between the twins and singletons across cognitive, motor, or language composite domains, with the only significant finding observed on a verbal fluency subtest, Word Generation. Notably, the significant association on this subtest revealed, in contrast to my hypothesis, a twin rather than singleton advantage. The remaining null findings are contrary to the previous results of our group (Raz et al., 2016), where twins exhibited poorer performance in both visual spatial processing and language. Null findings are also inconsistent with results of Wadhawan and colleagues (2009), who found higher rates of cerebral palsy and developmental delay in twins compared to singletons. It is possible that the discrepancies in results between the current investigation is related to differences in the age of the sample, as Wadhawan focused on infancy, and the previous investigation from our lab assessed differences at 5 years of age. It is possible that the disadvantage demonstrated in twins is less apparent in this stage of preschool development (age 3-4). As such, continued assessment will be useful to examine whether or not differences begin to manifest as the children grow into school age, and as task demand becomes more complex. In addition, changes in NICU care (e.g., Batton et al, 2011) that have been implemented in the US since the beginning of the new millennium, particularly in terms of enhanced resuscitation efforts at lower gestational ages, may also account for differences in the findings of outcome studies.

An important conclusion based on this portion of the current study is that in the new millennium, preterm twin birth does not appear to carry a poorer prognosis, relative to preterm singleton birth, in terms of neurodevelopmental outcomes in the preschool age. While these findings were discrepant with the proposed directional hypothesis, the comparable performance of twins and singletons is nonetheless consistent with the findings of several previous studies (Kyriakidou, Karagianni, & Iliodromiti, 2013; Hajnal et al., 2005; Asztalos, Barrett, Lacy, &

Luther, 2001; Eras et al., 2013; Einaudi et al., 2008; Gnanedran et al., 2014) who also found no significant differences between twins and singletons in neurodevelopmental outcomes.

The lack of differences demonstrated between twins and singletons leads one to consider the differences between these groups regarding etiology of premature birth. In the current total sample, although a non-significant trend, singletons were characterized by a higher overall number of complications (p = .084). Specific to the current sample, there was a significantly higher frequency of prolonged rupture of membranes, sepsis, chorioamnionitis, and retinopathy of prematurity in the singletons group. However, there were higher rates of diabetes and hypothyroid in the twins group. Despite the increased number of complications experienced by the singletons, comparisons adjusted as well as unadjusted for total complications revealed that singleton performance was similar to twins (who experienced fewer complications) across outcome domains. Of note, this finding is contrary to what one may anticipate, that the group with fewer complications (twin group in the current study) would outperform the group with a greater number of complications (singletons).

In this preschool age sample, preterm multiples were not at a disadvantage when compared to singleton counterparts and demonstrated comparable performances. However, it is important to highlight that the families recruited for this study were a predominantly white, educated group from middle class strata. Consistent with these demographics, a substantial portion of twin families (57% twins and 8% of singletons; Table 7) utilized artificial reproductive therapies. In addition to ART being a costly (both emotionally and physically) endeavor, it is important to consider the likely enhanced level of dedication experienced by parents who have put forth additional efforts to conceive a child (or children) using these methods. While not quantifiable in the current study (due to absence of a full-term comparison group), one may assume these parents would be

particularly active in early development and care for their children, seeking additional childhood care and interventions following preterm birth. Hence, in addition to the lower rate of complications in our twin group, enhanced motivation and increased access, supported by financial means, could potentially account for the equivalent performance of twins and singletons.

Discussion of findings from statistical analyses examining Hypothesis 1b:

As an exploratory follow-up to Hypothesis 1, in Hypothesis 1b, I aimed to better understand whether outcome differences within-twin pairs were related to level of risk. Specifically, I hypothesized poorer performance in the co-twin at greater risk, operationalized as either lower intrauterine growth or as having experienced a higher number of complications when compared with their co-twin. Intrauterine growth discordance was defined as within-pair birthweight SD differences > .33SD. Twins with fewer complications were deemed as lower risk than their co-twin. To address this exploratory hypothesis, I investigated outcomes in 28 pairs discordant for intrauterine growth and 27 pairs discordant for the total complications.

My prediction that twins at higher risk, as measured by growth discordance or number of complications, was partly supported. More specifically, in the anticipated direction, twins at higher risk demonstrated poorer performance in the cognitive and motor domains when compared to their lower risk counterparts. Specifically, when investigating risk as discordant birth weight (> .33SD), the lower birth weight co-twins showed significantly lower cognitive and motor performance. Notably, as demonstrated in Table 14, intrauterine growth accounted for 12.3% of the outcome variance in WPPSI-III/IV FSIQ, and 6% and 10% of outcome variance in PDMS-2 Total Motor and Gross Motor performance, respectively. No significant intra-pair differences were found in language outcomes when accounting for discordance in either intrauterine growth.

Additionally, in contrast with my predictions there were no significant within-pair effects when risk was defined in terms of complications in any outcome domain.

The exploratory hypothesis (Hypothesis 1b) was partly supported and my findings are consistent with previous literature documenting poorer cognitive performance in the smaller co-twins with discordant birthweight, at age 24-42 months (Halling et al., 2015) and age 3 (Goyen, Veddovi, & Lui, 2003; Ross, Krause, & Perlman, 2012). The results of the smaller co-twins (based on intrauterine growth in the current study, as defined above) demonstrating poorer cognitive performance is consistent with the findings of Ross and colleagues (2012) investigation of discordant and concordant twins. Consistent with Ross and colleagues, who found poorer performance in smaller discordant co-twins on both the VIQ and PIQ indices of the WPPSI-III, intra-pair differences in birthweight SD (intrauterine growth) were associated with a trend for discrepancy on the Information and Block Design subtest scores, in the predicted direction. The absence of statistically significant results for the VIQ and PIQ is likely due to the fact that my VIQ was based exclusively on the Information subtest, whereas the Performance IQ was based on Block Design. Additionally, Ross et al. (2012) used a smaller sample of twins discordant (>15% difference) for birthweight (16 twin pairs). Nonetheless, I was able to demonstrate that an intrapair discordance for one risk factor, i.e., birthweight SD, was associated with the FSIQ in accord with the predicted direction. However, this study was unique in the comparison of twins based on degree of risk as measured by number of complications, an investigation suggested by Ross and colleagues. As these analyses were conducted on a relatively small sample (27, 28 pairs), I believe that future investigations with a larger sample size may be required to promote our understanding of specific perinatal risks that have the capacity to modify neuropsychological outcome. Studies of twin pairs are well suited for the study of this relationship. In the current investigation,

intrauterine growth as indexed by birthweight SD, but not the sum of ante-, peri-, and neonatal complications was found to be significantly associated with cognitive and motor outcome, accounting for a 6 – 12 % of the variance, respectively (see Table 14). Future studies may investigate intra-pair differences in other risks, such as, for instance, perinatal hypoxia.

Discussion of findings from statistical analyses examining Hypothesis 2:

My second hypothesis, that increased hypoxic risk, as indexed by lower arterial cord pH would be linked to poorer performance at preschool age across neuropsychological domains was supported in the current investigation. As demonstrated in Table 16, umbilical cord pH was positively associated with WPPSI-III/IV FSIQ, CELF-P2 Core and Expressive Language Indices, and PDMS-2 Gross Motor performance. Specifically, arterial cord pH accounted for 2.5-3% of the variance in prorated intellectual/verbal performance, 6.5% of the variance in gross motor performance, and 7.4% of the variance in expressive language (Table 16). The results indicate that skills based on language and gross motor output are increasingly vulnerable to perinatal risk.

The results of the current study add to the growing area of literature investigating outcomes following acidosis. As demonstrated in the meta-analysis by Malin and colleagues, low umbilical cord pH is associated with adverse outcomes. However, few studies have investigated solely within the preterm population, and the samples were typically restricted to infants. The current findings are consistent with reported associations between arterial cord pH under 7.0 (Randolph et al., 2014; Lavrijsen et al., 2004) and 7.20 ((Kato et al., 1996) with poorer neuropsychological performance as documented in previous studies

The current study extends the understanding of the association between arterial cord pH and developmental outcomes to the preterm population. Moreover, the relationships here show higher levels of acidity (lower pH) was linearly related to decreases in cognitive, language, and

motor skills. Of note, the current investigation did not involve dichotomization of the arterial cord pH low pH consistent with perinatal hypoxia (e.g., <7.0 for metabolic acidemia) vs. normal pH (7.26; Acker, 2013). The perinatal pH levels in our study ranged from 6.95 to 7.42 and therefore the generalization of the findings of this investigation should be viewed as limited to this range. The findings of this study suggest that even in a sample with a restricted range of pH lower pH is associated with poorer cognitive, motor, and language domains at preschool age.

Perinatal hypoxic-ischemic risk is important to appreciate brain vulnerability during early development. During hypoxic-ischemic events, to maintain viability, cells alter their composition, structure, and associated maturation. Thus, the overall cellular environment in the developing brain is impacted. Perinatal hypoxic-ischemic events cause injury to vulnerable neurons and glia (astroglia, oligodendroglia; Salmaso, 2014). More specifically, Salmaso and colleagues propose perinatal hypoxia results impacts development globally, due to delay in the maturation of astroglia, oligodendria, and neurons. Animal research has specifically documented changes in brain functioning following perinatal hypoxic-ischemic brain damage, specifically to changes in functioning of potassium channels (Chen, et al., 2015) and reuptake of GABA in the hippocampus (Pozdnyakova, 2017), among others.

