GROWTH OUTCOMES AT 18 MONTHS CORRECTED AGE IN VERY LOW BIRTH WEIGHT INFANTS

BY

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LIST OF ABBREVIATIONS

BMI: body mass index

BPD: bronchopulmonary dysplasia

CDC: Centers for Disease Control and Prevention

ELBW: extremely low birth weight

ELGAN: extremely low gestational age newborn

FGR: fetal growth restriction

GA: gestational age

ICU: intensive care unit

IVH: intraventricular hemorrhage

LDL: low-density lipoprotein

NEC: necrotizing enterocolitis

NICU: neonatal intensive care unit

SD: standard deviation

VLBW: very low birth weight

WHO: World Health Organization

ABSTRACT

BACKGROUND: With increasing survival of preterm very low birth weight (VLBW) infants, the long-term effects of being born prematurely are now being recognized. Evidence is emerging that prematurity is associated with overweight or obesity status and long-term cardiometabolic derangements in adolescence or adulthood and that specific neonatal variables may affect this association.

OBJECTIVE: The objective of this study was to assess growth outcomes after NICU discharge at 18 months corrected age in very low birth weight infants (≤1500 grams) as compared to standardized norms and to compare weight-for-age and BMI-for-age z-scores at 18 months corrected age in VLBW infants with and without bronchopulmonary dysplasia as well as with and without fetal growth restriction.

METHODS: This is a retrospective cohort study for the time period 2002-2011. Inclusion criteria for this study include birthweight of ≤1500 grams and regular follow-up at our NICU Follow-Up Clinic. Over a ten-year period, 2572 infants were followed in clinic. Neonatal variables collected include bronchopulmonary dysplasia, necrotizing enterocolitis, and intraventricular hemorrhage, as well as growth parameters of the infants at birth and 18 months of age. To derive weight, height, and body mass index (BMI) percentiles and z-scores, we used the SAS macro from the Center for Disease Control. Linear regression was used to evaluate the associations between BPD, FGR, and growth outcomes, adjusting for maternal age, sex, and race.

RESULTS: Both female and male VLBW infants at 18 months corrected age had lower average weight-for-age z-scores as compared to normative data provided by the Centers for Disease Control and Prevention (CDC) (-0.3, -0.39 respectively). However both female and male VLBW infants had average BMI-for-age z-scores that were higher than their term counterparts (0.82, 1.77 respectively). BPD infants at 18 months corrected age had lower average weight-for-age z-

scores than non-BPD infants (-0.73 vs. -0.45; p=0.002). Average BMI-for-age z-scores were not different among infants with and without BPD (1.76 vs. 2.3; p=0.34). Weight-for-age z-score at 18 months corrected age was lower among those with FGR vs non-FGR infants (-1.36 vs. -0.48; p<0.0001). However, BMI-for-age z-scores were not significantly different between the two groups (1.24 vs. 2.16; p=0.11).

CONCLUSION: At 18 months corrected age VLBW infants have weight-for-age z-scores lower than reference standards. Alternatively, VLBW infants have BMI-for-age z-scores higher than reference standards. BMI-for-age z-scores were lower in both the BPD and FGR groups, as opposed to the non-BPD and non-FGR groups respectively, however there was not a significant difference. BMI-for-age z-scores at 18 months corrected age may an early predictor of long term growth in VLBW infants.

PART I – PROPOSAL

BACKGROUND

According to the CDC, one in nine children is born preterm (<37 weeks) in the United States. Therefore, the growth of approximately 11% of the US pediatric population is affected by prematurity status. Preterm infants are surviving the neonatal period more today than ever before.[1,2] As such, we are beginning to recognize some of the long-term correlates of being born prematurely. Studies are emerging that suggest that as premature infants age, they may be at greater risk for overweight and obesity status and associated cardiovascular diseases. Among individuals born prematurely, specific neonatal variables may be associated with risk for later onset of obesity and cardiometabolic disease in adolescence and early adulthood.

