1-1-2015

Twin Gestation And Neuropsychological Outcome Of Preschool Age Children Born Prematurely

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TWIN GESTATION AND NEUROPSYCHOLOGICAL OUTCOME OF PRESCHOOL AGE CHILDREN BORN PREMATURELY

by

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THESIS

Submitted to the Graduate School

of Wayne State University,

Detroit, Michigan

in partial fulfillment of the requirements

for the degree of

MASTER OF ARTS

2015

MAJOR: PSYCHOLOGY (Clinical)

Approved By:

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Advisor Date

ACKNOWLEDGMENTS

First and foremost, I would like to thank my supervisor, Dr. Sarah Raz, for her guidance and encouragement throughout this project. Second, thank you to my committee members, Drs. Rita Casey and Ty Partidge; I am truly grateful for your commitment to this project and my professional development. Thank you to the staff at William Beaumont Hospital in Royal Oak, MI, particularly Dr. Judith Klarr, Tammy Swails, and Beth Kring, for your hard work and service to both this project and your patients. Thank you to Brittany Peters and Andrew Heitzer for their invaluable contribution to this study; I feel incredibly lucky to have you both as colleagues. Thank you to the parents and children who agreed to participate in this project. Finally, I want to thank my family and friends, near and far, for their never-ending love and support.

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CHAPTER 1: INTRODUCTION

There are a multitude of causes for preterm birth, or the birth of an infant before 37 weeks gestation. In 2010, it was estimated nearly 15 million babies were born preterm, more than 11% of worldwide births (Blencowe et al., 2012). In the USA alone, it has been estimated that preterm birth costs the country at least $26.2 billion a year, or $51 600 per preterm infant (Behrman & Butler, 2007). Delivery before 37 weeks was reported to occur in 44% of all twin pregnancies compared to in 6% of all singleton pregnancies (Ozturk & Templeton, 2002). Preterm birth can be categorized into three groups: medically indicated based on maternal-neonatal outcomes, after spontaneous onset of labor, and after premature rupture of membranes (Chauhan, Scardo, Hayes, Abuhamad, & Berghella, 2010). These categories can be further simplified into spontaneous preterm birth, and provider-induced preterm birth (Blencowe et al., 2012). The cause of spontaneous preterm birth is often unidentified, though maternal factors such as history of preterm birth, low maternal body mass index (BMI), low or advanced maternal age, infection, and multiple pregnancy have been shown to significantly increased the risk of spontaneous preterm birth (Goldenberg et al., 2008). Provider-induced preterm birth, when the mother undergoes induction of cesarean section based on maternal or fetal evidence, is more common in industrialized countries.

Advances in perinatal care, such as improvements in ventilation and the use of surfactant therapy, have resulted in an improved survival rate of preterm born children (Chang et al., 2013). However, accompanying improved survival rates is an increased risk for developmental disabilities, such as cerebral palsy, impaired learning, visual disorders, white matter damage, and mental retardation, and increased risk of chronic disease in adulthood (Dammann & Leviton, 2006; Moster, Lie, & Markestad, 2008)

Traditionally twin pregnancies have been considered rare, however, the twin birth rate has increased 70% from 18.9 to 32.2 (of 1000 births) since 1980 (Datar & Jacknowitz, 2009). Previous challenges to natural conception, such as advanced maternal age and infertility, have been negated by the increase in the use of Artificial Reproductive Techniques (ARTs) (Cheong & Doyle, 2012). Approximately 18% of multiple births in the USA are the products of assisted reproduction technology (Boulet et al., 2008; Vulić et al., 2013). It has been established that in comparison to natural conception, these ARTs are more likely to result in prematurity, low birth weight, and multiple births, and up to a 30% increase in birth defects (Hansen, Bower, Milne, de Klerk, & J.Kurinczuk, 2005). With advanced maternal age, use of ARTs, as well as improvement in monitoring and risk assessment for twin gestations, there has been an increase of the prevalence of multiple pregnancies, now comprising around 3% of all births in the United States (Cheong & Doyle, 2012; Vohr, 2013). The optimal gestational age of twins is typically accepted as 38 weeks, compared to 40 weeks for singleton gestational age. Approximately one-third of preterm births are spontaneous, while 10% of the births occur after preterm premature rupture of membranes. The remainder of twin births are medically indicated, with some variation between African American and White pregnancies (Chauhan et al., 2010). More specifically, among twin births, 14.5% are moderately preterm (MPT; 32-33 weeks) and 49.8% are late preterm (LPT; 34-36 weeks)(Stock & Norman, 2010; Vohr, 2013).

Accompanying twin pregnancy are a plethora of complications in the ante-, peri- and neo-natal periods, with approximately 80% of multiple pregnancies characterized by antenatal complications (Norwitz, Edusa, & Park, 2005). Compared to singletons, twins have significantly lower birth weight, and increased risk of morbidity and mortality. Twin births account for up to 15% of perinatal mortality, with the highest risk for morbidity occurring in the lower gestational ages (<28 weeks) (Giuffré, Piro, & Corsello, 2012). Prematurity in twins can be accounted for by maternal complications such as: hypertension, preeclampsia, or infections. Multiplicity-related biological phenomena such as uterine crowding, monochorial placentation, twin-to-twin transfusion sequence, twin birth weight discordance, and fetal distress may also contribute to premature delivery (Einaudi et al., 2008; Giuffré et al., 2012). The intrauterine crowding and competition for resources, associated with multiple births, often results in intrauterine growth restriction (IUGR)(Behrman & Butler, 2007).

Growth rates of twins are anticipated to parallel the growth of singletons during the first and second trimesters, with a slowing in growth rate around 30-32 weeks (Norwitz et al., 2005). Intrauterine growth restriction (IUGR), or the poor growth of a fetus, contributes to neonatal mortality and morbidity, and is common in premature infants (Goyen, Veddovi, & Lui, 2003). IUGR, or a "small for gestational age" baby (SGA; weight below the 10^{th} percentiles of neonates with similar gestational age) may be the result of a multitude of antenatal risk factors including, but not limited to, maternal infections, maternal hypertension, preeclampsia, placental abruption, and multiple gestation. Specifically, 15% to 29% of co-twins are discordant in birth weight (Cheung, Bocking, & Dasilva, 1995; Ross, Krauss, & Perlman, 2012). IUGR presents an increased risk for morbidity in twin pregnancies, with up to 50% of growth-restricted twins presenting with additional morbidity such as meconium aspiration or pulmonary hemorrhage during the perinatal period (Pollack & Divon, 1992). Worse perinatal outcomes have been demonstrated when both twins were growth restricted, than when neither twin was growth restricted (Norwitz et al., 2005). Further, preterm infants with IUGR have a larger than twofold increase for cerebral dysfunction, such as cerebral palsy or learning disability (Norwitz et al., 2005).

At early gestational ages (< 28 weeks) the incidence of respiratory distress syndrome, where infants are born with structurally immature lungs and with delayed production of lung surfactant, was higher in both first- and second born twins relative to singletons (Marttila, Kaprio, & Hallman, 2004). RDS is inversely related to gestational age, and therefore prevalent in extremely premature (birth weight <1000 g, <27 weeks GA) and very premature (birth weight <1500 g, <32 weeks GA) infants (Anadkat, Kuzniewicz, Chaudhari, Cole, & Hamvas, 2012). Comparing twins to singletons, higher rates of other medical complications, such as neural and heart defects, gastro-intestinal malformations, and vascular disruptions, are seen among monozygotic twins than dizygotic twins (Giuffré et al., 2012).

Literature Review

Overview of the literature comparing preterm twins and singletons

A literature review was conducted using Web of Science, PsycINFO, and PubMed. Search terms included "prematur*", "low birth weight", "twin gestation", "twin pregnancy", "neurodev*", "neurobehav*", and "discordance." The bibliographies of the identified articles were also examined for research articles on the topic. A broad body of literature was identified, focusing on differing neonatal and developmental differences between multiple and singleton premature groups. The current review will focus only on neuropsychological comparisons of twin and singleton children born in the modern NICU. Table 1 summarizes the methodological features and findings of these six studies. For each study the main methodological characteristics (e.g. sample size, birth weight, gestational age, inclusion/exclusion criteria, and outcome measures) are outlined.

Language Comparisons Twin and Singletons

A significantly slower rate of language development in twins compared to single-born children has been documented in the general developmental literature. Primarily, the twin-singleton differences in language development literature focuses on the preschool age; when language skills are emerging. The extent of the delay appears to depend on the methodological approach (e.g., sample characteristics, nature of comparison group, outcome measures chosen); however, a review of studies suggests the delay ranges from 1.7 to 8 months (Thorpe, 2006). In comparing language performance between twins and singletons, consideration of rates and severity of disability or functional impairment in the twin group is necessitated, as twinning is associated with higher rates of prematurity complications and corresponding neurological sequelae. Though the use of mixed term and preterm born twins in studies using full-term singletons as controls may artificially lower the twin language performance, comparisons with this the preterm group excluded have nonetheless resulted in significant difference between twin and singleton (Rutter et al., 2003). Higher rates of articulation problems, mild delay in receptive and expressive language, and marked delay among twin boys have been demonstrated in literature aimed to specifically study twin-singleton language differences (Hay, Prior, Collett & William, 1987; Rutter et al, 2003; Thorpe, 2006). A study by Rutter and colleagues (2003) demonstrated a wider range of scores on language skills in the preschool age, with some twins scoring in the exceptionally advanced range. This wide performance range suggests that language delay is not inevitable, and that twin children may be more sensitive to factors affecting language development, particularly the language environment, compared to singletons. Further evidence detailed in Thorpe's review (2006) suggest that this delay in twin children is not attributable to factors such as twin perinatal or obstetric events, but that this difference is largely explained by social experiences during early development of twins.

The parent-child interaction with twins is unique. In order to address each individual child's needs the focus must be divided between both children. This splitting of attention often results in treating the twins as a "unit," or shifting their attention between children. This shifting decreases the moment-to-moment interaction with each child, and may interrupt prolonged interaction with each individual child to address the other twin's needs (Rutter & Redshaw, 1991). The interaction with the twins as a unit has resulted in considerable data exploring the communication style between mother and her twins, suggesting that twins receive less individually directed speech, with utterances of less complexity, and shorter conversations compared to mothers of singletons (Rutter & Redshaw, 1991, Conway, Lytton & Pysh, 1980). Whether it is related to a decrease in individually directed speech, or a lack of necessity to speak as a consequence of the twin dynamic, it has been shown that twins lag behind singletons in language development and verbal cognitive tasks (Rutter & Redshaw, 1991). The authors suggest this marked delay is potentially avoidable. Further, this delay is likely due to the postnatal environment, as a function of parents dividing their time and responsiveness between the children. In summary, regardless of the cause, there has been evidence of significant differences between full term twins and singleton children in language related developmental domains.

Outcome Comparison of Preterm Singleton and Preterm Twin Children

I reviewed here 9 studies conducted on cohorts born in the 90's or later, during the surfactant period (see Table 1). While 8 studies compared preterm-born twins, one study included in this review compared weight-concordant with weight discordant twins. Six studies focused on extremely preterm (<26 weeks gestation) infants as well as very preterm infants (26-

33 weeks gestational age) (Asztalos, Barrett, Lacy, & Luther, 2001, GA: 24-34 weeks; Eras et al., 2013, GA: <32 weeks; Einaudi et al., 2008, GA: 26-32 weeks; Kyriakidou, Karagianni, & Iliodromiti, 2013, GA: 25-35 weeks; Manuck, Sheng, Yoder, & Varner, 2014, GA: < 34 weeks, Bodeau-Livinec et al., 2013, GA: 22-32 weeks). Two studies focused on extremely low birth weight infants (Wadhawan et al., 2009; GA < 26 weeks, birth weight: 401-1000g, Hajnal et al., 2005, birth weight <1250 grams), and one study examined differences between concordant and discordant premature twins (Ross, Krause & Perlman, 2012). The main features of the studies described below are summarized in Table 1. As the Table reveals, there were 6 studies of infant twins, and 3 studies of preschool/school age twins (ages 3- 5).