Consistent with cellular findings, MRI studies have documented grey matter, periventricular white matter damage, and delayed myelination among preterm born children (Skranes et al., 1997). White matter injury is the most common neuropathology associated with preterm birth, with abnormalities most commonly occurring within bilateral frontal, parietal and temporal regions (Volpe, 2009, Cheong et al., 2009). However, motor and/or cognitive disabilities associated with mild-to-moderate white and gray matter injury are also frequently present in this population (Volpe, 2009). MRI studies have also documented persistent gray

matter abnormalities in the preterm population. Meng and colleagues discovered adverse, interrelated white matter alterations and gray matter loss in a sample of preterm-born adults (2016). Further, a delay in gyral development with enlarged subarachnoid space in preterm infants was documented by Inder's group (2003), largely associated with the presence of WM abnormalities.

In one MRI study, Varghese and colleagues detail differences between term and preterm neonates following perinatal hypoxic-ischemic brain injury. Basal ganglia, the thalamus, internal capsule, cortex, subcortical and periventricular white matter, and medial temporal lobe are described as the usual sites of brain injury in hypoxia-ischemia (Varghese et al., 2016). In the preterm neonate, mild to moderate hypoperfusion (inadequate oxygen supply) results in germinal matrix hemorrhages and periventricular leukomalacia; a white matter brain injury near the lateral ventricles. In contrast, severe insult is associated with damage to the deep gray matter (thalamus, dorsal brainstem, vermis) and the early or actively myelinating fibers (Varghese et al., 2016).

The current study further investigates relationships between perinatal hypoxia and developmental outcomes. More specifically, the current investigation demonstrates that increased risk to perinatal hypoxia is associated with poorer outcomes. However, it is important to note that some view pH as a biomarker of poorer medical status (Lynn & Beeby, 2006; Malin et al., 2010), which may or may not necessary equate solely to hypoxia risk.

Although this study focused on ante- and perinatal risk factors during pregnancy, sociodemographic factors were considered and investigated throughout both investigations. As SES has been established as a critical, if not the best, predictor of development among preterm children (e.g. Raz et al., 2015; Taylor et al., 2011; Wild, Betancourt, Brodsky, & Hurt, 2013), it was included and reviewed as central to the understanding of neurodevelopment in preterm born

preschoolers. At the cellular level, Salmaso and colleagues propose environmental enrichment may support or accelerate maturation processes and therefore reverse delayed maturation in brain cell types; with increased angiogenesis, dendritic complexity, and synaptic connectivity (2014). In the current investigation, across three hypothesis, SES accounted for a substantial proportion of the outcome variance (ranging for up to 10-16% of the model variance; Table 12-16). Consistent with previous studies, the effect of socioeconomic status on neuropsychological development was substantial across cognitive, motor, and fine motor domains.

A female advantage was evident across multiple measures reflecting findings addressing Hypothesis 1a, 1b, and 2. This advantage was evident on cognitive, language, and fine motor skills. Specifically, across the three hypothesis, sex accounted for a substantial portion of the variance, from 14% - 25% in fine motor skills (see Tables 12- 16). This female advantage is consistent with previous studies in the preterm population, as there has been ample documentation that males typically underperform compared to females (Skiöld et al., 2014; Raz et al., 1994; Lauterbach, Raz & Sanders, 2001; Peters, Heitzer, Piercy & Raz, 2014; Wolke et al., 2008; Sansavini et al., 2006).

Limitations and Future Directions:

Despite the breadth of this project, there are limitations of the current study that should be addressed in future research. First, it is important to note that perinatal and neonatal medical risk data were collected retrospectively. In terms of overall design, the study was retrospective, and cross-sectional. A longitudinal study design would allow further exploration of this vulnerable population over time. As such, additional data over early childhood would help to elucidate these relationships through neurodevelopmental periods. Lastly in terms of design, although recruiting efforts were put forth to all families born in the NICU, there could be a distinction between families who choose to participate and those who declined, yet the reasons for declining

participation could not be thoroughly investigated as nonparticipating families could not be thoroughly queried due to IRB constraints.

The preschool age is a pivotal period for cognitive development that warrants detailed study; however, there are unique challenges to assessment at this age, including cooperation, comprehension of instructions, and behavioral/attention issues. These concerns often result in higher rates of missing data than when children are seen at older ages. Therefore, a limitation in preschool age studies is the amount of missing data for the current study. In the current study with the full database, missing data was minimal for the cognitive and motor domains (<10%) with increased missing data for expressive language (11-12%). The CELF-P2 Expressive Language Index has notable language output demands. The highest missing data proportion (14%) was found on the Word Generation subtest, a subtest with notable executive and language demands. As such, with children who were unable to complete these measures excluded, the results of the current study could potentially be a lower estimate of the range of scores not captured by children with lower language functioning.

As seen in the results, social economic status was associated with outcomes across domains. It must be noted that our sample was relatively homogenous in term of SES, representing various middle-class substrata. While reducing the potential confounds associated with low SES allows for greater internal validity in studying the outcome effects of the medical risks central to this study, examination of more diverse SES samples should be the next step. Further, within this our (mostly) middle class SES strata, families had additional access to interventions such as speech, occupational, and physical therapy, all of which may moderate the impact of premature birth on outcomes as measured in the preschool years. This access available to families of higher SES is likely not seen in lower SES preterm counterparts. It is therefore important to consider the

potentially moderating influence of SES on outcome using more socioeconomically heterogeneous samples.

Table 1.
Literature Comparing Neuropsychological Outcomes of Twins and Singletons born Preterm

Author & Year	**GA-Cut off/BW cut-off**	**N per group Cohort birth year**	**Age at Testing**	**Comparison Group/Matching**	**Exclusion**	**Outcome Measures**	**Covariance/ Matching**	**Results**
Kyriakidou, Karagianni, & Iliodromiti, 2013	25-34 weeks	46 twins, 46 singletons	24 months corrected age	Singleton matched for gender and gestational age	Chromosomal anomalies, major genetic syndromes	Hammersmith infant neurological examination, Bayley Scales of Infant Development-III		No significant differences found between twins and singletons on the Bayley-III scales.
Hajnal et al., 2005:	<1250g	Cohort 2; 26 members of twin-sets and 9 members of triplets, compared to 57 singletons.	2 years corrected age	Cohort 2: low birth weight multiples compared to singletons	Death, CP, sensory deficit	BSID (MDI and PDI) Developmental delay <84, MR or severe motor delay <68		No significant differences between multiples and singletons in terms of CP, cognitive, or motor outcome. Within the multiple group, males were at significantly increased risk for severe cognitive delay compared to females
Wadhawan et al., 2009	401-1000g	7630 singletons, 1376 twins	18-22 months corrected age	Twin-singleton	Death before 12 hours of life, triplets and higher order multiples	Amiel-Tison, BSID-II, death, neurodevelopmental impairment (one or more of CP, blindness, bilateral hearing loss needing amplification, BSID-II MDI < 70, PDI <70)		Twins showed higher rates of CP as well as higher rates of developmental delay, with significantly more frequent occurrence of very low MDI and PDI (<70) compared to singletons.
Manuck, Sheng, Yoder & Varner, 2014	<34 weeks	1771 total, 302 twins	24 months corrected age		Chromosomal abnormalities, congenital malformation, incomplete outcome data, death in NICU, major anomaly or aneuploidy, lost to follow up	BSID-II, Gross Motor Function Classification System for CP severity, Neurodevelopmental impairment (defined as Moderate- Severe CP and/or Bayley MDI and/or PDI >2SD below mean).	Gestational age, maternal education, maternal race, tobacco/alcohol/ drugs during pregnancy, treatment group (magnesium sulfate vs. placebo), fetal sex, chorioamnionitis	Multiplicity did not significantly contribute to outcome variance.
Raz et al., 2016	<34 weeks	77 twins, 144 singletons	3-6 years corrected age	Twin-singleton comparison	Outborn, congenital anomalies, required ventilation after discharge.	WJ-III, PLS-3, PDMS-2	Birth weight, intrauterine growth, total complications.	Performance significantly lower in twins than singleton counterparts in visual processing and language indices.

Table 1. Continued

Author & Year	GA-Cut off/BW cut-off	N per group Birth year	Age at Testing	Comparison Group/Matching	Exclusion	Outcome Measures	Covariance/ Matching	Results
Asztalos, Barrett, Lacy, & Luther, 2001	24-30 weeks	52 sets of twins, 101 singleton infants	18-24 months corrected age	Singleton matched for gender and gestational age	Lost to follow up	Bayley Scales of Infant Development-Second Edition (BSID-II), Death, or neurodevelopmental deficit (deficit in one or more: visual, hearing, motor, cognitive domains).		No significant differences between twins and singletons in neurodevelopmental outcome.
Eras et al., 2013;	<32 weeks	159 multiples, 211 singletons	12-18 months corrected age	Cohort of preterm singletons	Death, lost to follow up	BSID -II. Neurodevelopmental impairment (any of: CP, bilateral blindness, bilateral deafness, BSID indices <70)		No significant differences between multiples and singletons in neurodevelopmental outcome.
Bodeau-Livinec et al., 2013	22-32 weeks	415 twins, 1058 singletons	5 years	Preterm singletons	Non-ambulatory CP, walking with aid, visual deficiency, hearing loss, could not complete testing.	Kaufman Assessment Battery for Children: Mental Processing Composite scale	GA, gender, IUGR, prenatal steroids, sociodemographics (maternal age, parity, maternal education, maternal birthplace, family social class).	
Einaudi et al., 2008	26-32 weeks	23 twins, 31 singletons	4 years	Preterm singletons	Death, CP, sensory deficit	Battery for Rapid Evaluation of Cognitive Functions (BREV)		No significant differences between twins and singletons on BREV cognitive domains.
Gnanedran et al., 2014	<29 weeks	392 multiples and 1081 singletons 182 first born, 210 second born multip-les	2-3 years corrected age	Twin – singleton comparison First born – second born comparison		Griffiths Developmental Scales (GQ) or BSID-II, cerebral palsy, sensorineural or conductive deafness, bilateral blindness.	Apgar score, antenatal corticosteroid, pregnancy-induced hypertension, outborn, gender, gestational age, assisted conception, postnatal corticosteroids, birth weight.	No difference was found between twins and singletons, or first and second born multiples in functional disability when compared to singletons.