A subset of preterm infants, those born at very low birth weight (<1500 grams), may be particularly at risk. These infants have higher caloric and protein demands in the first few weeks to months of their lives, due to their developing and growing bodies, even more so than other preterm infants with larger birth weights. Very low birth weight (VLBW) infants also require fat supplementation as their bodies have not yet developed the brown fat that typically develops later in gestation. Without brown fat, caloric intake is needed to maintain thermoregulation. Furthermore, the nutritional requirements are even greater if they are combating other neonatal comorbidities. One of these comorbidities is chronic lung disease of prematurity otherwise known as bronchopulmonary dysplasia (BPD). BPD is extremely prevalent in very low birth weight newborns, with prevalence estimates of approximately 30%.[3] Nutritional demands are higher in infants with BPD due to early growth failure and increased metabolic demands from increased work of breathing.[4] Another comorbidity is fetal growth restriction (FGR) or being born small for gestational age, which is birthweight less than 10% of expected for gestational age. For such infants, emphasis is placed during the first few months of life on attaining catch up growth. In a

large Dutch cohort study, catch-up growth in height by 10 years was more frequent among FGR children with a fast initial weight gain.[5] Growth and adequate nutrition is extremely important during the neonatal period in preterm infants. However, growth patterns outside of the neonatal period remain poorly understood in all preterm infants, but particularly in VLBW infants and VLBW infants with neonatal comorbidities. Studies suggest that preterm infants are at risk of becoming overweight or obese by the time they reach adolescence and/or adulthood.[6-7] There may be earlier signs in growth patterns that may characterize persons at increased risk of overweight or obesity status.

Current published data on the growth of preterm infants show a range of outcomes, with variable results and conclusions. Historically, there was concern that VLBW infants were at risk of growth failure early in life. Several published reports demonstrate poor growth outcomes in the first two years of life for those born preterm. Sices et al. performed a prospective cohort study of extremely low birth weight (<1 kg) infants through 20 months of age and found that growth failure was common in extremely low birth weight infants and that bronchopulmonary dysplasia was the main factor associated with growth failure.[8] Furthermore, in a prospective cohort study by Ehrenkranz et al. of infants with birthweight 501-1000g, they found that in-hospital weight gain influenced the likelihood of growth below the 10th percentile at 18 to 22 months' corrected age, even accounting for those born small-for-gestational age (or <10% than expected for any given gestational age).[9] Finally, in a retrospective review by Garcia et al. which evaluated 4,944 VLBW infants (≤1500g at birth), they found that at the age of two years, 44.2% of children had a weight more than 2 standard deviations below expected for age.[10] Further findings in this cohort showed those born ≤ 1000g had the worst growth outcomes at the age of two.

Children born preterm demonstrate poor growth outcomes beyond the first two years of life. In a longitudinal prospective study of a Swedish national cohort born at <26 weeks gestation, growth was assessed from birth to age 11 years. They found that extremely preterm children have growth failure in early extra-uterine life and remain lighter and shorter than control participants at

11 years of age.[11] Interestingly, there were significantly larger childhood gains of body mass index (BMI) in extremely preterm children than in control participants[11] indicating some attainment of catch-up growth though the extremely preterm cohort persist in being smaller than their full-term counterparts. Hack et al found similar results in their longitudinal study showing accelerated growth after a period of neonatal growth failure with extremely-low-birth weight infants remaining smaller than their term peers at 14 years of age.[12] The Epicure study, also supported this finding of poor somatic growth in extremely preterm infants (< 26 weeks gestation) during the first 6 years after birth as compared to matched participants born at term.[13] They found that "being born extremely preterm is associated with poor longitudinal somatic growth, with little catch-up over the preschool years. By 6 years the EP [extremely preterm] children remain significantly shorter, lighter, and have a smaller head circumference"[13] than matched classmates born at term.