Developmental Outcome Studies of Infant twins

Manuck and colleagues (2014) explored the neurodevelopmental outcomes of children delivered before 34 weeks gestation. Their sample was comprised of 1771 neonates, of which 302 were from twin pregnancies. These children were followed at 6, 12, and 24 months corrected age to assess the presence of neurodevelopmental impairment, measured using the Gross Motor Function Classification System (Palisano, Rosenbaum, Bartlett & Livingston, 2007) and the Bayley II Scales of Infant Development (BSDI-II, Bayley, 1993). The Gross Motor Function Classification System is a tool used to assess severity of CP based on self-initiated movement. Using these tasks, neurodevelopmental impairment was operationalized as moderate to severe CP, and/or a Bayley II Mental Developmental Index or Psychomotor Development Index greater than two standard deviations below the mean (MDI or PDI < 70). In total, 459 children met criteria for neurodevelopmental impairment, 82 of which were twins. Following adjustment for multiple potential confounds statistical analyses revealed that twins and singletons displayed equivalent rates of "neurodevelopmental impairment". Gestational age, delivery mode, maternal race, maternal education, use of tobacco and/or alcohol during pregnancy, treatment group of magnesium sulfate or placebo unique to this randomized controlled trial, sex, and presence of chorioamnionitis were used as covariates. In both adjusted and unadjusted models children with impairment were more likely to have had: bronchopulmonary dysplasia, retinopathy or prematurity, periventricular leukomalacia, neonatal seizures, or hemorrhages. However, multiplicity did not contribute significantly to developmental outcome variance.

Eras and colleagues (2013) conducted a prospective cohort study recruited from a NICU in Ankara, Turkey. Their sample compared 211 singletons to 153 multiples delivered before 32 weeks. Unfortunately, the authors did not provide the number of twins vs. higher order multiples that comprised their "multiples" group. These children were evaluated between 12-18 months corrected age. Cognitive development was measured using the Bayley Scales of Infant Development-Second Edition (BSID-II). The outcome of interest was neurodevelopmental impairment, defined as presence of CP, bilateral blindness, bilateral deafness, or BSID-II MDI or PDI scores less than 70. No statistical adjustments were made in the comparison of multiples and singletons. Based on these criteria, there were no significant differences found between multiples and singletons in neurodevelopmental impairment. Additionally, there were no differences in perinatal morbidity, with the exception of higher ROP in singletons.

Wadhawan and colleagues (2009) investigated the relationships between twin gestation and neurodevelopmental outcomes, perinatal complications, and rates of death and disability in extremely low birth weight infants. The sample was comprised of a large cohort of 7630 singleton infants and 1376 twins, born between 401 and 1000grams that had either died or had follow up data available at 18-22 months. Higher order multiples and infants who deceased before 12 hours of life were excluded from the sample. In this study children's neurologic, hearing, and vision development were investigated at 18 to 22 months corrected age with the primary outcome being risk-adjusted incidence of death or neurodevelopmental impairment. The infants were administered a neurological exam using the Amiel-Tison (1976) assessment. This neurological assessment is divided into six sections and covers neurosensory aspects, cranial morphology, passive and active muscle tones, spontaneous motor activity and primary reflexes. Thus, this examination was administered to evaluate tone, strength, reflexes, angles and posture. Abnormal muscle tone in more than one extremity and abnormal control of movement and posture resulted in a diagnosis of CP. Parents and audiology test reports provided hearing status, with deafness classified as the need for bilateral amplification. For visual status, an eye examination was completed and previous eye examination and procedural history was obtained as well. Blindness was classified as bilateral corrected visual <20/200. Lastly, the Bayley Scales of Infant Development-II was administered, with the MDI and PDI as composites of interest. A cutoff of two standard deviations below the mean (<70) was determined as significant delay. Children who were untestable were assigned outcome scores of 49 on the BSID-II scales. Neurodevelopmental impairment (NDI) was defined as having one or more of the following: moderate-severe cerebral palsy, blindness, bilateral hearing loss needing amplification, MDI less than 70, or a PDI less than 70. This study found differences in perinatal complications, with twins showing higher rates of need for supplemental oxygen, severe ROP, periventricular leukomalacia, and grade 3 or 4 IVH. Twins also had higher rates of death and disability (CP). Interestingly, twins increased risk for CP was found even after adjusting for gestational age and birth weight, suggesting that multiple gestation rather than prematurity alone, was associated with higher rates of CP in this sample. Lastly, twins showed higher rate of developmental delay, with significantly more frequent occurrence of very low MDI and PDI (<70) compared to singletons.

Hajnal et al. (2005) investigated two cohorts of very low birth weight multiples in relation to very low birth weight singletons. Two cohorts (Cohort 1, 1983-1985; Cohort 2, 1992-1994) of infants less than 1250 grams were compared. The first cohort of children was born in the pre-surfactant era, while the second was born in the surfactant era, and thus is of particular relevance to the current study. Neurodevelopmental outcome was assessed at two years corrected age, using The Bayley Scales of Infant Development. Children were classified with a developmental delay if one's score obtained on the Mental or Psychomotor Developmental Index was less than 84. Mental retardation or severe motor developmental delay was defined as having a MDI or PDI <68. The second cohort (which is relevant to the study proposed here), born in the surfactant era, was made up 26 members of twin-sets and 9 members of triplets, compared to 57 singletons. Statistical analyses of medical background data and developmental performance measures suggested that in this cohort multiples did not differ from singletons in cognitive and motor outcome, nor in the prevalence of cerebral palsy. However, within the multiple group, males were at significantly increased risk for severe cognitive delay compared to females. Importantly, they did not account for any other possible variables in their comparison of multiples and singletons.

Asztalos, Barrett, Lacy, & Luther (2001) compared the outcomes of members of twin-sets born 24-30 weeks each matched on gender and gestational age to a singleton control case. This group of researchers evaluated 52 sets of twins. Of these 52 sets, three members of twin-pairs were stillborn. Therefore, a total of 101 children twin-gestation children and 101 singleton controls were evaluated from birth to 18-24 months corrected age. Outcome in this study was evaluated across 4 categories: visual, hearing, motor, and cognitive. A severe visual deficit was defined as vision $< 20/200$ in one or both eyes, while a severe hearing deficit was operationalized as requiring cochlear implants or amplification. Motor development was assessed, with a severe deficit defined as abnormal tone preventing ambulation. Cognitive development was measured using the Bayley Scales of Infant Development-Second Edition (BSID-II). In the interest of the study, severe cognitive deficit was defined as 2 standard deviations below the mean on the BSID-II. The primary outcome in this study was either the occurrence of death by 18-24 months corrected age, or the presence of "severe neurodevelopmental outcome" in any of the four above-mentioned categories. With the exception of higher rates of necrotizing enterocolitis in twins, there were no significant differences in outcome of mortality and severe neurodevelopmental morbidity between twins and singletons. However, there was a non-significant statistical trend for the occurrence of neonatal morbidities (RDS, PDA, IVH, ROP) in twins.

Kyriakidou and colleagues (Kyriakidou, Karagianni, & Iliodromiti, 2013) conducted a prospective analysis comparing a sample of 46 preterm born members of twin-sets (25-34 weeks gestation) to 46 preterm singletons individually matched for gender and gestational age. Motor and cognitive development was assessed at 24 months corrected age. Neurologic status was measured with the Hammersmith Infant Neurological Examination, (Dubowitz et al. 1998), a tool used as a neurological examination of posture, cranial nerve function, reflexes, tone, movement, as well as the development of motor function, and state of behavior with children between 2 and 24 months of age. The Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III; Bayley, 2006) was used to measure motor and cognitive development. The Bayley-III assesses adaptive behavior, cognitive, language, motor, and social-emotional developmental domains. Cognitive, motor, and language scales are administered through child interaction, while the remaining domains are conducted through parent questionnaires. Prior to conducting evaluations of outcome differences amongst twins and singletons, the authors compared the ante- and perinatal medical complications in the two groups. They found that in terms of maternal morbidities, mothers of twins had significantly higher rates of IVF, pregnancy induced hypertension, IUGR, and antenatal steroid use. Twins had significantly lower birth weight compared to singletons, but did not significantly vary on any other perinatal characteristics. The authors did not control for other possible explanation of the relationship between twin-gestation and outcome. There were no significant differences found between twins and singletons in fine motor, gross motor, or cognitive scales of the Bayley-III. Additional investigation within the twin group revealed an association between pre-eclampsia and abnormal cognitive and motor Bayley-III results.

Developmental Outcome Studies of Preschool and School-Age Children

A. Differences amongst twins

A single prospective cohort follow-up study by Ross, Krauss, and Perlman (2012) assessed intra-twin differences within 84 members of premature twin sets, without singleton controls. In this sample, 26 twin-pairs were birth weight concordant and 16 twin-pairs were birth weight discordant, defined as 15% or more discrepancy in birth weight. Cognitive outcomes were assessed at age three using The Wechsler preschool and Primary Scale of Intelligence—third edition (WPPSI-III). Children were excluded for major congenital anomalies and syndromes, and ongoing medical illness. Within the four study groups (smaller members and larger members of concordant and discordant twin-sets) Full Scale and Verbal IQ scores on the WPPSI-III fell in the Average range. Although Performance IQ was in the Average range for all four groups, the PIQ scores were significantly lower in the small, discordant birth weight twins than in the other three groups (smaller discordant twins: 85.3 +/- 14.1; larger discordant twins: 97.8 +/- 17.0; smaller concordant twins: 102.2 +/- 16.3; larger concordant twins: 105.4 +/- 15.0). The groups were comparable in their perinatal complications with the exception of statistically greater number of small for gestational age (SGA) children in the discordant group. There were no twin sets in which both children were SGA. There were no significant difference between the groups on social economic status or gender; therefore these were not used as covariates in the study. One child in the discordant twin group had moderate cerebral palsy. There were no significant differences found between members of concordant twin sets. When examining intra-pair performance differences, results showed the smaller discordant twins displayed significantly lower Verbal, Performance, and Full Scale IQ scores than their larger co-twins. Interestingly, these twins did not differ significantly from their larger co- twins on growth parameters (height, weight, head circumference) at three years of age.

B. Differences between twins and singletons

Einaudui and colleagues (2008) conducted developmental evaluation of 23 preterm twins and 31 singletons all born between 26 and 32 weeks gestational age. The authors did not report any matching of the twins to singletons in terms of demographic or neonatal factors. Two children included in the sample were diagnosed with CP, 4 with PVL, and 5 had intraventricular hemorrhage. Neuropsychological screening was completed between the ages of 4 and 6, using the Battery for Rapid Evaluation of Cognitive Functions (BREV; (Billard et al., 2002). The BREV is a neuropsychological screener developed to detect acquired and developmental cognitive deficits in children aged 4 to 8. The screener is comprised of 17 subtests measuring oral language, non-verbal abilities, attention and memory, and educational achievement. The BREV is not an intelligence scale, but was established by comparing the child's cognitive profile to the cognitive profile of children diagnosed with learning disorders by the Wechsler Intelligence Scale for Children (WISC-III; over 6 years old) and the Wechsler Preschool and Primary Scale of Intelligence-Revised (WPPSI-R; children under 6 years). The profiles used by the authors were: "Normal profile" for children whose subtests fell within the normal range, "Comprehensive Retardation," for children with abnormal verbal and non-verbal performance, "Language Delay" for children with abnormal verbal performance, "Constructive dyspraxia" for children with abnormal non-verbal and normal verbal performance, "Attention Trouble" for children with motor attention problems (i.e. writing) but intact verbal and non-verbal performance, and lastly, "Learning Disorders" if school learning was abnormal with normal verbal and non-verbal performance. No relationships were found between neuropsychological results and perinatal and social factors: premature rupture of membranes, preeclampsia, chorioamnionitis, GA, birth weight, growth restriction, APGAR score, transfontanelle ultrasonography lesions, bronchopulmonary dysplasia, or family socioeconomic status. Overall, Einaudui and colleagues found that twins did not differ significantly from singletons on the BREV cognitive domains. However, they discovered that twin-members of pairs discordant for birth-weight (criteria for discordance not specified) had poorer non-verbal performance and more attention problems when compared to singletons. Further, they found that monochorial twins (sharing one chorion) had poorer non-verbal performance and a higher frequency of learning disorders than dichorionic (two individual chorion) twins.