Table 2.
Studies exploring biological factors influencing neurodevelopmental outcomes within twin cohorts born preterm or with low birthweight

Author & Year	**GA-Cut off/BW cut-off**	**N per group Cohort birth year**	**Age at Testing**	**Comparison Group /Matching**	**Exclusion**	**Outcome Measures**	**Covariance/ Matching**	**Results**
Ross, Krause & Perlman, 2012	15% or more BW discordance <36 weeks gestation	84 members of twin sets 52 concorda-nt twins, 32 discor-dant	3 years	Within-pair comparison between higher and lower birth weight twins.	Major congenital anomalies, congenital syndromes, ongoing medical illness	Wechsler Preschool and Primary Scale of Intelligence-III		The smaller discordant birth weight twins displayed significantly lower Verbal, Performance, and FSIQ scores than their larger co-twins.
Goyen, Veddovi, & Lui, 2003	15% or more BW discordance One or both VLBW (<1500 grams)	21 pairs of discord-ant twins 1987-1994	3 years	Within pair comparison between higher and lower birth weight discordant co-twins. 26 VLBW non-discordant pairs as comparison group		Griffiths Developmental Quotient (GQ), height, weight, head circumference	Gestational age, percent discordance, maternal and paternal education and occupation.	The smaller discordant birth weight twins displayed significantly lower performance in GQ. Largest difference in locomotor scale. Greater intra-pair GQ difference in 12 pairs with discordance >30%.
Gnanedr-an et al., 2014	<29 weeks gestation	392 multiples and 1081 singletons 182 first born, 210 second born multiples 1998-2004	2-3 years correct-ed age	Twin – singleton comparison First born – second born twin comparison		Griffiths Developmental Scales (GQ) or Bayley Scales of Infant Development Second Edition (BSID-II), cerebral palsy, sensorineural or conductive deafness, bilateral blindness.	Apgar score, antenatal corticosteroid, pregnancy-induced hypertension, outborn, gender, gestational age, assisted conception, postnatal corticosteroids , birth weight.	No difference was found between twins and singletons, or first and second born multiples in functional disability when compared to singletons.

Table 2. Continued

Author & Year	GA-Cut off/BW cut-off	N per group Cohort birth year	Age at Testing	Comparison Group /Matching	Exclusion	Outcome Measures	Covariance/ Matching	Results
Halling et al., 2015	>20% BW discordance GA: <30, 30-32, 32-34, 34-36, 36-37, >37 weeks BW: 2221 ±700gm	119 discordant pairs (24 MC twins) 2007-2010	24-42 months	Intra-pair differences 119 discordant compared to 111 concordant birth weight pairs	Chromosomal abnormalities, autism, monoamniotic twins, single twin survivors	BSID-III. Bayley Social Emotional and Adaptive Behavior Questionnaire, Child Behavior Checklist	Chronicity, prematurity	Smaller twin performed worse in cognition, language, and motor skills. No difference between the smaller and larger twins in adaptive or social-emotional behaviors. Prior to 33 weeks gestational age adversely effects cognitive development beyond effect of discordance.
Kawamura et al., 2015	<1500g	162 infants: 79 DCDA, 83 MCDA twins 2003-2010	24-48 months of age	MCDA compared to DCDA twins.	MCMA twins, acardiac twins, conjoined twins, chromosomal abnormalities, severe congenital heart disease, major malformations.	Composite of adverse outcomes (death, cerebral palsy, developmental delay). Kyoto Scale of Psychological Development Scale (DQ <70)		No significant differences were found between DCDA and MCDA twins in developmental delay, cerebral palsy, death, or adverse outcomes composite.
Adegbite et al., 2003	24-34 weeks gestation Discordant BW (>20%)	76 MC and 78 DC twins 1991-1997	2 years	MC compared to DC twins.	Pregnancies complicated by fetal aneuploidy, congenital malformation, feticide, embryo reduction, intrauterine death, incomplete data sets.	Cerebral palsy diagnosis, Griffith's Mental Development Scales (Developmental delay if Developmental Quotient <70).		Neurodevelopmental impairment higher in MC and DC infants with discordant birthweight than concordant twin. Higher risk of cerebral palsy in MC than DC infants.

Table 2. Continued

Author & Year	GA-Cut off/BW cut-off	N per group Cohort birth year	Age at Testing	Comparison Group /Matching	Exclusion	Outcome Measures	Covariance/ Matching	Results
Steingass et al., 2013	<1500 grams twins >15% BW discordance	88 twin pairs 1992-2005	20 months corrected age	Intra-pair differences in neurodevelopmental outcome between twins discordant for neonatal risk (i.e., SGA, abnormal ultrasound, BPD, sepsis) and intra-pair differences between lower and higher birth weight co-twins. MC compared to DC.	Congenital malformations	Bayley Scales of Infant Development Second and Third Edition. Neurodevelopmental impairment (MDI <70, deafness, blindness, cerebral palsy).	Gestational age, gender, maternal education	Higher rates of discordant neonatal risk (cerebral ultrasound) in twins with NDI. Birth weight discordance >15% was not associated with 20-month outcomes. No difference in neonatal risk or neurodevelopmental outcomes between MC and DC twin pairs.
Gonzalez-Mesa, Cazorla-Granandos & Gonzalez-Valenzuela, 2016	32-34; 34-37; >37 weeks	62 pairs 2005	6 years	First born-second born comparison across gestational age groups	Born less than 32 gestational weeks, children below first year of school	Neuropsychological Mature Questionnaire, Kaufman Intelligence Test, Psychoeped-agogic EVALUA-1 Battery	Backward stepwise inclusion, three blocks of variables including sociodemographic variables (maternal education) and clinical variables (mode of delivery)	Lower scores in preterm, second-twin males born vaginally in spatial structuring, nonverbal, and total development scores.

Table 3.

Investigations of Neuropsychological Outcomes and Arterial Cord pH in Preterm Born Children

Authors, Year	**GA-Cut off/ BW cut-off**	**Acidem-ic group Birth years**	**Acid-emia cut offs**	**Control Group**	**Age**	**Exclusion**	**Outcome Measures**	**Statistical Adjustment**	**Results**
Randolph, 2014	ELBW (<1000 g)	249 ELBW infants with acidosis 2002-2007	ACpH < 7.0 or BE <-12 mEq/L	3730 ELBW infants without acidosis	1 year	Congenital anomalies (heart defects, chromosom-al anomalies, CNS abnormal-ities)	NDI, defined as Bayley– II (MDI or PDI <70) or Bayley-III (cognitive index < 85) Gross Motor Function Classification System	Gestational age, birth weight, multiple gestation, sex, insurance, maternal hypertension, steroids	Acidosis significantly associated with death and NDI, grade III/IV IVH. After adjustments, acidosis predicted little above Apgar.
Lavrijsen et al., 2004	<32 weeks <1500 grams	44 acidotic preterm infants 1994-2002	ACpH <7.0	67 non-acidotic controls	1 year	Congenital anomalies, outborn, GA unclear, missing follow up data	Griffiths Developmen-tal Scale (<85 developmental quotient), cerebral palsy, IVH, seizures		Significantly more adverse outcomes (IVH, seizures) in preterm group, more severe development al delay in preterm group. No long term adverse outcomes in acidemia group.
Beeby et al., 1994	<32 weeks	58 preterm infants with ACpH <7.10 1985-1990	ACpH <7.10	565 preterm infants with ACpH > 7.1	1 year	Congenital anomalies	Griffiths Developmenta l Scale (DQ), CP diagnosis	Grade III/IV IVH, birth weight, HMD, antenatal steroids	ACpH was not a useful predictor of CP, death, or development-al quotient at one-year of age.

Table 3. Continued

Authors, Year	GA-Cut off/ BW cut-off	Acidem-ic group Birth years	Acid-emia cut offs	Control Group	Age	Exclusion	Outcome Measures	Statistical Adjustment	Results
Mikkelsen et al., 2017		9924 infants with ACpH <7.10 1991-2002	ACpH <7.10, 7.10-7.19, > 7.20	46 706 infants with ACpH 7.10-7.19, 239 057 infants with ACpH > 7.20	5-16 years	Multiples	ADHD diagnosis by ICD.10-Hyperkinetic disorder diagnosis	Smoking, parity, smoking, birth year, SES, marital status, birthweight, maternal age.	Low ACpH associated with increased risk of ADHD. Strongest relationships ACpH <7.15 and gestational age <32 weeks. Continuous ACpH relationship with lower ACpH higher risk of ADHD.
Kato et al., 1996	<1500 grams	23 infants with ACpH <7.2 1991	ACpH <7.20	124 infants with ACpH >7.2		Congenital anomalies, multiples, death	Cerebral palsy, mental retardation	Stepwise regression (mal-presentation, tocolytics, cord pH)	Mean ACpH significantly lower in the CP/MR group.
Huseman et al., 2011	< 35 weeks <1500 grams	1137 VLBW infants with ACpH and BE collected 1992-2004	ACpH <7.0, Base excess < - 16	Preterm infants with ACpH >7.0	12 mo. (N = 820) and 20 mo. (N= 551)		Griffiths Development al Scale; (NDI =DQ <75)		No relationship between ACpH and death or NDI. Weak predictive power of pH and development-al outcome at 12 or 20 months.
Mittendorf, 2008	<34 weeks	17 infants with ACpH <7.20 1995-1997	AVpH and ACpH < 7.20	83 infants with ACpH >7.20	18 mo.	Maternal infection, preeclampsia, antenatal steroid use, requiring reassuring fetal assessment.	Bayley PDI		No relation between ACpH or VCpH and Bayley PDI