In contrast to the data showing poor growth outcomes, some data exist that support accelerated growth in preterm infants. Accelerated growth in term infants can increase risk of obesity. In a longitudinal observational study in the US of a national cohort of 14,000 children, crossing the 85th percentile of BMI before kindergarten age was a powerful predictor of severe obesity and additionally those that had crossed by 9 months of age had double the odds of severe obesity by kindergarten age.[14] Additionally, in a prospective cohort study of full term infants, more-rapid increases in weight/length ratio in the first 6 months of life were associated with increased risk of obesity by age 3.[15] Less is known about risk factors for obesity in preterm infants, but new data are emerging. In a prospective cohort study of infants ≤37 weeks gestation, the overall conclusion was that increased weight gain in the first year of life predicted later obesity status at 8 years of age.[6] Gianni et al. examined growth at various time points in the lives of extremely low birth weight infants and concluded that growth trajectories should be monitored into adulthood in order to delineate potential long-term health implications and growth differences by gender.[16] Other studies suggest that the association between low birth weight and

cardiovascular and metabolic derangements are modified by postnatal factors, specifically early growth failure and rapid weight gain during adolescence and adulthood.[17-20] In a study of extremely low birth weight infants (501-1000g), Saigal et al. found initially growth failure with poor weight gain in the first year of life followed by accelerated weight gain through adolescence.[21] A prospective cohort study of preterm infants by Gaskins et al. found that accelerated growth during infancy increases risk of overweight and obesity status at 11 years of age.[7] And finally, Norris et al. report that accelerated weight gain between 0 and 24 months predicted higher insulin resistance whereas accelerated weight gain after 48 months increased risk for adult glucose intolerance.[22] These findings further support that early infant growth patterns in formerly preterm infants may be a risk factor not only for overweight and obesity status from childhood into adulthood, but that there may be other effects, including cardiovascular and metabolic derangements, that require further study.

In addition to descriptions of growth patterns exhibited by individuals born prematurely, emerging data suggest that there may be increased risk of adverse long-term cardiovascular and metabolic outcomes in preterm infants. Lewandowski et al. report that preterm birth is associated with an increase in cardiac myocardial mass and that preterm-born young adults have shorter cardiac ventricles, smaller internal ventricular cavity diameters, and distinct reductions in left and right ventricular function.[23] Therefore, preterm infants may have an altered cardiovascular phenotype related to prematurity that, in addition to structural effects on the heart, may put them at risk for cardiovascular and metabolic derangements. Dalziel et al. found that preterm birth was associated with increased systolic blood pressure and insulin resistance at age 30, and that preterm birth and not poor fetal growth was the major determinant of this association.[24] A large Swedish national cohort study was conducted to further evaluate the link between prematurity and hypertension. They found that extreme prematurity was associated with a 2.5 fold higher risk of antihypertensive medication prescription in young adulthood compared with those born at full term.[25] Furthermore, a systematic review of 27 observational studies compared blood pressure of

children, adolescents, or adults born preterm with those that were born at term. Average age at systolic blood pressure measurement was 17.8 years (range: 6.3-22.4 years). The reviewers concluded that infants born preterm have modestly higher systolic blood pressure later in life and may be at increased risk for developing hypertension and its sequelae.[26] In addition to hypertension, glucose regulation may also be affected by prematurity. Hovi et al administered an oral glucose-tolerance test to young adults divided between two groups, those born at very low birth weight (≤1500g) and those born at term but not small for gestational age. They measured insulin and glucose concentrations at baseline and at 120 minutes and found that those who were former very low birth weight infants had higher indices of insulin resistance, glucose intolerance, and higher blood pressure than those born at term.[27] However, a systematic review and meta-analysis arrived at the opposite conclusion. This review found that there were no differences between adults born preterm and term for the majority of outcomes associated with metabolic syndrome; however they did find that preterm birth was associated with significantly higher blood pressure and higher low-density lipoprotein (LDL).[28] Interestingly, the analyses also showed no significant difference in BMI in adults born preterm and term.

In addition to the association of prematurity and long term cardiovascular and metabolic outcomes, data are also emerging about long-term cardiovascular and metabolic effects associated with accelerated growth patterns. After comparing FGR and non-FGR term infants, Fabricius-Bjerre et al. suggested that accelerated growth during the first three months of life may increase risk of later metabolic disturbances in FGR individuals.[29] Also Whincup et al. reported an inverse relationship between birth weight and type 2 diabetes mellitus.[30] In a prospective cohort study of full term healthy young children, excess early postnatal weight gain led to thicker arterial walls, supporting the view that cardiovascular disease is associated with early growth patterns.[31] With overweight and obesity status in this country now a major health problem in terms of morbidity and mortality, as well as contributing to significant healthcare costs, prematurity and early growth patterns may be an under-recognized risk factor that warrants further investigation. Furthermore,

neonatal comorbidities associated with prematurity and its effect on postnatal growth should be examined.