Bodeau-Livinec and associates (Bodeau-Livinec et al., 2013), explored whether preterm singletons and twins differed in neurodevelopment at 5 years of age. Their sample was comprised of 415 very-preterm-born (22-32 weeks gestational age) twins (28.1%) and 1058 singletons (22-32 weeks gestational age) from a French regional study. A physician trained specifically for the study assessed neurodevelopmental status (hearing, vision). Cognitive development was measured using the Kaufman Assessment Battery for Children (KABC; Kaufman & Kaufman, 1983). The KABC includes five scales with a total of 19 subtests. The investigators chose to use the Mental Processing Composite (MPC) as their primary developmental outcome measure, defining cognitive deficiency as a score less than 70 (MPC < 70). Children with non-ambulatory CP, visual deficiency defined as visual acuity less than 3/10 in both eyes, severe hearing loss, and untestable children were excluded from the study. In the Multivariate linear model used by these investigators, twins vs. singleton status was the variable of interest. Statistical adjustments were made for potential confounders including gestational age, gender, and use of perinatal steroids. Additional adjustment for demographic factors such as maternal age at birth, parity, education, maternal birthplace and SES were applied for cognitive outcomes. The results revealed that twins showed lower cognitive scores than singletons. Outcomes within the twin group revealed that, overall, twins with IUGR were at higher risk of mortality and poor cognitive outcomes than twins without IUGR. In-depth inquiry into IUGR twins suggested higher mortality and lower Mental Processing Composite in co-twins discordant for IUGR than in non-discordant twin-pairs.

Brief summary of surfactant period twin literature

In summary, the existing research has yielded mixed results; 2 of 8 studies in which twins were compared to singletons (Bodeau-Livinec et al., 2013; Wadhawan et al., 2009), reported that twins were characterized by poorer performance on developmental measures than were singletons while 6 of 8 studies reported comparable performance (Asztalos, Barrett, Lacy, & Luther, 2001; Einaudi et al., 2008; Eras et al., 2013; Kyriakidou, Karagianni, & Iliodromiti, 2013; Hajnal et al., 2005: Manuck, Sheng, Yoder, & Varner, 2014). Of the total of eight studies comparing the neurodevelopmental outcome of twins and singletons, one study (Einaudi et al., 2008) used a brief screener for neuropsychological classification (BREV; Billard et al., 2002), while the majority of studies (Asztalos, Barrett, Lacy, & Luther, 2001; Kyriakidou, Karagianni, & Iliodromiti, 2013; Eras et al., 2013; Manuck, Sheng, Yoder, & Varner, 2014; Hajnal et al., 2005; Wadhawan et al., 2009) used the Bayley Scales of Infant Development (Bayley, 1968, 2005). Preschool/school age measures were used in only two studies: The Wechsler Preschool and Primary Scale of Intelligence- Third edition (WPPSI-III, Wechsler, 2002) was used in a single study without singleton controls to compare the cognitive outcomes of concordant and discordant premature twins (Ross, Krause & Perlman, 2012) while the Kaufman Assessment Battery for Children (KABC; Kaufman & Kaufman, 1983) was used by Bodeau-Livinec and colleagues (2013) as a measure of mental processing.

In the preschool age, the results were mixed. One study found twins to have lower cognitive scores than singletons (Bodeau-Livinec et al., 2013), while the other (Einaudi et al., 2008) revealed no difference between twins and singletons at the preschool age across cognitive domains.

Within the twins subsamples, significantly poorer cognitive performance (Bodeau-Livinec et al., 2013) were observed in weight-discordant co-twins compared to weight-concordant twins. Differences between weight discordant co-twins have also been shown in Perceptual, Verbal, and Full Scale IQ, with the smaller twin obtaining significantly lower scores compared to their larger co-twin (Ross, Krauss, & Perlman, 2012).

Methodological Considerations in Comparison of Twin and Singletons

As demonstrated in Table 1, from a design standpoint, some of the studies reviewed (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;) prospectively compared cohorts of twins and singletons born within a given time frame. One study (Ross, Krause & Perlman, 2013) compared a cohort of birth weight concordant to birth weight - discordant twins. Other studies reviewed (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 confounders. For those with large sample sizes, gestational age and gender serve as appropriate match criteria, as lower gestational age results in higher risk for complications. Additionally, in the preterm population, there are often differences between males and females, with males typically having poorer outcomes.

As noted earlier and shown in Table 1, seven studies reviewed focused on infants (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; Ross, Krause & Perlman, 2013) while only two investigations focused on the preschool and school age (Einaudi et al., 2008; Bodeau-Livinec et al., 2013). As the long-term implications of twin gestation in the preterm group are unclear, further investigation beyond infancy is warranted. Additionally, there is extreme variability within the preterm population in terms of SES, gestational age, and the number of perinatal complications such as IVH, and CP. It is important to remove confounding influences of these variables on outcome variance.

Beyond these general methodological considerations, there are several specific methodological shortcomings in surfactant era studies of developmental outcome in preterm twin (or multiple) gestation as described below

Limitations in the coverage of neuropsychological outcome domains. As shown in Table 1, of the studies reviewed, all nine utilized only performance measures of cognitive ability. Though they used other modes of assessment for neurological functioning (vision, hearing, CP) to measure neurobehavioral outcomes, all nine studies only used one method to assess cognitive development in their PT samples. Demonstrated in Table 1, 6 of 9 studies reviewed focused on the infant period and reported the Bayley indices, and did not include additional measures of language, memory, or motor skills. This is problematic as information gleaned is limited to rely on only one domain. Thus, to gain a more accurate depiction of the deficits in this population it is important to measure multiple domains of neuropsychological functioning.

Dichotomization of outcome data: As described above, several of the twin outcome studies used binary classification of performance data to form groups 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).

Insufficient Exclusionary Criteria. A few of the studies reviewed failed to control for perinatal complications and neurological handicaps, such as CP, PVL, IVH, or sensory impairments. 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). Importantly, those who chose to include children with neurological disorders failed to adjust for these disorders in their statistical analyses. Because they did not statistically adjust for this variable in their analyses, the effect of twinship may have been confounded by the presence of neurological disorder in their sample.

Failure to adjust for socioeconomic status. Several of the studies reviewed (see 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). This background factor needs to be taken into account because has a large 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 has a noteworthy impact on outcome variance in this population, such that multiplicative effects have been demonstrated between low SES and prematurity and the risk of developmental delay (Potijk, Kerstjens, Bos, Reijneveld & de Winter, 2013).

Failure to adjust for sex. As seen in Table 1, 2 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, the others studies failed to match for gender (Wadhawan et al., 2009), or 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 premature literature (Peters, Heitzer, Piercy & Raz, 2014; Wolke et al., 2008; Sansavini et al., 2006) it is necessary to account for the variance attributable to sex effects.

Failure to consider background perinatal risk-factors. As demonstrated in Table 1, many of the studies that compared preterm twins to preterm singletons did not statistically adjust for gestational age, for the medical status of the infant (perinatal complications) or for intrauterine growth rate (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). Intrauterine growth rate and discordant-weight are common in twins, and have shown to have a significant impact on preterm-twin developmental outcome (Ross, Krauss, & Perlman, 2012). Further, when comparing twin and singletons, statistical analyses should be adjusted for IUGR, preferably as a continuous variable reflecting gestational age.

Use of birth-weight instead of gestational age cut-off. As shown in Table 1, 1 of the 9 reviewed studies (Wadhawan et al., 2009) used birth weight cutoffs instead of gestational age. This practice leads to overrepresentation of the effect of twin children born SGA. Therefore, the effects that rely on birth weight cutoffs are actually confounded by the impact of SGA on cognitive outcome.

Hypotheses and Rationale:

Overall rationale:

As the rates of twin births have substantially increased with the rise in the application of ARTs since the 1980's, it is critical to address developmental outcome differences between twin and singleton births in the modern, surfactant era, NICU. As noted above, twin gestations involve greater perinatal risk than singleton pregnancy (Boulet et al., 2008), as exemplified by very preterm (<32 weeks) birth or extremely low birth weight (<1000g). Not surprisingly, twins are also at higher risk than singletons for neurodevelopmental impairment that may persist throughout early childhood. Yet, there is dearth of research investigating the long-term neurodevelopmental outcomes of twin gestation. As mentioned in the literature review above, only three of the studies included in Table 1 focused on preschool/school age. Although 8 of the

9 reviewed studies do compare the cognitive abilities of twins versus singletons, there is a dearth of information regarding intelligence and its components, language, and motor skills of the products of multiple births in the preschool age. Thus, the major aim of the proposed study is to compare the neuropsychological outcome of preterm twins with the outcome of preterm singletons at early preschool age.

Specific Hypotheses:

1. It is hypothesized that twin gestation (i.e., a dichotomous variable contrasting twin vs. singleton birth) will contribute significantly to explaining developmental outcome variance, over and above the effects of prematurity alone. Further, the effect of twinship will account for outcome variance beyond that explained by demographic factors such as, sex, and socioeconomic status, and perinatal (medical risk) factors such as gestational age, the number of birth complications, or adequacy of antenatal growth.

2. The proposed effect of twin gestation will be observable on measures of intelligence, language, and motor skills. As noted above, no studies are currently available in which preschool-age twins and singletons born in the surfactant era were compared on motor skills, and only one study is available on intellectual abilities (see Table 1). Interestingly, it has been demonstrated that twins lag in language development and verbal cognitive tasks (Thorpe, 2006; Rutter et al., 2003). Thus, in accord with language performance findings observed in the term-born population, it is hypothesized that preterm-born twins will perform significantly lower on measures of language ability than preterm-born singletons. However, language differences have not been explored

specifically in the preterm twin population and it is therefore to be determined whether the magnitude of the differences observed between term-born twins and singletons, is similar to the differences observed between preterm-born twins and singletons.

3. Lastly, there has been documentation within the preterm literature that males typically underperform compared to females (Raz et al., 1994; Lauterbach, Raz & Sanders, 2001; Peters, Heitzer, Piercy & Raz, 2014; Wolke et al., 2008; Sansavini et al., 2006), I do expect to replicate a sex effect in this sample. More importantly, I would like to explore the possible presence of a multiplicative effect, a twinship by sex interaction, with the expectation that the combination of male sex and twinship will have a particularly adverse effect, over and above the individual main effects of twin gestation and male sex.

CHAPTER 2: METHOD

Participants

One hundred and twenty-four subjects were recruited for the current segment of this study, with twins comprising approximately 40% of the proposed sample (n= 49). The children were recruited as a 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 children born before 34 weeks gestation that were born and treated in the Neonatal Intensive Care Unit (NICU) at William Beaumont Hospital (Royal Oak, Michigan) between 2007 and 2011 were contacted to determine interest in participating. The inclusion and exclusion criteria for the study are provided below.