BW: Birthweight; MC: monochorionic; DC: dichorionic; ACpH: Arterial cord pH; VCpH: Venous cord pH; DQ: Developmental Quotient; PDI: Psychomotor Developmental Index; NDI: neurodevelopmental impairment; HMD: hyaline membrane disease; IVH: intraventricular hemorrhag

Table 4.
Psychometric Properties of Cognitive, Language, and Motor measures

		Internal Consistency		Test-Retest Reliability	
		3 years old	4 years old	3 years old	4 years old
COGNITIVE:					
WPPSI-III	Block Design	.84 (all ages)		.9 (2:6- 3:11)	.5 (4:0- 5:5)
	Information	.88 (all ages)		.3 (2:6-3:11)	.9 (4:0-5:5)
	FSIQ (prorated)	.713	NA	.919	NA
WPPSI-IV	Block Design	NA	NA	.81 (all ages)	
	Information	NA	NA	.83 (all ages)	
	FSIQ (prorated)	NA	NA	NA	NA
MOTOR:					
PDMS-2	Stationary	.71	.77	NA	NA
	Locomotion	.95	.96	NA	NA
	Object Manipulation	.90	.92	NA	NA
	Grasping	.74	.96	NA	NA
	Visual-Motor Integration	.94	.96	NA	NA
	Gross Motor Quotient	.93	.94	NA	NA
	Fine Motor Quotient	.91	.98	NA	NA
	Total Motor Quotient	.95	.97	NA	NA
NEPSY-II					
	Word Generation (Semantic total score)	.59	.59	NA	NA
LANGUAGE:					
CELF-P2	Core Language	3:0-3:5: .91 3:6-3:11: .91	4:0-4:5: .93 4:6-4:11: .93	.92	.89
	Receptive Language	3:0-3:5: .91 3:6-3:11: .92	4:0-4:5: .94 4:6-4:11: .91	.92	.95
	Expressive Language	3:0-3:5: .93 3:6-3:11: .92	4:0-4:5: .94 4:6-4:11: .94	.95	.92

Table 5.
Group Comparison of Demographic and Sociofamilial Characteristics

Characteristics	Singletons (n = 109)	Twins (n = 83)
Adjusted age (mos.)[a] **	44.204 ± 3.00 [38.60 – 53]	45.332 ± 2.672 [40.90 -53.10]
Gender (M:F)[b]	54:55 [50%:50%]	33:50 [40%:60%]
Race (W:O)[c]	83:25 [77%: 23%]	72:11 [87%:13%]
SES[d]	49.216 ± 10.397 [24-66]	48.157 ± 9.630 [24-66]
Maternal VIQ[e]	100.587 ± 12.295 (92) [70-136]	99.735 ± 10.922 (68) [74-122]
Mother's education (yrs.)	16.203 ± 1.902 [11-20]	16.222 ± 1.753 (81) [12-20]
Father's education (yrs.)*	15.268 ±2.35 [10-20]	15.952 ± 1.841 [12-20]

*$p < .05$, **$p < .01$, ***$p < .001$, # $p < .10$

Note. Frequencies are reported for discrete data, means and standard deviations for continuous data. t-tests were used to test continuous data; 2x2 chi-square with Yates correction were used for discrete data, and Fisher's exact probability test were used for discrete data with less than five cases per cell. In the case of missing data, number of subjects used in calculating group means and SD's is provided in parentheses.

a Adjusted age at first testing session

b M=male, F=female

c W=White, O = Other (Singletons: 23 African American, 2 Indian; Twins: 9 African American, 2 Indian)

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 (Wechsler, 2008); Testing was completed on the biological mothers in all 91 singleton cases (one father completed), and all 68 cases in twin group.

Table 6.
Antenatal, Perinatal, and Neonatal Factors by Group[a]

Characteristics	Singletons n = 109	Twins n = 83
Antenatal Complications		
*Abruption of the placenta (per OB)**	21 [19%]	6 [7%]
Chorioamnionitis[a] *(histological)**	28 (97)[29%]	12 (75) [16%]
Diabetes[b]*	9 [8%]	16 [19%]
HELLP syndrome[c]	7 [6%]	5 [6%]
Hypertension in pregnancy	42 [39%]	25 [30%]
Intrauterine growth (z-score)[d]	-.172 ± .872 [-2.40-2.42]	-.2195 ± .695 [-.199-1.20]
Membranes ruptured >12hrs[e]**	34(105) [32%]	11 [13%]
Previa	11 [10%]	7 [9%]
*Maternal hypothyroid***	11 [10%]	21 [25%]
Mother's age at delivery (years)	32.868 ± 4.865 (106) [21-45]	32.781 ± 4.682 [24-46]
Oligohydraminos	7 (101) [7%]	8 (76) [11%]
Parity	.729 ± .875 (107) [0-3]	.710 ± .982 [0-5]
Smoking during pregnancy[f]	3 [3%]	2 (81) [2%]
Total antenatal complications[g~]	1.574 ± .909 [0-4]	1.337 ± 1.119 [0-4]
Perinatal Factors		
Abnormal presentation[h]	43 [39%]	40 [48%]
Birth weight (g)	1470.20 ± 528.61 [490-3070]	1498.47 ± 419.91[576-2507]
Birth length (cm)	39.84 ± 5.09 [28.5-49.5]	40.570 ± 4.014 [30.8- 49.5]
Birth head circumf. (cm)	27.83± 3.06(108) [19.3 -33.5]	28.51 ± 2.61 [21-34]
Gestational age (weeks)[i]	30.34 ± 2.78 [23.6 – 33.9]	30.83 ± 2.53 [24.3-33.9]
Nuchal cord	25 [23%]	10 [12%]
1 minute Apgar	6.43 ± 2.22 [1-9]	6.95 ± 1.814 [1-9}
5 minute Apgar	8.110 ± 1.157 [3-9]	8.325 ± .912 [4-9]
Total perinatal complications[j]	.630 ± 0.573 [0-2]	.602 ± 0.562[0-2]

Table 6. Continued

Characteristics	Singletons n = 109	Twins n = 83
Neonatal Factors		
Anemia at birth[k]	19 (105) [18%]	9 (81)[11%]
Apnea	69 [63%]	52 [63%]
Bronchopulmonary dysplasia	22 [20%]	13 [16%]
Hyaline membrane disease[l]	66 [61%]	45 [54%]
Hyperbilirubinemia[m]	13 [12%]	8 [10%]
Hypoglycemia	17 [16%]	18 [22%]
Intracranial hemorrhage[o]	17 [16%]	13 [16%]
Necrotizing enterocolitis[p]	6 [6%]	2 [2%]
Patent ductus arteriosus[q]	21 [19%]	16 [19%]
Peak bilirubin (mg/dl)~	9.15 ± 2.29 (107) [4.90-16.90]	8.95 ± 2.08 [4.70-14.40]
Pneumothorax	3 [3%]	3 [4%]
Retinopathy of prematurity*	20 [18%]	5 [6%]
Sepsis (initial or acquired[r]*	12 [11%]	2 [2%]
Thrombocytopenia	14 [13%]	6 [7%]
Total neonatal complications[s]	1.862 ± 1.702 [0-7]	1.578 ± 1.354 [0-5]
Total complications[t]	4.045 ± 2.165 [1-11]	3.518 ± 2.020 [1-10]

*p < .05, **p < .01, ***p < .001, ~ p <.10

Note. Frequencies are reported for discrete data, means and standard deviations for continuous data. t-tests were used to test continuous data; 2x2 chi-square with Yates correction were used for discrete data, and Fisher's exact probability test were used for discrete data with less than five cases per cell. In the case of missing data, number of subjects used in calculating group means and SD's is provided in parentheses.

a. Includes only cases confirmed via histopathology (with or without funisitis)

b. Includes both gestational diabetes and diabetes mellitus.

c. Hemolysis, elevated liver enzymes and low platelets.

d. A z-score expressing the deviation of an infant's birth weight from the mean weight of his/her gestational age group, at delivery, according to norms published by Kramer et al. (2001).

e. Time from spontaneous or artificial rupture of membranes to delivery.

f. Smoking behavior: >30 Weeks Group: 1 case < 5 cigarettes per day

g. Total antepartum complications includes placental abruption, chorioamnionitis, maternal diabetes, HELLP syndrome, maternal hypertension, membranes ruptured >12 hours, previa, oligohydramnios, maternal hypothyroid.

h. Includes various atypical presentations such as breech or transverse lie.

i. As determined by obstetrician; > 95% of cases were corroborated by antenatal ultrasound.

j Total perinatal complications include abnormal presentation and nuchal cord.

k Initial hematocrit < 40 %
l Based on a chest roentgenogram and clinical evaluation.
m Peak bilirubin ≥ 12 mg/dl
n Requiring treatment
o Documented on the basis of cranial ultrasound.
p Documented by radiographic changes, positive stool and abdominal distention.
q Diagnosed by clinical manifestations and echocardiographic information.
r Established by positive blood culture.
s. Total neonatal complications includes anemia at birth, hyaline membrane disease, bronchopulmonary dysplasia, hyperbilirubinemia, hypoglycemia, intracranial hemorrhage, patent ductus arteriosus, sepsis, and need for oxygen following discharge (see below in Table 7 detailing intervention procedures)
t. Total complications calculated as sum of perinatal, neonatal, and antenatal complications (listed above in g, j, and s).