One of these neonatal comorbidities is bronchopulmonary dysplasia or BPD. BPD is a common neonatal comorbidity in VLBW infants with an incidence of approximately 30%, as previously mentioned.[3] Investigators have evaluated growth outcomes in very low birth weight infants with the complication of BPD. In a retrospective cohort study conducted by Natarajan et al, infants born at < 28 weeks gestation who developed *severe* BPD, commonly had progressive postnatal growth failure during their NICU hospitalization.[32] FGR has been shown to be a risk factor for the development of BPD in extremely preterm infants.[33] In a prospective cohort study conducted by Madden et al, they compared z-scores of weight, length and head circumference in infants born <28 weeks with BPD between 2 time periods, 1996-1999 and 2000-2003, in order to "determine whether changes in neonatal practice and morbidity since 2000 have improved the growth attainment of infants with bronchopulmonary dysplasia (BPD)".[34] They found that despite improvements in weight since 2000, poor growth attainment was a major problem among these infants. Interestingly, in a preliminary study by Perlin et al., suggestion of an increased risk for abnormally accelerated growth in BPD infants was found,[35] which contradicts many earlier studies. In fact, these infants did not merely have a greater risk of being overweight, but a statistically significant greater risk in obesity status by 2 years of age.

Another neonatal factor that impacts postnatal growth independently from other neonatal comorbidites is fetal growth restriction (FGR) or birthweight that is small for gestational age (<10th percentile for gestational age). Ibanez et al. found that, FGR children continued to gain excess abdominal fat after completion of catch-up weight gain.[36] Gaskins et al. reported that FGR was a significant independent predictor of overweight at 11 years of age.[21] And Ong et al. reported that infants with lower birth weights were more likely to show rapid infancy growth between zero and two years of age.[37-38] Infants with fetal growth restriction appear to have

abnormal growth patterns that need further elucidation. Furthermore, whether FGR status is predictive of growth outcomes in infants with BPD has yet to be studied.

The following conceptual model (Figure 1) is a visual representation of some of the multifactorial effects contributing to growth outcomes in the first two years of life in VLBW infants and perhaps even beyond into adolescence and adulthood. It lists demographic and neonatal variables that will be included in this study. The demographic variables are gestational age at birth, race, gender, maternal age, and marital status. The neonatal characteristics include fetal growth restriction, bronchopulmonary dysplasia, necrotizing enterocolitis, and intraventricular hemorrhage. These neonatal variables may directly impact infant growth outcomes in the first years of life.