Inclusion Criteria. Participants for this segment of the study were recruited from a cohort of VP infants (<34 weeks of completed gestation) who were born and treated in the NICU at William Beaumont Hospital in Royal Oak, Michigan. Participants included children who were born between 2007 and 2011, who were between the ages of 3 and 4 years (adjusted for prematurity) at the time of recruitment. Approximately 20% of families contacted agreed to take part in the study.

General Exclusion Criteria. Infants were excluded from this segment of the Steroid Study under the following circumstances: presence of major congenital anomalies (e.g., spina bifida), chromosomal disorders, children with perinatal neonatal meningitis, periventricular leukomalacia, and children who required mechanical ventilation at discharge from the NICU. Infants were also excluded if they were transported to Beaumont from a different hospital (i.e., “outborn”). It has been reported that during transport from one hospital to another, infants may receive less than optimal treatment (Lee et al., 2003). Additionally, children whose parents reported on the Background Questionnaire that the child had a seizure disorder that required extended antiepileptic medication (in contrast to neonatal seizures), history of severe head trauma with loss of consciousness, severe cerebral palsy (or any CP involving upper extremities), or uncorrected sensory deficits (e.g., blindness, deafness) were excluded.

Additional exclusion criteria for the Premature Twin Study. Three cases with possible drug abuse and two cases with a grade three intracranial hemorrhage were included in the sample. The data were analyzed with and without these cases, with no significant outcome differences observed in any of the analyses, as reported in the Results.

Sample characteristics. In total, 124 participants were initially recruited for the study (75 singletons and 49 twins). Six participants (2 twins and 4 singletons) were eliminated as they were unable to complete any testing and their parents did not complete ratings of their behavior, resulting in a final sample of 118 infants. Participants were divided into two groups based on type of gestation (singleton or multiple). Within the multiple group, for two sets of twins we could not test the co-twin 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). Therefore, altogether 47 multiples were available for this study. Four children within the multiple gestation group (3 males and 2 females) did not have a co-twin available to test as they died prior to the current study. Thus, the multiple group was comprised of 9 sets of female twins, 5 sets of male twins, 6 sets of male-female twins, 5 members of twin sets without a co-twin, and one set of male-male-female triplets. Altogether 71 singletons, and 47 children who were products of multiple gestation participated in the study.

The demographic and socio-familial characteristics of each group, prior to the removal of the 6 participants noted above, are presented in Table 3. As the table shows significant group differences were observed in in the level of paternal education (t (1, 111) = -2.163, p = .033), with fathers of multiples having more education than fathers of singletons. The adjusted age at testing was also slightly, though significantly, higher for children in the multiple group (t(1, 119)= -2.124, p = .036). As the table shows, no significant group differences were observed in racial distribution, gender, maternal years of education, maternal VIQ (as measured by the WAIS-IV Information, Vocabulary, and Similarities subtests), or SES.

The antenatal, perinatal, and neonatal complications by type of gestation are described in Table 4. As the table shows, although trending toward significance, the groups did not differ significantly in the relative frequency of multiple antenatal risk factors, including placental abruption, chorioamnionitis, maternal diabetes, hypertension, or abnormal vaginal bleeding. However, there was a significant difference in the occurrence of prolonged rupture of membranes (p = .002, Fisher's exact test), with higher relative frequency in singletons. There were no significant group differences in maternal age or intrauterine growth, as indexed by the intrauterine growth *z*-score. The intrauterine growth *z*-score was computed by calculating the deviation of an infant's birth weight from the mean weight of his or her gestational age group, split by sex. Normative data for each of the sexes were based on Kramer and colleagues (2001).

In terms of perinatal complications, the groups did not differ significantly in birth weight, length, head circumference, or gestational age. Additionally, the groups did not differ significantly in the relative frequency of complications such as abnormal presentation, need for forceps, general anesthesia during delivery, or nuchal cord. However, as may be expected, the multiples group had significantly higher rates of birth by caesarean section (χ^2(1, N = 122) = 8.442, *p* = .004).

As shown in table 4, the groups did not differ significantly in overall neonatal risk. Although the prevalence of meconium aspiration in singletons was trending toward significance (*p* = .082, Fisher's exact test), there were no significant differences between twins and singletons in the frequency of any individual neonatal complications such as anemia, intracranial hemorrhage, sepsis, hyaline membrane disease retinopathy of prematurity, patent ductus arteriosus, hyperbilirubinemia, hypermangesmia, hypotension, necoritizing enterocolitis, or thrombocytopenia.

In terms of antenatal and neonatal diagnostic and intervention procedures (see Table 5), twins had significantly higher occurrences of conception using artificial reproductive techniques (χ^2(1, N = 112) = 27.394, *p* < .001). Singletons were exposed to a significantly higher dose of antenatal steroids to promote lung maturation (*t*(1, 120) = 3.05, *p* = .004), and the percentage of mothers requiring hypertension medications was significantly higher in the singletons' group (χ^2(1, N = 111) = 5.433, *p* = .020). Additionally, the singleton group required significantly higher oxygen concentration *t* (1, 85) = 2.01, *p* = .035) for peak oxygen required during NICU stay. The groups did not differ in the need for antenatal magnesium sulfate, neonatal steroids, or surfactant. The groups also did not differ in the relative frequency of going home on oxygen, nor in the mean number of days on respiratory support, or days on ventilator.

Overall, the groups were similar in total perinatal and neonatal complications as indicated by the total peri- and neonatal complication scores. However, total antenatal complications were trending toward significance (*t*(1, 122) = 1.849, *p* = .067), with higher number of complications seen in singletons. The total number of complications, including the ante-, peri- and neonatal did not differ between groups ($t(1, 122) = .685$, $p = .495$).

Psychological 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. Prior to evaluation, the parents signed an informed consent form, approved by both Wayne State University and William Beaumont Hospital IBT, verifying that they understood the nature of the assessment and agree to the evaluation and background data collection methods. During the evaluation, the parents completed a background questionnaire designed to obtain information about their child's medical and developmental history as well as current functioning. Following the assessment, the consenting parent was re-contacted and administered 3 subtests from the WAIS-IV (Similarities, Vocabulary, and Information).

Intellectual Ability. Intellectual functioning was evaluated using the Wechsler Preschool and Primary Scale of Intelligence-Third Edition (WPPSI-III; Wechsler, 2002). Children evaluated later in the study were evaluating using the Wechsler Preschool and Primary Scale of Intelligence-Fourth Edition (WPPSI-IV). 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. Reliability and validity properties of the WPPSI-III and WPPSI-IV can be found in Table 2. The intellectual ability for children who were administered the

WPPSI-IV was determined, for the purpose of the current study, based on the Information and Block Design subtests, in order to equate our participants.

Language Skills. Expressive (i.e., the ability to produce meaningful speech) and receptive (i.e., the ability to understand language) language skills were assessed using the Clinical Evaluation of Language Fundamentals—Preschool, Second Edition (CELF-P2; Wiig, Secord & Semel, 2004). The CELF-P2 provides five composite scores (Core Language Score, Receptive Language Index, Expressive Language Index, Language Content Index, and Language Structure Index) for three to four year olds that are comprised of varying combinations of the six core subtests (Sentence Structure, Word Structure, Expressive Vocabulary, Concepts and Following Directions, Basic Concepts, Recalling Sentences), which are all described below. Reliability and validity properties of the CELF-P2 can be found in Table 2.

The Core Language Score (CLS) is a composite measure of overall language performance. The CLS is comprised of three subtests: Sentence Structure, Word Structure, and Expressive Vocabulary. Sentence Structure requires the child to point to a picture from a choice of four that corresponds to an oral prompt (e.g., "The boy is sitting under the tree."). In Word Structure, the child is given a picture and asked to complete a partial phrase based on cues given (e.g., "This girl has one pony. This girl has two _____" [ponies]). Expressive Vocabulary is a picture-naming task in which the child is shown a picture and is asked to name the object or activity shown.

The Receptive Language Index (RLI) is an index of auditory comprehension. The RLI is comprised of 3 subtests: 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 objects in the stimulus book, and is asked to point to specific objects in a certain order (i.e., “Point to the small cat then the large butterfly”). For Basic Concepts, the child is shown three to four pictures on a page and is asked to point to a concept spoken by the examiner (e.g., “point to the one in front,” “point to the one that is on the bottom”). The Expressive Language Index (ELI) is a measure of oral language production, and it is comprised of Word Structure, Expressive Vocabulary, and Recalling Sentences. During Recalling Sentences, the child is asked to listen to the examiner carefully and repeat a sentence verbatim. The sentences gradually increase in difficulty. The CELF-P2 also provides a comparison score, analyzing the discrepancy between the RLI and ELI.

The Language Content Index (LCI) is a measure of several aspects of semantic knowledge and skills. The LCI is comprised of 3 subtests: Expressive Vocabulary, Concepts and Following Directions, and Basic Concepts (all described above). The Language Structure Index (LSI) is a measure of knowledge and skills regarding word and sentence structure. The LSI is comprised of Sentence Structure, Word Structure, and Recalling Sentences (all described above). The CELF-P2 also provides a comparison score, analyzing the discrepancy between the LCI and LSI.

Scores from two Likert rating parent-rating scales were administered. The item responses range from 1 (Never) to 4 (Always). The Descriptive Pragmatics Profile is a checklist that consists of items inquiring about children’s social use of language, specifically their use of nonverbal language and their ability to use language socially. The Pre-Literacy Rating Scale is a checklist the parent fills out that provides a score, which represents the child’s early reading skills (e.g., letter and sound identification). The parent is asked to respond to each item based on the frequency in which the child engages in that particular skill.

Motor Skills. The Peabody Developmental Motor Scale – Second Edition (PDMS-2; Folio & Fewell, 2000) was administered to each child. The PDMS-2 is a developmental motor assessment that measures both fine and gross motor development using a variety of directive tasks. Stationary, locomotion, object manipulation, grasping, visual motor integration domains were assessed. The PDMS-2 provides Total, Gross, and Fine Motor Quotient scores. Reliability and validity properties of the PDMS-2 can be found in Table 2.

Mathematical Knowledge. Two subtests from the Woodcock Johnson – III Tests of Achievement (Woodcock, McGrew, & Mather, 2001) were used to measure mathematical knowledge and reasoning (Quantitative Concepts, Applied Problems). Quantitative Concepts requires the application of mathematical concepts and numerical relationships to solve problems. This includes counting and identifying numbers, shapes, and sequences. This subtest also requires the child to look at a number series, identify the pattern, and provide the missing number using mental computation. Applied Problems includes counting and oral math word problems. This measures comprehension and the solution of relatively simple mathematical calculations. Paper and pencil can be used for the word problems on this subtest.

Neurocognitive Performance Measures. Two subtests from the NEPSY- Second Edition: *A Developmental Neuropsychological Assessment* (NEPSY-II; Korkman, Kirk, & Kemp, 1997) were administered to each child (Oromotor Sequences, Word Generation, Statue). Oromotor Sequences is a subtest of oromotor coordination, and requires the child to repeat nonsense words and "tongue twisters." The Statue subtest requires children to silently hold a pose, and inhibit their response to noises and distracting stimuli made by the examiner. Lastly, word Generation is a verbal fluency task, in which the child is given one minute to name as many objects as possible within a given category (e.g. fruits and vegetables). Since single subtests are being used from the NEPSY, scaled scores (range 0 to 19) will be used as dependent variables as opposed to overall domain scores. The available psychometric properties for these subtests can be found in Table 2.