Table 7.
Antenatal and Neonatal Diagnostic and Intervention Procedures[a] by Group

Diagnostic and intervention procedures	Singletons (n = 109)	Twins (n = 83)
Cesarean section***	74 [68%]	75 [90%]
Forceps	1 [1%]	2 [2%]
General anesthesia	8 [7%]	9 [11%]
Artificial Reproduction Techniques***	11 (5 IVF, 4 Clomid, 2 Other) [8.26%]	47 (35 IVF, 5 Clomid, 7 Other) [57%]
Antenatal magnesium sulfate[b]	77 [71%]	64 [77%]
Antenatal steroids[c]	98 [90%]	73 [88%]
Antenatal steroids dose	1.603 ± .682 (106) [0-2]	1.446 ± .702 (83) [0-2]
Hypertension medications (m)	30 (106) [28%]	22 (82) [27%]
Days in NICU	46.027 ± 41.320 [3-245]	37.916 ± 23.864 [8-102]
Surfactant administration	31 [28%]	21 [25%]
Home on O_2	16 [15%]	7 [8%]

*p < .05, **p < .01, ***p < .001, ˜ p <.10
Note. Frequencies are reported for discrete data, means and standard deviations for continuous data. t-tests were used to test continuous data; 2x2 chi-square with Yates correction were used for discrete data, and Fisher's exact probability test were used for discrete data with less than five cases per cell. In the case of missing data, number of subjects used in calculating group means and SD's is provided in parentheses.
a All comparisons between the singleton and multiple gestation groups.
b Magnesium sulfate, administered to inhibit preterm labour and/or control seizures in preeclampsia
c Betamethasone, to promote fetal lung maturation

Table 8.
Acid-base status of subsample with cord blood data

Characteristics	Total Sample (N = 151)
Arterial cord pH	7.29 ± 0.07 [6.95-7.42]
Arterial cord pO_2	19.172 ± 11.38 [5-80]
Arterial cord pCO_2	53.702 ± 10.53 [32-103]
Arterial cord HCO_3	24.807 ± 2.50 (140) [17-31]
Arterial cord base excess	-2.25 ± 2.98 (150) [-16 – (+)3]
Venous cord pH	7.33 + 0.07 (145) [6.95- 7.49]
Venous cord pO_2	24.660 ± 9.94 (141) [6- 67]
Venous cord pCO_2	47.050 ± 9.35 (141) [24- 103]
Venous cord HCO_3	23.74 ± 2.25 (141) [18-29]
Venous cord base excess	-2.191 ± 2.77 (141) [-16 – (+)3]

Table 9.
Demographic and Sociofamilial Characteristics of Sample with Arterial Cord Blood Data

Characteristics	Total Sample (N = 151)
Adjusted age (mos.)[a]	44.681 ± 2.88 [38.60-53.00]
Gender (M:F)[b]	68:83 [45%/55%]
Multiple Gestation	65 twins [43%]
Race (W:O)[c]	123:28 [81%/19%]
SES[d]	48.397 ± 9.81 [24-66]
Maternal VIQ[e]	100.401 ± 12.37 (127) [70-136]
Mother's education (yrs.)	16.161 ± 1.90 (149) [11-20]
Father's education (yrs.)	15.517 ± 2.16 (149) [10-20]

Frequencies are reported for discrete data, means and standard deviations for continuous data.
a Adjusted age at first testing session
b M=male, F=female
c W=White, O = Other (23 African American, 3 Indian)
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 (Wechsler, 2008); Testing was completed on the biological mothers in all 127 cases.

Table 10.
Antenatal, Perinatal, and Neonatal Factors of Sample with Arterial Cord pH data

Characteristics	Total Sample

	(N = 151)
Antenatal Complications	
Abruption of the placenta (per OB)	18 (149) [12%]
Chorioamnionitis[a] (histological)	47 (131) [28%]
Diabetes[b]	23 [15%]
HELLP syndrome[c]	10 [7%]
Hypertension in pregnancy	51 [34%]
Intrauterine growth (z-score)[d]	-.166 ± .814 [-1.99 – 2.42]
*Membranes ruptured >12 hrs****[e]	33 [22%]
Previa	12 (148) [8%]
Maternal hypothyroid	29 [19%]
Mother's age at delivery (years)	32.773± 4.90 (150) [21-46]
Oligohydraminos	11 (139) [8%]
Parity	.658 4 ± .852 (149) [0 -5]
Smoking during pregnancy[f]	4 [3%]
Total antenatal complications[g]	1.463 ± 1.05 [0-4]
Perinatal Factors	
Abnormal presentation[h]	69 [46%]
Birth weight (g)	1503.477 [490 – 3070]
Birth length (cm)	40.360 ± 4.640 [21.00-28.50]
Birth head circumference (cm)	28.307 ± 2.916 (150) [19.34 – 34.00]
Gestational age (weeks)[i]	30.623 ± 2.64 [23.6 – 33.9]
Nuchal cord	24 [16%]
1 minute Apgar	6.642 ± 2.067 [1-9]
5 minute Apgar	8.279 ± .981 [3-9]
Total perinatal complications[j]	.629 ± .561 [0-2]

Table 10. Continued

Neonatal Factors

Anemia at birth[k]	23 [15%]
Apnea	98 [65%]
Bronchopulmonary dysplasia	25 (17%)
Hyaline membrane disease[l]	90 [60%]
Hyperbilirubinemia[m]	20 [13%]
Hypoglycemia	27 [18%]
Intracranial hemorrhage[o]	25 [17%]
Necrotizing enterocolitis[p]	6 [4%]
Patent ductus arteriosus[q]	31 [21%]
Peak bilirubin (mg/dl)	9.20 ± 2.242 (149) [5.30-16.90]
Pneumothorax	6 [4%]
Retinopathy of prematurity	17 [11%]
Sepsis (initial or acquired)[r]	10 [7%]
Thrombocytopenia	17 [1%]
Total neonatal complications[s]	1.782 ± 1.553 [0-7]
Total complications[t]	3.874 ± 2.139 [1-11]

a. Includes only cases confirmed via histopathology (with or without funisitis)
b. Includes both gestational diabetes and diabetes mellitus.
c. Hemolysis, elevated liver enzymes and low platelets.
d. A z-score expressing the deviation of an infant's birth weight from the mean weight of his/her gestational age group, at delivery, according to norms published by Kramer et al. (2001).
e. Time from spontaneous or artificial rupture of membranes to delivery.
f. Smoking behavior: >30 Weeks Group: 1 case < 5 cigarettes per day
g. Total antepartum complications includes placental abruption, chorioamnionitis, maternal diabetes, HELLP syndrome, maternal hypertension, membranes ruptured >12 hours, previa, oligohydramnios, maternal hypothyroid.
h. Includes various atypical presentations such as breech or transverse lie.
i. As determined by obstetrician; > 95% of cases were corroborated by antenatal ultrasound.
j Total perinatal complications include abnormal presentation and nuchal cord.
k Initial hematocrit < 40 %
l Based on a chest roentgenogram and clinical evaluation.
m Peak bilirubin ≥ 12 mg/dl
n Requiring treatment
o Documented on the basis of cranial ultrasound.
p Documented by radiographic changes, positive stool and abdominal distention.
q Diagnosed by clinical manifestations and echocardiographic information.
r Established by positive blood culture.

s. Total neonatal complications includes anemia at birth, hyaline membrane disease, bronchopulmonary dysplasia, hyperbilirubinemia, hypoglycemia, intracranial hemorrhage, patent ductus arteriosus, sepsis, and need for oxygen following discharge (see below in Table 11 detailing intervention procedures)
t. Total complications calculated as sum of perinatal, neonatal, and antenatal complications (listed above in g, j, and s).

Table 11.

Antenatal and Neonatal Diagnostic and Intervention Procedures of Sample with Arterial Cord pH Data

Diagnostic and intervention procedures	Total Sample (N = 151)
Cesarean section	117 [78%]
Forceps	3 [2%]
General anesthesia	13 [9%]
Artificial Reproduction Techniques	32 IVF, 6 Clomid, 7 Other [30%]
Antenatal magnesium sulfate[a]	112 [74%]
Antenatal steroids[b]	135 [89%]
Antenatal steroids dose	1.56 ± .688 [0-2]
Hypertension medications (m)	38 [26%]
Days in Neonatal Intensive Care	42.086 ± 35.616 [5-245]
Surfactant administration	43 [29%]
Home on O_2	18 [12%]

a. Magnesium sulfate, administered to inhibit preterm labour and/or control seizures in preeclampsia
b. Betamethasone, to promote fetal lung maturation

Table 12.