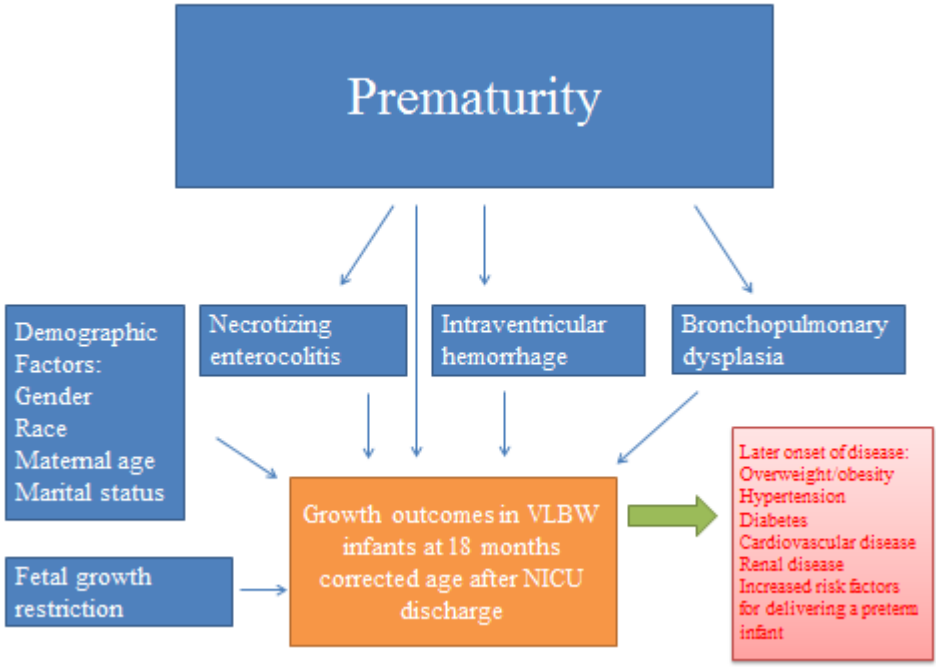

Figure 1. Conceptual model for prematurity, demographic factors, and neonatal comorbidities that may be associated with adverse growth outcomes at 18 months corrected age.

In summary, these studies of growth patterns of infants born preterm lack consistency with regard to whether: 1) during early childhood, preterm infants exhibit less weight gain than infants born at term; 2) during early childhood, preterm infants exhibit accelerated growth as compared to infants born at term; 3) preterm infants with BPD exhibit a pattern of growth that differs from preterm infants without BPD; and 4) FGR infants exhibit a pattern of growth that differs from non-FGR infants. The lack of consistency may be related to the exclusion of various neonatal comorbidities that may significantly impact growth. Overweight or obesity status may further predict other health risk factors in this population including cardiovascular and metabolic derangements that can affect quality and length of life.

The objective of this study is to evaluate growth outcomes at 18 months corrected age in VLBW infants, and to further assess growth outcomes in the subset of infants with BPD and FGR at 18 months corrected age. This study is clinically significant in that the comprehension of growth patterns in early life will further our understanding of later health risks and outcomes, and inform interventions to decrease the risk of long-term adverse health outcomes. By identifying infants at high risk of overweight or obesity later in life, we can provide earlier anticipatory guidance to parents during healthcare visits by discussion of the change in nutritional requirements as a child versus as a small neonate in the ICU.

SPECIFIC AIMS

1. AIM #1: Assess achieved growth after NICU discharge at 18 months corrected age in very low birth weight infants (≤1500 grams) as compared to standardized norms.

    a. Hypothesis #1: VLBW infants at 18 months corrected age will have positive weight-for-age and BMI-for-age z-scores.

2. AIM #2: Compare growth after NICU discharge at 18 months corrected age in very low birth weight infants (≤1500 grams) with and without bronchopulmonary dysplasia.

    a. Hypothesis #2: VLBW infants with bronchopulmonary dysplasia will have higher weight-for-age and BMI-for-age z-scores at 18 months corrected age than those very low birth weight infants without bronchopulmonary dysplasia.

3. AIM #3: Compare growth after NICU discharge at 18 months corrected age in very low birth weight infants (≤1500 grams) with FGR status and without FGR status.

    a. Hypothesis #3: VLBW infants that have fetal growth restriction will have higher weight-for-age and BMI-for-age z-scores at 18 months corrected age than those without fetal growth restriction.

METHODS

The purpose of this study is to assess growth outcomes after NICU discharge at 18 months corrected age in VLBW infants (≤1500 grams) as compared to standardized norms provided by the Centers for Disease Control and Prevention. Additionally, we will compare weight-for-age and BMI-for-age z-scores after NICU discharge at 18 months corrected age in VLBW infants with and without BPD as well as with and without FGR. This is a retrospective cohort study utilizing an existing database, the Wake Forest Baptist Health NICU Follow-Up Clinic database for the time period 2002-2011. Data collected include demographic information like gestational age, race, and gender. Neonatal factors include bronchopulmonary dysplasia, necrotizing enterocolitis, and intraventricular hemorrhage, as well as growth parameters of the infants at birth and 18 months of age. Growth parameters include weight, length, head circumference, and body mass index. Growth at 18 months will be charted using World Health Organization growth charts for males and females (0-2 years).[39] Fenton growth charts will be used for birth growth parameters.[40] Outcomes are weight-for-age z-scores and BMI-for-age z-scores at 18 months corrected age in VLBW infants. Secondary outcomes are weight-for-age z-scores and BMI-for-age z-scores in VLBW infants with and without BPD as well as with and without FGR.