Statistical Analyses: General Considerations

The independent variable of interest was type of pregnancy (singleton or multiple), along with birth weight, socioeconomic status (SES), intrauterine growth rate (z-score), sex, adjusted age at testing, and total complications selected as conceptual covariates. The dependent variables were scores on cognitive, language and motor performance measures based on the child's age adjusted for degree of prematurity. Inspection of predictor variables revealed an unremarkable number of missing data, therefore no steps were taken to interpolate for missing data or correct for skew within the predictor variables.

The data was analyzed using simultaneous multiple regressions. Covariates that may contribute significant variance to the outcome measures were identified and carefully selected and included as conceptual "covariates" in the analyses. Group differences on demographic and perinatal variables were explored using t-tests and chi-square analyses. As previously discussed, the two groups (based on type of gestation) varied significantly on demographic variables (see Table 3), as well as frequency of several medical complications (see Table 4) and exposure to diagnostic and intervention procedures (see Table 5).

The chief variable of interest, multiplicity, as well as three socio-demographic (SES, sex, and age at testing) variables, as well as three variables linked to early medical status (birth weight, intrauterine growth rate, and total number of complications) and believed to be potential confounders, were entered simultaneously as predictors in all multiple regression analyses. SES was chosen as a covariate as it has been demonstrated to predict a substantial portion of neuropsychological outcome (e.g., Raz et al., 2010). Additionally, using SES as a covariate accounts for maternal and paternal education and occupation, which are used in the computation of this variable. As noted above, early medical risk factors added to prediction models included birth weight (grams), intrauterine growth z score, and total number of complications. All of these risk factors have been demonstrated to contribute to outcome in earlier prematurity outcome research from this, and other research groups (e.g., Raz et al. 2010, Newman, DeBastos, Batton, and Raz, 2011; Raz et al. 2012), As gestational age and length of hospital stay were highly correlated with birth weight ($r(123) = .818$, $p < .001$; $r(123) = -.735$, $p < .001$) they were not used as covariates.

Results of simultaneous multiple regression analyses are presented in Table 6. As noted earlier, each performance score was based upon the child's age, adjusted for prematurity. Interactions were examined between the two binary variables, sex and multiplicity, in order to test Hypothesis 3. In addition, all interactions between the binary and continuous variables were examined for each of the simultaneous regression models used in the current investigation. Significant interactions were entered into the regression models, as shown in Table 7, and as detailed below, in the Results section. Otherwise, when no significant interactions could be detected, the reduced simultaneous regression models were used (see Table 6).

CHAPTER 3: RESULTS

As Table 6 shows, multiple gestation was associated with 4 outcomes measures, including PDMS-2 Total Motor Quotient, PDMS Fine Motor Quotient, NEPSY-2 Word Generation, and NEPSY-2 Oromotor Sequences. Interestingly, the direction of the effect was opposite to the one predicted (Hypotheses one and two), with twin performance being superior to singleton performance on all aforementioned measures. There was a non-significant trend observed on the WPPSI FSIQ, again with twins obtaining higher scores than singletons.

Among perinatal predictors, birth weight was associated with performance on a number of outcome measures (Receptive Language, Language Content, Language Structure, Expressive Language, Total and Fine Motor Quotients). Not surprisingly, children with higher birth weight obtained higher scores on all the aforementioned measures. Although the total number of perinatal complications was typically not associated with outcome, this predictor was unexpectedly directly linked to three outcome measures, Block Design, Word Generation, and parent Pre-literacy ratings. Thus, children who had experienced a greater number of perinatal complications obtained higher scores. Lastly, although adequacy of antenatal growth was not linked to outcome on the preponderance of our outcome measures, contrary to expectations an inverse relationship was observed between antenatal growth and performance on a single task, Word Generation, with higher scores linked to less adequate antenatal growth.

Among socio-demographic predictors, SES had significant direct associations with the greatest number of outcome measures (FSIQ, Block Design, Information, Core, Receptive, Content, Structure, and Expressive Language, Descriptive Pragmatics Ratings, Pre-literacy Ratings, Fine Motor Quotient, Quantitative Reasoning, and Applied Problems). Sex was also linked to several outcome measures (Information, Pre-literacy Ratings, Oromotor Sequences, Total Motor Quotient, Fine Motor Quotient, Applied Problems), with females consistently performing better than males. Adjusted age at testing was also linked to outcome measures with older children outperforming younger ones on the parent rating instruments of the CELF-P2 (Descriptive Pragmatics and Pre-Literacy). In contrast, older children obtained lower scores on direct motor performance indices: the Total and Gross Motor Quotients.

To test (exploratory) hypothesis three, the sex by twin interaction with triplets removed, was examined for all outcome measures (see Table 7). As the effect was not significant for the majority of cognitive and language outcome measures, the reduced regression model without the interaction term was used for these analyses and is displayed in the table. In contrast, the sex by twin interaction was found to be significant for the NEPSY-2 Oromotor Sequences ($p = .05$; see Table 7), as well as PDMS-2 indices of motor performance: the Total Motor Quotient ($p < .05$, see Table 7) and trending for the Fine Motor Quotient ($p = .060$, see Table. 7.). Therefore, the interaction term was included in the regression model for these outcome variables and is displayed in the table. Visual inspection of the interaction revealed a distinct female-, but not male, twin advantage over singleton performance [Adjusted Means ± SE= 98.77 ± 1.87; 100.58 ± 1.68; 96.645 ± 2.59; 107.57 ± 2.04, for Total Motor Quotient for singleton boys, singleton girls, twin boys, and twin girls, respectively; Adjusted Means ± SE = 94.88 ± 2.25; 99.34 ± 2.03; 94.10 ± 3.21; 109.02 ± 2.54 for Fine Motor Quotient for singleton boys, singleton girls, twin boys, and twin girls, respectively; Adjusted Means ± SE = 3.11 ± .203; 3.31 ± .191; 3.21 ± .288; 4.21 ± .232 for Oromotor Sequences category for singleton boys, singleton girls, twin boys, and twin girls, respectively).

A simultaneous linear regression was conducted examining interactions between dichotomous (multiplicity and sex) and all other continuous variables, excluding children of triplet gestation. A significant interaction was observed between multiplicity and total number of complications [*t* (1, 87) = -2.895, *p* = .005] on Fine Motor performance. Therefore, this interaction was added only to the model predicting the Fine Motor Quotient (see Table 6). With the addition of this interaction term, the model produced lower adjusted means for singletons than twins (Singletons: *M* = 97.88, *SD* = 13.17; Twins: *M* = 102.71, *SD* = 14.14), with higher adjusted means observed at lower number of complications within the twin group. When adding the multiple by total number of complications interaction to the reduced model, the sex by twin interaction becomes a non-significant trend [*t* (1, 100) = 1.902, *p* = .060].

To test interactions, the multiple group was examined without children born of triplet gestation. To insure no significant differences existed between these models, supplemental analyses were conducted to evaluate the impact of removing the triplets. With the triplets removed, no significant difference was observed in outcome measures using the reduced model. Table 6 provides the final regression models for the twins vs. singletons data, with significant interactions added to the appropriate models. Thus, the reduced model was used for all outcome variables with the exception of Oromotor (sex by twin interaction was added), Total Motor (Sex by twin interaction was added); and Fine Motor (sex by twin, and total complications by twin interactions were added).

As Table 7 shows, after removing the triplets, a main effect of multiple gestation was seen in Word Generation performance, with twins obtaining higher scores than singletons. Significant twin by sex interactions were evident on two outcome measures, and one non-significant trend, all involving a motor component: Oromotor Sequences (Adjusted means ± SE = 3.11 ± .203; 3.31 ± .191; 3.21 ± .288; 4.21 ± .232, for singleton boys, singleton girls, twin boys, and twin girls, respectively), Total Motor (Adjusted Means ± SE= 98.77 ± 1.87; 100.58 ±

1.68; 96.65 ± 2.59; 107.57 ± 2.04 for singleton boys, singleton girls, twin boys, and twin girls, respectively) and Fine Motor performance (Adjusted means ± SE = 94.88 ± 2.25; 99.34 ± 2.03; 94.10 ± 3.21; 109.02 ± 2.54 for singleton boys, singleton girls, twin boys, and twin girls, respectively). Thus, twin girls outperformed twin boys and singletons on each of these motor measures.

Amongst early complications, birth weight was significantly related to outcomes in Receptive Language, Language Content, Language Structure, Expressive Language, Total and Fine Motor Quotients. As would be expected, increase in birth weight was associated with better outcome for all of these measures. Additionally, significant inverse relationship was observed between antenatal growth rate and performance on Word Generation. Number of perinatal complications was significantly positively associated with performance on Block Design, Pre-literacy ratings, and Word Generation. Socioeconomic status was a significant positive predictor of performance across numerous performance measures: FSIQ, Block Design, Information, Core, Receptive, Content, Structure, and Expressive Language, Descriptive Pragmatics Ratings, Pre-literacy Ratings, Fine Motor Quotient, Quantitative Reasoning, and Applied Problems. Age at testing was significantly positively related to CELF-P2 Parent Ratings (Pre-Literacy and Descriptive Pragmatics), and negatively related to performance in Block Design, Oromotor Sequences, and Total Motor and Gross Motor performance. Sex was positively associated with Pre-Literacy parent ratings, Applied Problems, and NEPSY-2 Statue.

CHAPTER 4: DISCUSSION

The initial hypothesis (Hypothesis 1) that twin gestation would significantly contribute to explaining developmental outcome variance beyond that explained by prematurity or demographic factors alone was supported, but not in the expected direction. As Table 6 shows, prior to examination of statistical interactions, significant multiplicity main effects were found, yet twins outperformed singletons on 4 out of 16 outcome measures, in the fine-motor and oral-verbal fluency domains. Hence, the directional hypothesis that adverse effect of multiple gestation would be observed across intelligence, language, and motor skills (Hypothesis 2) was not supported. Non-significant trends for association were observed between multiple gestation and global Intelligence (FSIQ), while significant associations were seen between multiplicity and two language (NEPSY-2 Word Generation and Oromotor Sequences), and two motor (PDMS-2 Total, and Fine Motor, Quotients), measures. Clearly, the association between multiplicity and the Total Motor Quotient, a combination of the GMQ and FMQ, was primarily the result of the influence of the participants' latter score. Again, in contrast to Hypotheses 1 and 2, both the trends and the significant associations described above revealed, in contrast to my hypotheses, a multiple rather than singleton advantage. I would like to note though that the observed multiple advantage on 4 of 16 measures was reduced to a significant advantage on only one measures (NEPSY-2 Word Generation) and a non-significant trend (PDMS-2 Fine Motor Quotient) on another, once the Sex X Multiplicity interactions were included in the regression models (see Table 7). Nonetheless, an important conclusion based on the current study is that being born a twin, in the (post) surfactant era, does not appear to carry a poorer prognosis in terms of cognitive, language, or motor performance compared to being born a singleton. This conclusion is generalizable to preterm-born three year olds, based on my findings.

As Table 7 shows the final exploratory hypothesis (Hypothesis 3) of Sex X Multiplicity effect was statistically supported, with significant interactions observed on three outcome measures, all involving a motor component (Total Motor, Fine Motor, Oromotor Sequences). However, the interaction observed resulted from twin girls advantage compared to twin boys on all three neuropsychological outcome measures, a sex difference not seen in the singletons group. Specifically, the twin girls outperformed the singletons and twin boys on the PDMS-2 Fine Motor quotient (adjusted means ± SE = 94.88 ± 2.25; 99.34 ± 2.03; 94.10 ± 3.21; 109.02 ± 2.54 for singleton boys, singleton girls, twin boys, and twin girls, respectively) with girls obtaining scores one full standard deviation above the twin boys' performance on this index. Similar performance patterns were seen in Total Motor Quotient (adjusted Means ± SE= 98.77 ± 1.87; 100.58 ± 1.68; 96.65 ± 2.59; 107.57 ± 2.04 for singleton boys, singleton girls, twin boys, and twin girls, respectively) with differences between twin boys and twin girls reaching .73 SD.