Summary of mixed model analyses of the relationships between multiple (twin) gestation and neuropsychological measures[a]

Index	Source	t	*df*	*p*	ΔR^2
Cognitive					
WPPSI-III/IV FSIQ[b]	Sex	2.75	1, 120.11	.007	.060
	Socioeconomic Status	4.04	1, 140.52	<.001	.100
	Gestational Age	1.19	1, 168.54	.237	
	Intrauterine Growth[1]	1.34	1, 165.07	.182	
	Total Complications[2]	-0.40	1, 181.60	.692	
	Multiple Gestation[3]	1.50	1, 122.93	.137	
WPPSI-III/IV Information	Sex	3.27	1, 159.35	.001	.081
	Socioeconomic Status	4.85	1, 131.74	<.001	.136
	Gestational Age	0.81	1, 154.90	.422	
	Intrauterine Growth	0.57	1, 186.20	.572	
	Total Complications	-1.61	1, 184.33	.109	
	Multiple Gestation	1.86	1, 99.10	.066	.022
WPPSI-III/IV Block Design	Sex	1.81	1, 147.76	.072	
	Socioeconomic Status	2.47	1, 149.89	.015	.038
	Gestational Age	1.26	1, 170.73	.208	
	Intrauterine Growth	0.89	1, 178.46	.377	
	Total Complications	0.70	1, 186.65	.482	
	Multiple Gestation	0.66	1, 131.33	.513	
Language					
CELF-P2 CLS[c]	Sex	2.23	1, 132.76	.027	.020
	Socioeconomic Status	3.23	1, 138.13	.002	.066
	Gestational Age	-0.13	1, 159.65	.894	
	Intrauterine Growth	0.73	1, 169.41	.465	
	Total Complications	.065	1, 173.99	.948	
	Multiple Gestation	1.26	1, 120.24	.209	

Table 12. Continued

Index	Source	t	*df*	*p*	ΔR^2
CELF-P2 ELI[d]	Sex	3.05	1, 119.22	.003	.040
	Socioeconomic Status	3.22	1, 131.99	.002	.057
	Gestational Age	1.01	1, 156.15	.314	
	Intrauterine Growth	0.52	1, 158.90	.604	
	Total Complications	-0.31	1, 165.45	.758	
	Multiple Gestation	0.96	1, 117.85	.338	
CELF-P2 RLI[e]	Sex	3.07	1, 147.39	.003	.046
	Socioeconomic Status	3.60	1, 138.73	<.001	.082
	Gestational Age	0.64	1, 158.01	.526	
	Intrauterine Growth	0.51	1, 173.97	.614	
	Total Complications	-0.37	1, 175.99	.710	
	Multiple Gestation	0.39	1, 119.85	.701	
NEPSY-2 Word Generation[f, i]	Sex	1.13	1, 123.01	.263	
	Socioeconomic Status	2.14	1, 125.40	.035	.033
	Gestational Age	1.22	1, 147.91	.223	
	Intrauterine Growth	-1.24	1, 158.25	.217	
	Total Complications	-0.51	1, 163.39	.613	
	Multiple Gestation	2.80	1, 122.28	.006	.053
Motor					
PDMS-2 FMQ[g]	Sex	5.23	1, 179.80	<.001	.131
	Socioeconomic Status	3.03	1, 141.48	.003	.049
	Gestational Age	3.02	1, 150.11	.003	.048
	Intrauterine Growth	0.13	1, 175.71	.893	
	Total Complications	0.12	1, 156.62	.905	
	Multiple Gestation	0.53	1, 108.01	.595	
PDMS-2 GMQ[h]	Sex	1.41	1, 177.82	.333	
	Socioeconomic Status	0.08	1, 138.94	.857	
	Gestational Age	0.64	1, 151.37	.692	
	Intrauterine Growth	0.75	1, 176.95	.357	
	Total Complications	-1.54	1, 167.79	.090	
	Multiple Gestation	-0.42	1, 106.40	.717	

Note. Cognitive outcomes determined from the Wechsler Preschool and Primary Scale of Intelligence – III or IV (WPPSI-III; Wechsler, 2002) (WPPSI-IV; Wechsler, 2012) full scale

intelligence quotient (FSIQ) prorated from the Information and Block Design subtest scores; language outcomes determined by the Core Language Score (CLS), Receptive Language Index (RLI) and Expressive Language Index (ELI) of the Clinical Evaluation of Language Fundamentals – Preschool II (Wiig et al., 2004); additional language outcomes determined by the NEPSY-Second Edition (NEPSY-II; Korkman, Kirk, & Kemp, 1997),Word Generation subtest; motor outcomes determined by the Peabody Developmental Motor Scales-2 (M.R. Folio & Fewell, 2000) Gross Motor Quotient (GMQ) and Fine Motor Quotient (FMQ).

1) Intrauterine growth rate expressed as a continuous variable based on the deviation from mean birthweight for gestational age and sex.
2) Total complications variable calculated as the sum of antenatal, perinatal, and neonatal risk factors outlined in Table 10 (detailed in footnote s).
3) Multiple gestation variable coded as singleton = 1, twin = 2.

a) Sample includes 192 preschoolers. Eight cases with an intracranial hemorrhage greater than grade two and six cases with cerebral palsy were included in the analyses.
b) Neuropsychological outcome data missing for 6 cases from whole sample (3%), data missing for 3 cases (1.6%) following exclusion of neurological cases.
c) Neuropsychological outcome data missing for 16 cases from whole sample (8%), data missing for 11 cases following exclusion of neurological cases (6%).
d) Neuropsychological outcome data missing for 22 cases (11%), data missing from 17 cases following exclusion of neurological cases (9%).
e) Neuropsychological outcome data missing from 16 cases from whole sample (8%), 11 cases missing following exclusion of neurological cases (6%).
f) Neuropsychological outcome data missing from 27 cases from whole sample (14%), data missing from 22 cases following exclusion of neurological cases (11%).
g) Neuropsychological outcome data missing from 9 cases from whole sample (5%), data missing from 7 cases following exclusion of neurological cases (4%).
h) Neuropsychological outcome data missing from 13 cases from whole sample (7%), data missing from 10 cases following exclusion of neurological cases (6%).
i) When 13 neurological cases excluded, this effect remained significant (t[1, 107.23] 2.89 p = .005), with significantly higher performance in twins.

Table 13.
Neuropsychological outcome: adjusted group means (± *SE*) *for twins and singletons*[a]

Measure	Singletons	Twins
Cognitive		
WPPSI-III/IV FSIQ	105.80 ± 1.74	110.07 ± 2.50
WPPSI-III/IV Block Design	10.55 ± 0.34	10.88 ± .0.48
WPPSI-III/IV Information	11.38 ± 0.31	12.31 ± .43
Language		
CELF-P2 CLS	105.31 ± 1.36	107.33 ± 1.87
CELF-P2 RLI	104.06 ± 1.23	104.75 ± 1.66
CELF-P2 ELI	104.80 ± 1.39	106.93 ± 1.91
NEPSY-2 Word Generation	10.31 ± 0.26	11.60 ± 0.34
Motor		
PDMS-2 Gross Motor	102.46 ± 1.22	101.48 ± 1.52
PDMS-2 Fine Motor	98.49 ± 1.44	99.59 ± 1.64

Note. Cognitive outcomes determined from the Wechsler Preschool and Primary Scale of Intelligence – III or IV (WPPSI-III; Wechsler, 2002) (WPPSI-IV; Wechsler, 2012) full scale intelligence quotient (FSIQ) prorated from the Information and Block Design subtest scores; language outcomes determined by the Core Language Score (CLS), Receptive Language Index (RLI) and Expressive Language Index (ELI) of the Clinical Evaluation of Language Fundamentals – Preschool II (Wiig et al., 2004); additional language outcomes determined by the NEPSY-Second Edition (NEPSY-II; Korkman, Kirk, & Kemp, 1997),Word Generation subtest; motor outcomes determined by the Peabody Developmental Motor Scales-2 (M.R. Folio & Fewell, 2000) Gross Motor Quotient (GMQ) and Fine Motor Quotient (FMQ)

a) Means and standard errors are based on the mixed model analyses depicted in Table 12.
b) As shown in Table 12, significant group differences in Word Generation [$t(1, 122.28) = 2.80$, $p = .006$].

Table 14.
Summary of linear mixed model analyses of the relationships between co-twins discrepant birth weight standard deviation (accounting for sex) and intra-pair differences in neuropsychological functioning[a]

Index	Source	t	*df*	*p*	ΔR^2
Cognitive					
WPPSI-III/IV FSIQ[b]	Sex	1.38	1, 37.51	.176	
	Intrauterine Growth	2.91	1, 24.48	.008	.123
Information	Sex	1.45	1, 42.58	.153	
	Intrauterine Growth	2.34	1, 23.15	.029	.081
Block Design	Sex	.998	1, 41.36	.324	
	Intrauterine Growth	1.54	1, 27.13	.136	
Language					
Core Language[c]	Sex	.747	1, 41.28	.459	
	Intrauterine Growth	.335	1, 25.49	.740	
Expressive Language[d]	Sex	1.99	1, 32.36	.055	.045
	Intrauterine Growth	1.10	1, 23.99	.285	
Receptive Language[e]	Sex	2.21	1, 38.95	.033	.170
	Intrauterine Growth	,034	1, 26.09	.974	
Motor					
Total Motor[f]	Sex	3.10	1, 53.93	.003	.154
	Intrauterine Growth	2.40	1, 26.99	.024	.936
Gross Motor[g]	Sex	1.83	1, 53.94	.073	
	Intrauterine Growth	2.50	1, 26.98	.019	.097
Fine Motor[h]	Sex	4.20	1, 55.99	<.001	.254
	Intrauterine Growth	1.84	1, 27.81	.077	.004

a. Sample includes 56 twins, evaluated as 28 pairs. Of the 56 cases, one child (brain injury; PVL) was unable to complete any of the outcome measures. Missing outcome data listed in b-h.
b. Neuropsychological outcome data available for 54 cases.
c. Neuropsychological outcome data available for 52 cases.
d. Neuropsychological outcome data available for 52 cases.
e. Neuropsychological outcome data available for 53 cases.
f. Neuropsychological outcome data available for 54 cases.
g. Neuropsychological outcome data available for 54 cases.
h. Neuropsychological outcome data available for 55 cases.