Upon inspection of the Sex X Twin interaction effects (Table 7) within the motor domains, the observed sex effect within the twin group is of interest. The observed direction of the adjusted means for the two sexes amongst preterm twins deviates not only from that of preterm singletons, but also from sex differences observed in previous research. Saraiva and colleagues (2013) examined motor development in 367 typically developing convenience sample of pre-school age children using the same motor measure used in the current study (PDMS-2) and in the same age-group. The authors did not specify whether or not the sample included twins, or solely singleton children, yet I believe that I would be justified in assuming that the rate of multiples in a sample of typically developing preschoolers, if included, would be extremely small. Using the PDMS-2, the same measure used in the current investigation, their analyses demonstrated that at 3 years of age (i.e., 42 months plus/minus 3.4, a similar average age to our sample as presented in Table 1), females exceeded males in fine motor abilities (0.58 SD and .38 SD's higher than boys on the Grasping and Visual-Motor Integration subtests comprising the PDMS-2 FMQ, respectively). In contrast, male advantage was apparent in two of the three PDMS-2 domains of gross motor performance (with effect size of moderate magnitude reaching .46 SD's for the Object Manipulation GMQ subtest, and a trend for male advantage of .23 SD's observed for Locomotion, a second GMQ subtest). Similarly, in our sample females outperformed males on the Fine Motor scale, (see Table 7), with the difference resulting from superior performance of twin girls compared to twin boys as revealed by the significant Sex X Twin interaction effect. Preterm singleton females did not demonstrate the female fine motor advantage observed in Saravia et al's (2013) study. However, no significant Sex or Sex X Twin interaction effect was observed for gross motor skills. From a different perspective, neither preterm male twins nor preterm male singletons showed the expected gross motor advantage observed in the Saravia et al's (2013) study. In brief, in considering the motor performance in our sample compared to that of Saravia and colleagues' sample of typical 3-year olds, only preterm female twins demonstrated the expected gender/sex-based pattern of motor skills, when compared to their singleton counterparts or to preterm males, whether singletons or multiples.

In this preschool age sample, preterm multiples were not at a disadvantage when compared to singleton counterparts, demonstrating either equivalent or superior neuropsychological performance. However, the families recruited for this study were a predominantly white, educated group of middle class strata. Further, a number of our families (59% twins and 13% of singletons) utilized artificial reproductive therapies, which has been established as a financially and psychologically costly endeavor (Connolly, Hoorens & Chambers, 2010). Fiscal expense aside, partaking in ART allows one to assume, from the lengths these parents are driven to conceive, that they will continue their dedication to their growing child. Thus, it is more than likely that these parents would be particularly proactive in learning about helpful education and in obtaining early childhood care following the preterm birth of their children. This motivation could potentially account for the equivalent or improved performance of multiples in our sample. Although there was no disadvantage attributed to multiplicity in the preschool age, continued assessment will be helpful to examine whether or not differences begin to manifest as the children grow and as task demand becomes more complex.

It is important to acknowledge the increased likelihood of premature birth in both twins and singletons with the use of artificial reproductive techniques (ART). As aforementioned, these techniques were highly used in both our twin and singleton groups (see Table 5). As such a high proportion of the multiple subsample was a result of ART, a larger sample size is necessitated to attain sufficient power to examine differences between twins and singletons born with and without this assistance.

The intriguing relationships observed here between preterm twin-birth and neurodevelopmental outcome at preschool age are unlike those found in the very limited body of research of preschool age twins served by the modern NICU during the surfactant era (Einaudi et al., 2008; Bodeau-Livinec et al., 2013). While the former study has found similar, the latter documented slightly poorer performance in preterm twins compared to singletons. Unlike the current investigation, Einaudi and colleagues did not adjust for gender or socioeconomic status, which may account for the discrepancy in findings. It is possible that the discrepancies in results between the current investigation and Bodeau-Livinec and colleagues is related to differences in the age of the sample, as they were assessing differences at 5 years of age. This suggests that it may be possible that with age the neurodevelopmental performance of twins compared to singletons is less favorable. Additionally, it is important to consider that the Bodeau-Livinec sample size was comprised of 415 twins and 1058 singletons; with a sample this large even small discrepancies in performance may result in statistically significant outcomes.

The results of the current study allow one to speculate that there may be an inherent influence of the cause of premature birth on the outcome of children born prematurely in the modern NICU and in the surfactant era. The specific etiology may result in improved outcomes for twins or, alternatively, in a singleton disadvantage. As indicated earlier, a vast number of twins (around 40%) will have preterm spontaneous labor, while others will have indicated delivery due to complications such as preeclampsia or infection (Goldenberg, Culhane, Ians & Romero, 2008). Hence, for a large proportion of this group (up to 60%), the risk and later cause of preterm labor is related to multiplicity. On the other hand, the preterm birth of singletons is more often caused by the influence of severe complications (such as antenatal infection and chorioamnionitis, or maternal diabetes, hypertension, preeclampsia and HELLP syndrome), rather than the "crowding effect" often associated with prematurity in multiples. Observations from the current sample, although a non-significant trend, demonstrate a higher number of antenatal complications for singleton pregnancies (p = .067). Consistent with the notion of a higher frequency and/or more severe complications in preterm singleton birth, there was a significantly higher frequency of maternal hypertension medication use in the singleton group compared to the multiples. Within the singleton group there was also a significantly higher frequency of ruptured membranes, a risk for sepsis.

In terms of limitations, first, it is important to note that perinatal and neonatal medical risk data were collected retrospectively. Further, although this study examined differences between preterm born children, no control group of term-birth children was used, limiting comparisons beyond the preterm group. Although recruiting efforts were put forth to all families born in the NICU, there may be a distinction between families who choose to participate and those who declined, which may limit the generalizability of this study. A larger sample size will allow for further identification of sources of variances associated with multiple gestations, etiology of premature birth, and the influence of ART on neurodevelopmental outcomes.

APPENDIX A

Table 1.

Methodological Characteristics and Findings of Prior Research on Preterm Singleton and Twin Neuropsychological Performance

Author & Year	GA-Cut off/BW cut-off	N per group	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-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	Bayley Scales of infant Development (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 twins3	18-22 months corrected age	Twin-singleton	Death before 12 hours of life, triplets and higher order multiples	Amiel-Tison, Bailey Scales of Infant Development-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.

Table 1 (continued)

Manuck, Sheng, Yoder & Varner, 2014	<34 weeks	1771 neonates 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	Bayley II Scales of Infant Development, 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/alc/drugs during pregnancy, treatment group (magnesium sulfate vs. placebo), fetal sex, chorioamnionitis	Multiplicity did not significantly contribute to outcome variance.
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	Bailey Scales of Infant Development-II. Neurodevelopmental impairment (any of: CP, bilateral blindness, bilaterial deafness, BSID indices <70)		No significant differences between multiples and singletons in neurodevelopmental outcome.

Table 1 (continued)

Ross, Krause & Perlman, 2012	15% or more discordance	84 members of twin sets No singleton controls	3 years	Intra-twin differences	Major congenital anomalies, congenital syndromes, ongoing medical illness	Wechsler Preschool and Primary Scale of Intelligence-III, height, weight, head circumference.		The smaller weight discordant twins displayed significantly lower Verbal, Performance, and Full Scale IQ scores than their larger co-twins
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	Gestational age, gender, IUGR, prenatal steroids, sociodemographics (maternal age, parity, maternal education, maternal birthplace, family social class).	Twins showed lower cognitive scores than singletons. Within the twin group, twins with IUGR were at higher risk of mortality and poor cognitive outcomes than twins without IUGR
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.

Table 2

Psychometric Properties of Measures Used

	Internal Consistency	**Internal Consistency**	**Test-Retest Reliability**	**Test-Retest Reliability**
	3 years Old	4 years old	3 years old	4 years old
WPPSI-III				
Block Design	Average for all ages: .84		2:6-3:11: .9	4:0-5:5: .5
Information	Average for all ages: .88		2:6-3:11: .3	4:0-5:5: .9
FSIQ (prorated)	.713	Not Available	.919	Not Available
CELF-P2				
Core Language	3:0-3:5: .91	4:0-4:5: .93	.92	.89
	3:6-3:11: .91	4:6-4:11: .93		
Receptive Language	3:0-3:5: .91	4:0-4:5: .94	.92	.95
	3:6-3:11: .92	4:6-4:11: .91		
Expressive Language	3:0-3:5: .93	4:0-4:5: .94	.95	.92
	3:6-3:11: .92	4:6-4:11: .94		
NEPSY				
Word Generation (Semantic total score)	.59	.59	Not Available	Not Available
Oromotor Sequences	Not Available	Not Available	Not Available	Not Available
Statue	.82	.82	Not Available	Not Available
PDMS-2				
Gross Motor	.93	.94	Not Available	Not Available
Fine Motor	.91	.98	Not Available	Not Available
Total Motor	.95	.97	Not Available	Not Available

Table 3
Group Comparison of Demographic and Sociofamilial Characteristics

Characteristics	Singletons n = 75	Multiples n = 49
Adjusted age (mos.)[a] *	43.675 ± 3.193	44.944 ± 3.244
	(38.60 – 53.00)	(40.90-53.10)
Gender (M:F)[b]	35:40(47%/53%)	20:29 (41%/59%)
Multiple Gestation		46 twins; 3 triplets
Race (W:O)[c]	53:22 (71%/29%)	41:8 (84%/16%)
SES[d]	48.655 ± 10.425 (74)	48.245 ± 10.371
	24-66	(24-66)
Maternal VIQ[e]	100.672 ± 10.068 (62)	100.857 ± 10.096 (42)
	(76-122)	(83-122)
Mother's education (yrs.)	15.992 ± 1. 711 (66)	15.957 ± 1.744 (47)
	(11-20)	(12-18)
Father's education (yrs.)*	14.833 ± 2.324 (66)	15.660 ± 1.736 (47)
	(10-18)	(12-18)

Note. *$p < .05$, **$p < .01$, ***$p < .001$, ~ $p < .10$
Frequencies are reported for discrete data, means and standard deviations for continuous data. Group differences examined via t test (continuous data) or 2 X 2 $\chi 2$ with Yates correction (discrete data) or Fisher exact probability test (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: 17 African American, 3 Indian, 1 Pacific Islander, 1 Middle Eastern, 1 Filipino; Multiples: 5 African American, 2 Middle Eastern)
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 101 out of 104 cases

Table 4.