Table 15.
Summary of linear mixed model analyses of the relationships between co-twins' discrepancy in total medical complications (accounting for sex) and intra-pair differences in neuropsychological functioning[a]

Index	Source	t	*df*	*p*	ΔR^2
Cognitive					
WPPSI-III/IV FSIQ[b]	Sex	1.44	1, 31.20	.160	
	Total Complications	1.35	1, 22.80	.192	
Information	Sex	1.51	1, 37.44	.138	
	Total Complications	2.03	1, 22.12	.054	.082
Block Design	Sex	1.15	1, 32.95	.258	
	Total Complications	-0.29	1, 25.18	.775	
Language					
Core Language[c]	Sex	1.13	1, 44.93	.266	
	Total Complications	0.23	1, 23.94	.820	
Expressive Language[d]	Sex	2.18	1, 31.05	.037	.049
	Total Complications	0.75	1, 21.86	.460	
Receptive Language[e]	Sex	1.77	1, 44.05	.084	
	Total Complications	1.51	1, 24.75	.144	
Motor					
Total Motor[f]	Sex	2.69	1, 49.34	.010	.125
	Total Complications	0.03	1, 25.70	.976	
Gross Motor[g]	Sex	1.93	1, 50.72	.059	.074
	Total Complications	1.11	1, 25.94	.278	
Fine Motor[h]	Sex	3.48	1, 50.37	.001	.185
	Total Complications	-0.97	1, 26.05	.343	

a. Sample includes 54 twins, evaluated as 27 pairs. One of the 54 participants was unable to complete tasks required on any of the outcome measures (brain injury; PVL).
b. Neuropsychological outcome data available for 51 cases.
c. Neuropsychological outcome data available for 49 cases.
d. Neuropsychological outcome data available for 49 cases.
e. Neuropsychological outcome data available for 50 cases.
f. Neuropsychological outcome data available for 51 cases.
g. Neuropsychological outcome data available for 51 cases.
h. Neuropsychological outcome data available for 54 cases.

Table 16.

Summary of mixed model analyses of the relationships between arterial cord pH in pregnancy and neuropsychological measures[a,j]

Index	Source	*t*	*df*	*p*	ΔR^2
Cognitive					
WPPSI-III/IV FSIQ[b, h]	Sex	2.63	1, 111.35	.010	.068
	Socioeconomic Status	4.02	1, 117.03	<.001	.114
	Gestational Age	1.24	1, 133.09	.218	
	Intrauterine Growth[1]	2.06	1, 142.51	.042	.006
	Total Complications[2]	-.61	1, 145.90	.541	
	Arterial Cord pH	2.06	1, 144.52	.041	.025
WPPSI-III/IV Information[c, i]	Sex	3.45	1, 135.59	.001	.106
	Socioeconomic Status	4.67	1, 115.14	<.001	.146
	Gestational Age	1.21	1, 128.09	.228	
	Intrauterine Growth	1.81	1, 146.84	.072	
	Total Complications	-1.54	1, 143.99	.125	
	Arterial Cord pH	2.31	1, 139.70	.022	.030
WPPSI-III/IV Block Design	Sex	1.13	1, 120.02	.214	
	Socioeconomic Status	2.58	1, 123.16	.011	.047
	Gestational Age	0.82	1, 135.89	.414	
	Intrauterine Growth	1.38	1, 143.80	.170	
	Total Complications	0.09	1, 145.98	.930	
	Arterial Cord pH	1.31	1, 144.69	.191	
Language					
CELF-P2 CLS[d]	Sex	1.74	1, 129.55	.085	
	Socioeconomic Status	4.26	1, 110.52	<.001	.137
	Gestational Age	-0.20	1, 122.24	.842	
	Intrauterine Growth	0.45	1, 137.63	.657	
	Total Complications	-0.67	1, 135.99	.503	
	Arterial Cord pH	2.06	1, 131.79	.041	.042

Table 16 Continued.

Index	Source	*t*	*df*	*p*	ΔR^2
CELF-P2 RLI	Sex	2.43	1, 134.66	.017	.039
	Socioeconomic Status	4.36	1, 116.40	<.001	.161
	Gestational Age	0.44	1, 125.22	.661	
	Intrauterine Growth	0.81	1, 137.04	.417	
	Total Complications	-0.77	1, 134.94	.443	
	Arterial Cord pH	1.79	1, 132.13	.076	.033
CELF-P2 ELI[e]	Sex	2.47	1, 117.39	.015	.039
	Socioeconomic Status	3.73	1, 106.77	<.001	.118
	Gestational Age	1.23	1, 119.73	.220	
	Intrauterine Growth	-0.10	1, 132.00	.919	
	Total Complications	-0.13	1, 131.76	.893	
	Arterial Cord pH	2.81	1, 128.17	.006	.074
NEPSY-2 Word Generation[f]	Sex	0.21	1, 103.87	.833	
	Socioeconomic Status	1.59	1, 107.11	.115	
	Gestational Age	0.48	1, 121.30	.632	
	Intrauterine Growth	-0.86	1, 129.10	.392	
	Total Complications	-1.08	1, 129.56	.281	
	Arterial Cord pH	2.01	1, 128.60	.046	.029
Motor					
PDMS-2 FMQ	Sex	4.80	1, 142.00	<.001	.139
	Socioeconomic Status	2.98	1, 142.00	.003	.059
	Gestational Age	2.81	1, 142.00	.006	.052
	Intrauterine Growth	0.58	1, 142.00	.565	
	Total Complications	-0.01	1, 142.00	.991	
	Arterial Cord pH	1.81	1, 142.00	.073	.022
PDMS-2 GMQ[g]	Sex	1.03	1, 138.99	.307	
	Socioeconomic Status	-0.35	1, 125.68	.724	
	Gestational Age	1.12	1, 130.84	.264	
	Intrauterine Growth	1.19	1, 137.29	.235	
	Total Complications	-1.51	1, 134.86	.132	
	Arterial Cord pH	3.06	1, 134.07	.003	.065

Note. Cognitive outcomes determined from the Wechsler Preschool and Primary Scale of Intelligence – III or IV (WPPSI-III; Wechsler, 2002) (WPPSI-IV; Wechsler, 2012) full scale intelligence quotient (FSIQ) prorated from the Information and Block Design subtest scores; language outcomes determined by the Core Language Score (CLS), Receptive Language Index (RLI) and Expressive Language Index (ELI) of the Clinical Evaluation of Language Fundamentals – Preschool II (Wiig et al., 2004); additional language outcomes determined by the NEPSY-Second Edition (NEPSY-II; Korkman, Kirk, & Kemp, 1997),Word Generation subtest; motor outcomes determined by the Peabody Developmental Motor Scales-2 (M.R. Folio & Fewell, 2000) Gross Motor Quotient (GMQ) and Fine Motor Quotient (FMQ).

1) Intrauterine growth rate expressed as a continuous variable based on the deviation from mean birthweight for gestational age and sex.
2) Total complications variable calculated as the sum of antenatal, perinatal, and neonatal risk factors outlined in Table 10 (detailed in footnote s).

a) Sample includes 151 preschoolers. Eight cases with an intracranial hemorrhage greater than grade two and six cases with cerebral palsy were included in the analyses.
b) When 13 neurological cases excluded, this effect became a nonsignificant trend (t[1, 134.45] = 1.88, p = .061)
c) When 13 neurological cases excluded, this effect became was reduced to a nonsignificant trend (t[127.65] = 1.83, p = .069)
d) When 13 neurological cases excluded, this effect remained significant (t[1, 124.59] = 2.18, p = .031).
e) When 13 neurological cases excluded, this effect remained significant (t[1, 121.41] = 2.80, p = .006).
f) When 13 neurological cases excluded, this effect remained significant (t[[1, 121.90] = 2.68, p = .008).
g) When 13 neurological cases excluded, this effect remained significant (t[1, 126.60] = 2.04, p = .044).
h) When neurological cases were excluded and version of IQ test (third or fourth edition) was accounted for, this was reduced to a nonsignificant trend t[1, 134.76] = 1.92, p = .057).
i) When neurological cases were excluded and version of IQ test (third or fourth edition) was accounted for, this was reduced to a nonsignificant trend (t[1, 128.704] = 1.88, p = .063).
j) Neuropsychological outcome data missing for subtest with whole sample and following exclusion of neurological cases:
    i. FSIQ: Neuropsychological outcome data missing for 5 cases from whole sample (3%), data missing from 2 cases following exclusion of neurological cases (1.5%).
    ii. CLI: Neuropsychological outcome data missing for 13 cases from whole sample (8%), data missing from 8 cases following exclusion of neurological cases (6%).
    iii. ELI: Neuropsychological outcome data missing for 19 cases (12%); data missing from 14 cases following exclusion of neurological cases (10%).
    iv. RLI: Neuropsychological outcome data missing from 13 cases from whole sample (8%), 8 cases missing following exclusion of neurological cases (6%).
    v. Word Generation: Neuropsychological outcome data missing from 21 cases from whole sample (14%); data missing from 16 cases following exclusion of neurological cases (12%).
    vi. FMQ: Neuropsychological outcome data missing from 9 cases from whole sample (6%), data missing from 7 cases following exclusion of neurological cases (5%).
    vii. GMQ: Neuropsychological outcome data missing from 12 cases from whole sample (8%), data missing from 8 cases following exclusion of neurological cases (6%).