Antenatal, Perinatal, and Neonatal Factors by Group[a]

Characteristics	Singletons n = 75	Multiples n = 49
Antenatal Complications		
Abruption of the placenta	6 (8%)	3 (6%)
Chorioamnionitis (histological)	19 (73; 26%)	12 (24%)
Diabetes[b]	4 (69; 5%)	6 (46; 13%)
HELLP syndrome[c]	7 (69; 9%)	6 (44; 14%)
Hypertension in pregnancy	35 (47%)	17 (35%)
Intrauterine growth (z-score)[d]	0.2940 ± .830	-.2464 ±.741
(<10%ile)	8 (11%)	7 (48; 15%)
IUGR hospital diagnosis	12 (16%)	4 (8%)
Membranes ruptured >12 hrs***[e]	24 (32%) (16-1278hr)	4 (8%) (23-408hr)
Mother's age at delivery (years)	32.211 ± 4.790 (71) (21-44)	32.163 ± 4.069 (24-40)
Mother's height (inch)	65.536 ± 3.197 (69) (59-72)	65.798 ± 2.704 (47) (60-71)
Oligohydraminos	4 (65; 6%)	1 (42; .2%)
Parity*	.681 ± .917 (0-3)	.408 ± .497 (0-1)
Smoking during pregnancy[f]	2 (68; 3%)	0 (44)
Vaginal bleeding (abnormal)	10 (69; 14%)	4 (44; 9%)
Total antenatal complications[g~]	1.240 ± 1.025 (0-4)	.918 ± .812 (0-3)
Perinatal Factors		
Abnormal presentation[h]	28 (72; 39%)	19 (39%)
Birth weight (g)	1405.453 ± 453.945 (524-2483)	1359.396 ± 382.247 (576-2253)

Birth length (cm)	39.515 ± 4.968	39.545 ± 4.000 (48)
	(22.00-48.30)	(30.75-47.50)
Birth head circumference (cm)	27.659 ± 2.614(72)	27.811 ± 2.583 (48)
	(19.30-32.00)	21.00-32.00)
Cesarean section**	51 (73) (70%)	44 (92%)
Forceps	0	0
General anesthesia	6 (72; 8%)	3 (6%)
Gestational age (weeks)[i]	30.272 ± 2.489	30.165 ± 2.563
	(23.40-33.90)	(24.30-33.60)
Nuchal cord	16 (69; 23%)	7 (47; 15%)
Fetal Tachycardia	2 (70; 3%)	2 (4%)
1 minute Apgar	6.693 ± 1.852	6.708 ± 1.988
	(2-9)	(1-9)
5 minute Apgar	8.160 ± 1.091	8.229 ± 1.076
	(4-9)	(4-9)
Total perinatal complications[j]	1.333 ± .949	1.510 ± .767
	(0-3)	(0-3)
Neonatal Factors		
Anemia at birth[k]	19 (25%)	12 (24%)
Apnea	45 (60%)	34 (71%)
Bradycardia	33 (44%)	22 (45%)
Bronchopulmonary dysplasia	7 (9%)	2 (4%)
Days in Neonatal Intensive Care	43.067 ± 37.560	44.930 ± 23.169
	(5-245)	(9-102)
Hayline membrane disease[l]	49 (65%)	36 (76%)
Hyperbilirubinemia[m]	11 (74; 15%)	6 (12%)
Hypermagnesemia	6 (8%)	0
Hypotension[n]	1 (1%)	1 (2%)
Intracranial hemorrhage[o]	8 (11%)	7 (14%)
Meconium aspiration[~]	5 (73; 7%)	0 (0%)
Necrotizing enterocolitis[p]	2 (3%)	1 (2%)

Patent ductus arteriosus[q]	17 (23%)	12 (25%)
Peak bilirubin (mg/dl)[~]	9.412 ± 2.376 (74)	8.727 ± 2.064
	(5.40-16.90)	(5.3-13.60)
Persistent pulmonary stenosis	1 (1%)	0
Pneumothorax	0	0
Retinopathy of prematurity[r]	14 (19%)	7 (14%)
Sepsis (initial or acquired)[s]	8 (11%)	2 (4%)
Thrombocytopenia	6 (8%)	2 (4%)
Total neonatal complications[t]	2.000 ± 1.838	1.857 ± 1.173
	(0-7)	(0-5)
Total complications	4.573 ± 2.584	4.286 ± 1.732
	(0-11)	(1-8)

*p < .05, **p < .01, ***p < .001
Note. Frequencies are reported for discrete data, means and standard deviations for continuous data. Group differences examined via t test (continuous data), 2 X 2 $\chi 2$ with Yates correction (discrete data), or Fisher exact probability test (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 singleton and multiple gestation groups.
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, IUGR, membranes ruptured >12 hours, smoking during pregnancy.
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, C- section, forceps, general anesthesia, nuchal cord, and fetal tachycardia.
k 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 guiacs and abdominal distention.
q Diagnosed by clinical manifestations and echocardiographic information.
r ≤30 weeks group had 2 with Stage 1, 1 with Stage 2, 1 with Stage 3; >30 weeks group had 1 of unknown stage
s Established by positive blood culture.
t Total neonatal complications includes anemia, apnea, hyaline membrane disease, bronchopulmonary dysplasia, hyperbilirubinemia, hypermagnesemia, hypotension, intracranial hemorrhage, meconium aspiration, necrotizing enterocolitis, patent ductus arteriosus, persistent pulmonary stenosis, pneumothorax, retinopathy of prematurity, sepsis, and thrombocytopenia

Table 5
Antenatal and Neonatal Diagnostic and Intervention Procedures[a]

Diagnostic and intervention procedures	Singleton n=75	Multiples n=49
Artificial Reproduction Techniques***	10 (4 IVF, 4 Clomid, 2 other; 13%)	29 (21 IVF, 3 Clomid, 5 other; 59%)
Antenatal magnesium sulfate[b]	47 (73; 63%)	33 (69%)
Antenatal steroids[c~]	52 (69; 75%)	23 (40; 58%)
Antenatal steroids dose**	1.658 ± .606 (0-2)	1.286 ± .736 (0-2)
Hypertension medications (m)*	27 (68; 40%)	8 (43; 19%)
Neonatal cranial ultrasound	62 (74; 84%)	38 (80%)
Neonatal steroids	1 (1%)	0
Surfactant administration	21 (28%)	19 (39%)
Days respiratory support[d]	22.822 ± 43.380 (73) (0-245)	20.167 ± 30.922 (0-102)
Days ventilation	5.987 ± 20.90 (0-143)	1.796 ± 6.773 (0-47)
Highest percentage O_2 *	44.704 ± 27.895 (21-100)	33.333 ± 21.188 (21-93)
Home on O_2	8 (11%)	5 (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 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
d Including mechanical ventilation, continuous positive airway pressure (CPAP), nasal cannulae and oxyhood

Table 6

Summary of simultaneous multiple regression analyses for 47 multiples and 71 singletons

Index	Source	F	*df*	*p*	sr^2
WPPSI					
FSIQ	Multiple gestation	3.344	1,108	.070	.026
	Birth weight (grams)	2.065	1,108	.154	
	Growth rate (z-score)	.227	1,108	.635	
	Sex	1.685	1,108	.197	
	Socioeconomic status	17.090	1,108	<.001	.130
	Age at testing	3.250	1,108	.074	.025
	Total complications	1.026	1,108	.313	
Block Design	Multiple gestation	1.346	1,108	.248	
	Birth weight (grams)	3.014	1,108	.085	.025
	Growth rate (z-score)	.055	1,108	.814	
	Sex	.003	1,108	.985	
	Socioeconomic status	5.499	1,108	.021	.045
	Age at testing	4.163	1,108	.044	.034
	Total complications	5.001	1,108	.027	.041
Information	Multiple gestation	2.691	1,109	.104	.019
	Birth weight (grams)	.069	1,109	.793	
	Growth rate (z-score)	.068	1,109	.407	
	Sex	4.462	1,109	.795	
	Socioeconomic status	20.033	1,109	<.001	.144
	Age at testing	.692	1,109	.407	
	Total complications	1.188	1,109	.278	
CELF-P2					
Core	Multiple gestation	1.053	1,107	.307	
	Birth weight (grams)	2.175	1,107	.143	.017
	Growth rate (z-score)	.296	1,107	.587	
	Sex	.210	1,107	.647	
	Socioeconomic status	12.935	1,107	<.001	.102
	Age at testing	2.986	1,107	.087	.024
	Total complications	.001	1,107	.976	
Receptive	Multiple gestation	.714	1,109	.400	
	Birth weight (grams)	5.315	1,109	.023	.040
	Growth rate (z-score)	.967	1,109	.328	
	Sex	1.229	1,109	.270	
	Socioeconomic status	18.998	1,109	<.001	.141
	Age at testing	.935	1,109	.336	
	Total complications	.179	1,109	.673	
Expressive	Multiple gestation	.478	1,108	.491	
	Birth weight (grams)	4.176	1,108	.044	.035
	Growth rate (z-score)	.426	1,108	.516	
	Sex	2.086	1,108	.152	
	Socioeconomic status	9.550	1,108	.003	.081
	Age at testing	3.109	1,108	.081	.026
	Total complications	.070	1,108	.792	

Table 6. cont.

Index	Source	F	*df*	*p*	sr^2
Structure	Multiple gestation	.869	1,108	.354	
	Birth weight (grams)	4.179	1,108	.044	.033
	Growth rate (z-score)	.585	1,108	.446	
	Sex	2.940	1,108	.090	.023
	Socioeconomic status	15.486	1,108	<.001	.124
	Age at testing	3.232	1,108	.075	.026
	Total complications	.192	1,108	.662	
Content	Multiple gestation	.531	1,107	.468	
	Birth weight (grams)	5.262	1,107	.024	.042
	Growth rate (z-score)	.512	1,107	.476	
	Sex	1.093	1,107	.298	
	Socioeconomic status	11.065	1,107	.001	.087
	Age at testing	1.160	1,107	.284	
	Total complications	.010	1, 107	.922	
Pre-Literacy Rating Scale	Multiple gestation	.897	1,108	.346	
	Birth weight (grams)	1.037	1,108	.311	
	Growth rate (z-score)	.072	1,108	.789	
	Sex	4.860	1,108	.030	.029
	Socioeconomic status	17.614	1,108	<.001	.106
	Age at testing	25.920	1,108	<.001	.157
	Total complications	4.822	1,108	.030	.029
Descriptive Pragmatics	Multiple gestation	1.680	1,108	.346	
	Birth weight (grams)	.085	1,108	.771	
	Growth rate (z-score)	.376	1,108	.541	
	Sex	.071	1,108	.790	
	Socioeconomic status	5.874	1,108	.017	.047
	Age at testing	4.281	1,108	.041	.034
	Total complications	1.732	1,108	.191	
WJ-III					
Applied Problems	Multiple gestation	.757	1, 99	.386	
	Birth weight (grams)	.691	1, 99	.408	
	Growth rate (z-score)	.146	1, 99	.704	
	Sex	4.660	1, 99	.033	.040
	Socioeconomic status	13.340	1, 99	<.001	.114
	Age at Testing	.535	1, 99	.466	
	Total complications	.117	1, 99	.733	
Quantitative Reasoning	Multiple gestation	.722	1, 96	.398	
	Birth weight (grams)	.084	1, 96	.773	
	Growth rate (z-score)	3.162	1, 96	.079	.028
	Sex	.178	1, 96	.674	
	Socioeconomic status	11.854	1, 96	.001	.104
	Age at testing	.285	1, 96	.594	
	Total complications	.620	1, 96	.433	

Table 6. cont.