Figure 1. Participant flow chart for twin singleton comparison sample

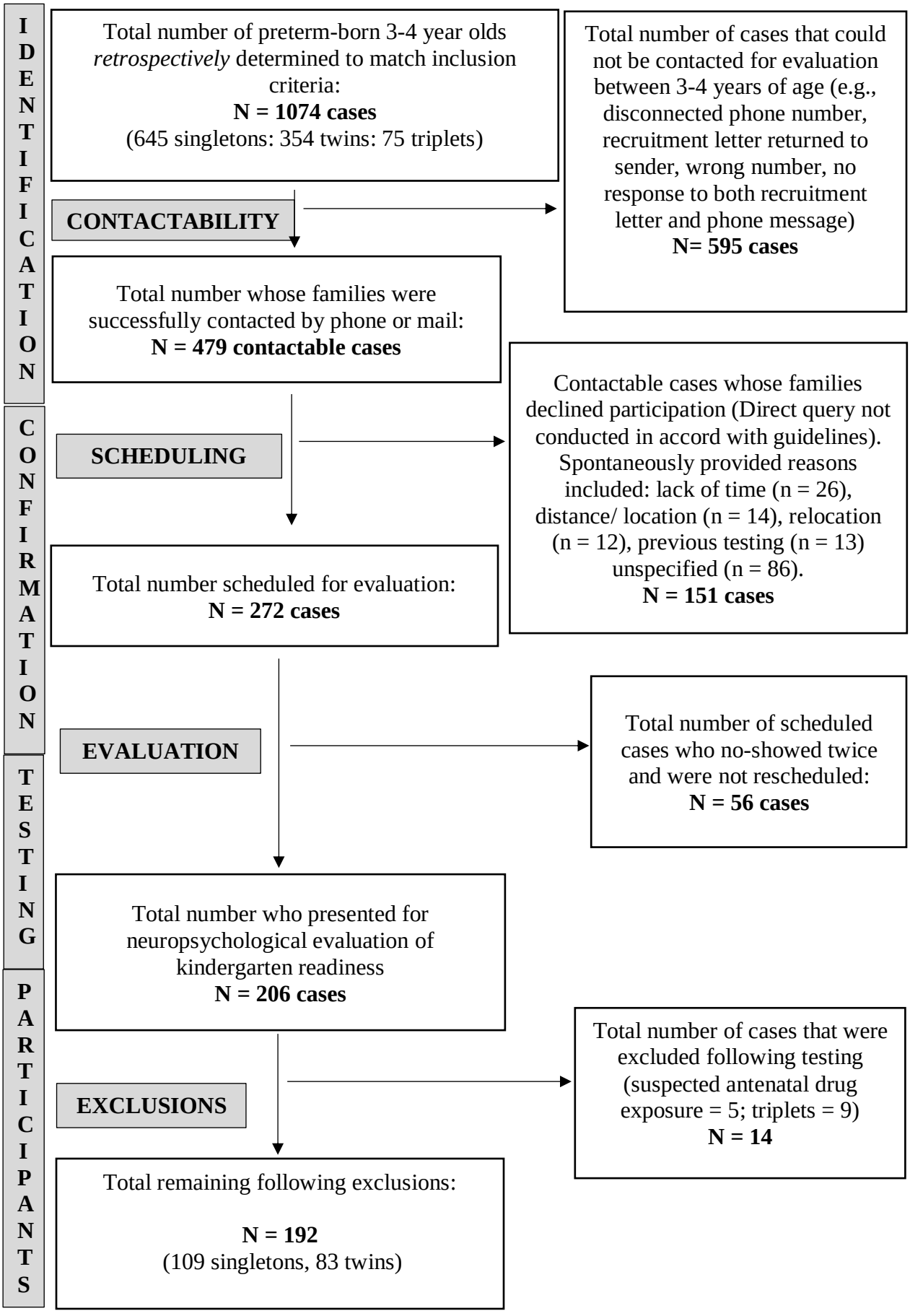
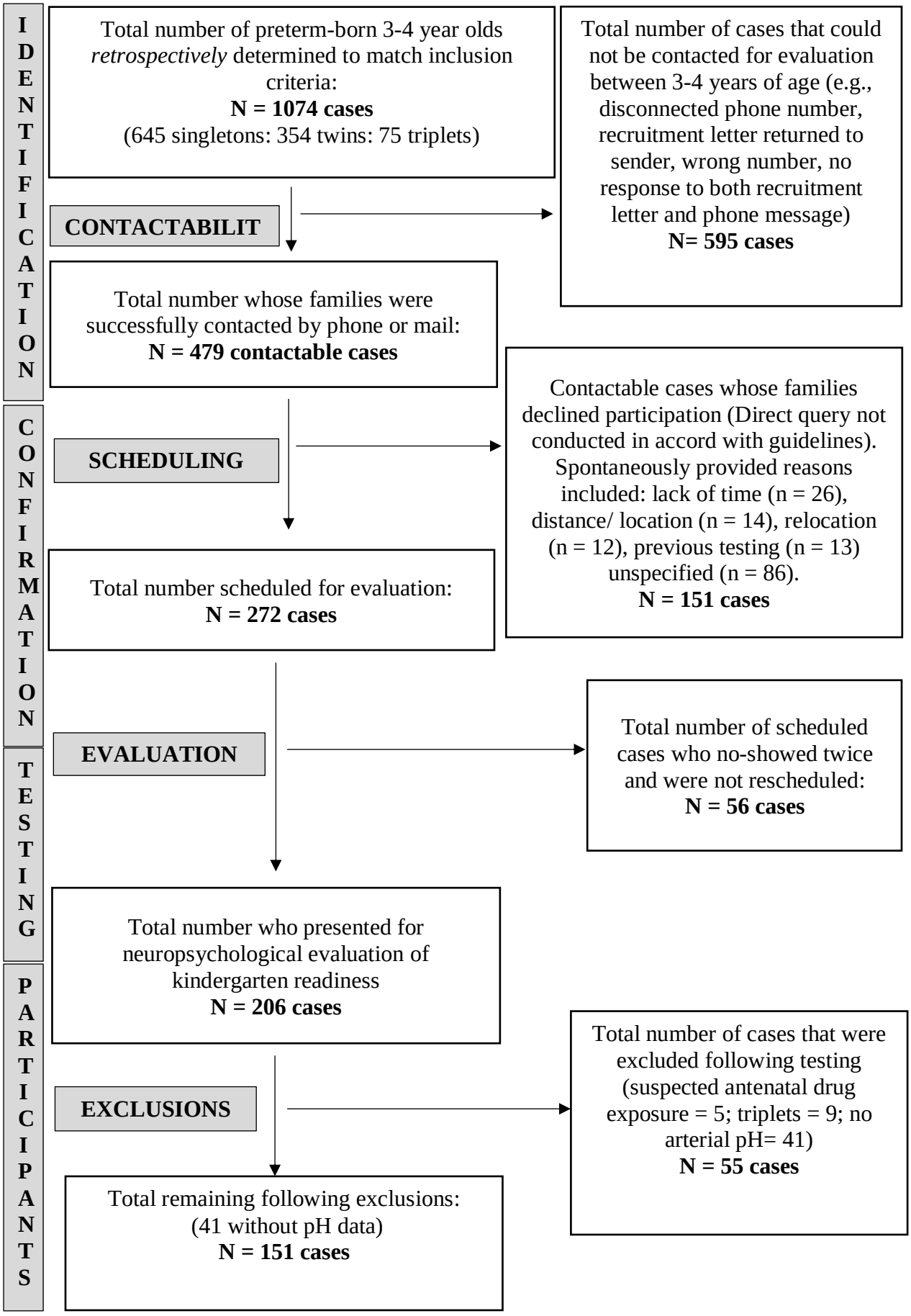


Figure 2. Flow chart for sample with cord blood information



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ABSTRACT

ANTE- AND PERINATAL RISK FACTORS AND NEUROPSYCHOLOGICAL OUTCOME: EXPLORATION OF THE ROLE OF MULTIPLE BIRTH AND ACID-BASE STATUS IN PRETERM BORN PRESCHOOLERS

by

JAMIE CHRISTINE PIERCY

August 2018

Advisor: Dr. Sarah Raz

Major: Psychology (Clinical)

Degree: Doctor of Philosophy

Increased attention to medical risk factors that precede or accompany preterm birth is necessary in order to better understand functional deficits in this vulnerable population. Children who are born preterm are subject to increased risk of neurodevelopmental deficits in the preschool years and beyond. As such, the current study aimed to gain a better understanding of the influence of two disparate biological risk factors, one antenatal and the other perinatal, on neuropsychological development. More specifically, the influence of twin gestation and low arterial pH (reflecting hypoxic risk) on neuropsychological outcomes was examined in a sample of preterm-born (before 34-weeks gestation) preschoolers (age 3-4). Additionally, differences within-twin pairs with discordant risk were explored.

Contrary to my prediction, there were no differences between twin and singleton performance on cognitive, language, or motor outcomes. However, significant within-pair differences were found when exploring differences between higher and lower risk co-twins with discordant (>1/3 SD) birth weight (n = 28 pairs). The higher risk twins (lower birthweight) demonstrated poorer performance in the cognitive and motor domains relative to their lower risk

co-twins. Consistent with my predictions, lower pH values (higher hypoxic risk) in a combined group of twins and singletons (n = 151) were associated with poorer cognitive, language, and gross motor performance in preterm-born preschoolers. Taken together, while this study did not reveal a unique effect of multiple birth on outcome, I was able to show that relatively small differences in birth weight SD between co-twins resulted in outcome effects. The findings from the second major component of this study suggest that even subtle changes in pH, an index of fetal physiology, in preterm born children may be linked to corresponding changes in developmental outcomes in the cognitive, motor, and language domains at preschool age.

AUTOBIOGRAPHICAL STATEMENT

Jamie Christine Piercy was raised in Kelowna, British Columbia. She began her training in psychology in her undergraduate work, where she focused on biological components of behavior and executive functioning, at the University of Victoria. This fostered a specific interest in the field of developmental neuropsychology, combining her interest areas into one applied field. After graduating from UVic in Spring of 2013 with a Bachelor of Science in Psychology, she moved to Detroit, Michigan to pursue her doctoral degree at Wayne State University.

At Wayne State, Jamie began her work on her Master of Arts in Clinical Psychology, where she focused on pediatric neuropsychology in her investigations of the unique features of preterm twins. Clinically, she developed her skills further at the Children's Hospital of Michigan and The Children's Center Developmental Disabilities Services, where she worked with children with epilepsy, brain injuries, and autism. To explore her interests of biology and risk in the preterm population, she designed her doctoral dissertation to focus on the risk associated with twins, as well as perinatal hypoxia. Jamie will complete her pre-doctoral internship at the Hospital for Sick Children in Toronto, Ontario in 2018-2019. She will officially complete her doctoral degree upon the completion of this internship.