Index	Source	F	*df*	*p*	sr^2
NEPSY-2					
Word Generation	Multiple gestation	11.701	1,95	.001	.092
	Birth weight (grams)	3.490	1,95	.065	.028
	Growth rate (z-score)	4.027	1,95	.048	.032
	Sex	3.418	1,95	.068	.027
	Socioeconomic status	2.028	1,95	.158	
	Age at testing	3.302	1,95	.072	.026
	Total complications	5.074	1,95	.027	.04
Statue	Multiple gestation	.271	1,96	.604	
	Birth weight (grams)	.404	1,96	.526	
	Growth rate (z-score)	1.592	1,96	.210	
	Sex	7.722	1,96	.007	.070
	Socioeconomic status	.101	1,96	.751	
	Age at testing	.554	1,96	.458	
	Total complications	1.738	1,96	.190	
Oromotor Sequences	Multiple gestation	7.336	1,92	.008	.056
	Birth weight (grams)	.549	1,92	.460	
	Growth rate (z-score)	.073	1,92	.787	
	Sex	4.301	1,92	.041	.036
	Socioeconomic status	12.541	1,92	.001	.104
	Age at testing	4.393	1,92	.039	.036
	Total complications	.512	1,92	.476	
PDMS-2					
Total Motor Quotient	Multiple gestation	4.390	1, 101	.039	.035
	Birth weight (grams)	4.261	1, 101	.042	.033
	Growth rate (z-score)	.022	1, 101	.882	
	Sex	5.134	1, 101	.026	.041
	Socioeconomic status	2.917	1, 101	.091	.023
	Age at testing	11.953	1, 101	.001	.095
	Total complications	.012	1, 101	.915	
Fine Motor Quotient	Multiple gestation	5.936	1, 105	.017	.043
	Birth weight (grams)	8.177	1, 105	.005	.059
	Growth rate (z-score)	.462	1, 105	.498	
	Sex	12.313	1, 105	.001	.089
	Socioeconomic status	8.608	1, 105	.004	.063
	Age at testing	1.329	1, 105	.252	
	Total complications	.567	1, 105	.453	
Gross Motor Quotient	Multiple gestation	1.569	1, 102	.213	
	Birth weight (grams)	.561	1, 102	.456	
	Growth rate (z-score)	.229	1, 102	.633	
	Sex	.943	1, 102	.334	
	Socioeconomic status	.145	1, 102	.704	
	Age at testing	25.649	1, 102	<.001	.196
	Total complications	.103	1, 102	.749	

Table 7
Summary of simultaneous multiple regression analyses for 44 twins and 71 singletons including interactions

Index	Source	F	*df*	*p*	sr^2
WPPSI					
FSIQ	Twin gestation	.043	1,104	.836	
	Sex	.698	1,104	.405	
	Multiple*Sex	.096	1,104	.757	
	Birth weight (grams)	2.045	1,104	.156	
	Growth rate (z-score)	.209	1,104	.648	
	Socioeconomic status	15.264	1,104	<.001	.123
	Age at testing	3.010	1,104	.086	.024
	Total complications	1.043	1,104	.310	
Block Design	Twin gestation	.704	1,104	.403	
	Sex	.095	1,104	.759	
	Multiple*Sex	.304	1,104	.582	
	Birth weight (grams)	3.129	1,104	.080	.027
	Growth rate (z-score)	.080	1,104	.778	
	Socioeconomic status	4.365	1,104	.039	.037
	Age at testing	3.259	1,104	.074	.028
	Total complications	5.006	1,104	.027	.043
Information	Twin gestation	.560	1,105	.456	
	Sex	.868	1,105	.868	
	Multiple*Sex	1.595	1,105	.209	
	Birth weight (grams)	.053	1,105	.818	
	Growth rate (z-score)	.035	1,105	.853	
	Socioeconomic status	19.431	1,105	<.001	.145
	Age at testing	1.009	1,105	.318	
	Total complications	1.139	1,105	.288	
CELF-P2					
Core	Twin gestation	.492	1,103	.485	
	Sex	.126	1,103	.724	
	Multiple*Sex	1.057	1,103	.306	
	Birth weight (grams)	2.033	1,103	.157	
	Growth rate (z-score)	.218	1,103	.641	
	Socioeconomic status	12.434	1,103	.001	.102
	Age at testing	3.280	1,103	.073	.027
	Total complications	.004	1,103	.952	
Receptive	Twin gestation	.749	1,103	.389	
	Sex	.019	1,103	.890	
	Multiple*Sex	1.227	1,103	.271	
	Birth weight (grams)	5.513	1,103	.021	.004
	Growth rate (z-score)	.744	1,103	.390	
	Socioeconomic status	17.689	1,103	<.001	.136
	Age at testing	1.067	1,103	.304	
	Total complications	221	1,103	.639	

Table 7. cont.

Index	Source	F	df	p	sr^2
Expressive	Twin gestation	1.739	1,96	.190	
	Sex	.058	1,96	.810	
	Multiple*Sex	2.294	1,96	.133	
	Birth weight (grams)	4.644	1,96	.034	.004
	Growth rate (z-score)	.346	1,96	.558	
	Socioeconomic status	8.487	1,96	.004	.073
	Age at testing	3.567	1,96	.062	.031
	Total complications	.157	1,96	.693	
Structure	Twin gestation	2.198	1,96	.141	
	Sex	.080	1,96	.778	
	Multiple*Sex	3.093	1,96	.082	.025
	Birth weight (grams)	4.710	1,96	.032	.039
	Growth rate (z-score)	.441	1,96	.508	
	Socioeconomic status	14.212	1,96	<.001	.116
	Age at testing	3.885	1,96	.052	.032
	Total complications	3.093	1,96	.082	.002
Content	Twin gestation	.194	1,103	.660	
	Sex	.171	1,103	.680	
	Multiple*Sex	.394	1,103	.531	
	Birth weight (grams)	5.449	1,103	.022	.045
	Growth rate (z-score)	.418	1,103	.519	
	Socioeconomic status	9.712	1,103	.002	.079
	Age at testing	1.090	1,103	.299	
	Total complications	.028	1,103	.868	
Pre-Literacy Rating Scale	Twin gestation	.245	1,102	.621	
	Sex	3.278	1,102	.073	.020
	Multiple*Sex	.040	1,102	.841	
	Birth weight (grams)	.885	1,102	.349	
	Growth rate (z-score)	.026	1,102	.872	
	Socioeconomic status	16.712	1,102	<.001	.105
	Age at testing	23.564	1,102	<.001	.147
	Total complications	4.450	1,102	.037	.028
Descriptive Pragmatics	Twin gestation	.132	1,104	.717	
	Sex	.081	1,104	.776	
	Multiple*Sex	<.001	1,104	.988	
	Birth weight (grams)	.084	1,104	.772	
	Growth rate (z-score)	.312	1,104	.578	
	Socioeconomic status	5.371	1,104	.022	.050
	Age at testing	3.919	1,104	.050	.028
	Total complications	1.702	1,104	.195	

Table 7 cont.

Index	Source	F	*df*	*p*	sr^2
WJ-III					
Applied Problems	Twin gestation	.689	1,95	.409	
	Sex	1.118	1,95	.293	
	Multiple*Sex	1.185	1,95	.279	
	Birth weight (grams)	.759	1,95	.386	
	Growth rate (z-score)	.095	1,95	.758	
	Socioeconomic status	12.449	1,95	.001	.110
	Age at testing	.782	1,95	.379	
	Total complications	.194	1,95	.660	
Quantitative Reasoning	Twin gestation	.240	1,92	.626	
	Sex	.032	1,92	.859	
	Multiple*Sex	.586	1,92	.446	
	Birth weight (grams)	.108	1,92	.743	
	Growth rate (z-score)	2.793	1,92	.098	.026
	Socioeconomic status	11.378	1,92	.001	.104
	Age at testing	.449	1,92	.504	
	Total complications	.583	1,92	.447	
NEPSY-2					
Word Generation	Twin gestation	.123	1,93	.727	
	Sex	1.123	1,93	.292	
	Multiple*Sex	.523	1,93	.471	
	Birth weight (grams)	2.815	1,93	.097	.022
	Growth rate (z-score)	3.454	1,93	.066	.028
	Socioeconomic status	2.708	1,93	.103	
	Age at testing	2.306	1,93	.132	
	Total complications	4.650	1,93	.034	.037
Statue	Twin gestation	.043	1,92	.836	
	Sex	4.124	1,92	.045	.040
	Multiple*Sex	.066	1,92	.797	
	Birth weight (grams)	.140	1,92	.709	
	Growth rate (z-score)	1.537	1,92	.218	
	Socioeconomic status	.000	1,92	.999	
	Age at testing	.292	1,92	.590	
	Total complications	1.208	1,92	.275	
Oromotor Sequences	Twin gestation	1.274	1, 90	.262	
	Sex	.173	1,90	.679	
	Multiple*Sex	4.149	1,90	.045	.034
	Birth weight (grams)	.662	1, 90	.418	
	Growth rate (z-score)	.134	1,90	.716	
	Socioeconomic status	14.446	1,90	<.001	.120
	Age at testing	6.515	1,90	.012	.054
	Total complications	.554	1,90	.458	

Table 7 cont.

Index	Source	F	*df*	*p*	*sr*^{2}
PDMS-2					
Total Motor Quotient	Twin gestation	2.674	1, 97	.105	
	Sex	.340	1, 97	.561	
	Multiple*Sex	5.011	1, 97	.027	.040
	Birth weight (grams)	4.979	1, 97	.028	.040
	Growth rate (z-score)	.033	1, 97	.855	
	Socioeconomic status	2.783	1, 97	.099	.022
	Age at testing	13.484	1, 97	<.001	.108
	Total complications	.002	1, 97	.961	
Fine Motor Quotient	Multiple gestation	.180	1,100	.673	
	Sex	2.796	1,100	.098	.020
	Multiple*Sex	3.619	1,100	.060	.025
	Birth weight (grams)	8.910	1,100	.004	.062
	Growth rate (z-score)	.254	1,100	.615	
	Socioeconomic status	7.424	1,100	.008	.052
	Age at testing	3.222	1,100	.076	.022
	Total complications	3.311	1,100	.072	.023
	Multiple*Total complications	6,326	1, 100	.013	.044
Gross Motor Quotient	Twin gestation	1.526	1,98	.220	
	Sex	.030	1,98	.862	
	Multiple*Sex	2.301	1,98	.133	
	Birth weight (grams)	1.100	1,98	.297	
	Growth rate (z-score)	.146	1,98	.703	
	Socioeconomic status	.020	1,98	.887	
	Age at testing	26.052	1,98	<.001	.205
	Total complications	.003	1,98	.960	

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ABSTRACT

TWIN GESTATION AND NEUROPSYCHOLOGICAL OUTCOME OF PRESCHOOL AGE CHILDREN BORN PREMATURELY

by

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August 2015

Advisor: Dr. Sarah Raz

Major: Psychology (Clinical)

Degree: Master of Arts

Multiples are thought to be at increased risk for developmental outcome deficits in the preschool years, following preterm birth. However, little research has been conducted to determine whether this group remains at higher risk in the age of artificial reproductive techniques and the modern NICU. The purpose of this study was to investigate whether multiplicity is a risk factor for neuropsychological outcome deficits in a sample of 118 preschoolers (49 multiples, 75 singletons) born prematurely (<34 weeks gestation). As predicted, there were significant relationships between multiplicity and outcome measures, however, the direction of the effects were opposite to our prediction, with multiplies demonstrating superior performance. Additionally, significant multiplicity by sex interactions revealed a female twin advantage over male twin and singleton performance. In this preschool age sample, preterm multiples were not at a disadvantage when compared to singleton counterparts, demonstrating either equivalent or superior neuropsychological performance.

AUTOBIOGRAPHICAL STATEMENT

Jamie Piercy was raised in Kelowna, British Columbia, Canada. She moved to Victoria, BC to complete her undergraduate degree at the University of Victoria. While spending her third year of study at the University of British Columbia, Jamie took her first neuropsychology class and was a practicum student in a neuropsychological rehabilitation unit. This experience and associated mentorship further inspired her career goals in Clinical Neuropsychology. She graduated with her Bachelor of Science in Psychology from the University of Victoria in 2013 with aims of learning more about brain-behavior relationships across the lifespan.

Jamie moved to Michigan to study Clinical Psychology at Wayne State University in 2013. She works with Dr. Sarah Raz studying child neuropsychology, specifically investigating relationships between preterm birth and neurodevelopmental outcomes in preschoolers. Clinically, Jamie works with children and adults at the Wayne State Psychology Clinic, where she conducts assessments and provides group and individual psychotherapy. She plans to continue to seek research and clinical experience with children who suffer from various neurological impairments. She plans to complete her Master of Arts in Clinical Psychology from Wayne State University in August of 2015.