The Wake Forest Baptist Health NICU Follow-Up Clinic is a clinic for high-risk former NICU infants following discharge through 24 months corrected age. This clinic follows children with a birthweight of ≤1500 grams. Historically, infants were followed in clinic until the corrected age of 18 months, which is the case for the time frame of this retrospective study. Inclusion criteria for this study include birthweight of ≤1500 grams and regular follow-up at our NICU Follow-Up Clinic from 2002-2011. Approximately 200 new infants per year are seen at the follow-up clinic who were born ≤1500 grams. Over a ten-year period, 2572 infants were followed in the clinic. This should be a representative sample of the population of VLBW infants born in our region, as we have the only two level III NICUs in the area (Brenner Children's NICU and

Novant Health Forsyth Medical Center NICU). All infants that were ≤1500 grams at birth and inpatient at one of the aforementioned two NICUs are referred upon discharge to our clinic.

This chart review was submitted to Wake Forest University Health Sciences Institutional Review Board for an expedited review due to the retrospective nature of the study and was approved (Jan 2015; study ID# 00023520).

DATA ANALYSIS

Statistical tests used to compare baseline characteristics were chi-square test for categorical variables and Student's two-sample t-test for continuous variables. For specific aim 1, data were analyzed using the one-sample t-test. The exposure in aim 1 was premature birth and the outcome was weight-for-age and BMI-for-age z-scores at 18 months corrected age. For specific aims 2 and 3, data were analyzed using linear regression, adjusting for maternal age, infant gender and infant race. The exposure was BPD or FGR respectively and the outcome was weight-for-age and BMI-for-age z-scores at 18 months corrected age. The z-scores already take into account gender. For further analyses, we adjusted for maternal age, infant gender and infant race, in addition to neonatal comorbidities that may impact growth including necrotizing enterocolitis and intraventricular hemorrhage.

Table 1. Maternal and Infant Characteristics of the VLBW cohort

	Total	BPD	Non-BPD	p[§]	FGR	Non-FGR	p[§]
Gestational age							
Birthweight							
Female %							
Race African American Caucasian Asian Hispanic Other							
Maternal age							
Marital status							

[§] P values are derived from Student's two-sample t-test for continuous variables and Chi square test for categorical variables.

Table 2. Anthropometric results at 18 months corrected age for VLBW males and females as compared to standardized norms.

	N	Mean	SD	CI
Males				
WEIGHT (kg)				
WEIGHT (z-score)				
LENGTH (cm)				
LENGTH (z-score)				
HEAD CIRC (cm)				
HEAD CIRC (z-score)				
BMI (kg/m^2)				
BMI (z-score)				
Females				
WEIGHT (kg)				
WEIGHT (z-score)				
LENGTH (cm)				
LENGTH (z-score)				
HEAD CIRC (cm)				
HEAD CIRC (z-score)				
BMI (kg/m^2)				
BMI (z-score)				

Table 3. Results for BPD and FGR predicting weight-for-age and BMI-for-age z-scores at 18 months corrected age

	BPD	Non-BPD	p[§]	FGR	Non-FGR	p[§]
N(%)						
WEIGHT						
Mean kg±SD						
Mean z-score±SD						
Z-score>2, n(%)						
BMI						
Mean BMI±SD						
Mean z-score±SD						
Z-score>2, n(%)						

[§] P values are derived from linear regression analyses adjusting for maternal age, infant gender, and infant race.

TIMETABLE

	Time Block		
	1 **(Sept 2015 - Apr 2016)**	**2** **(May-July 2016)**	**3** **(Aug-Dec 2016)**
Revision of protocol	X	X	
Obtain IRB approval	X		
Extract data from database	X		
Statistical analyses		X	X
Thesis draft submission		X	X
Thesis final submission and oral defense			X
Manuscript writing and submission			X

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PART II - MANUSCRIPT

BACKGROUND

Very low birth weight (≤1500 grams), which affects about 1% of all newborns in the US, is a strong risk factor for poor growth in childhood. Explanations for this association include inadequate caloric intake and abnormally high caloric demands in the first weeks of life, due to serious illnesses associated with very low birth weight (VLBW) birth. Despite efforts to improve neonatal nutrition[1-2] and reduce the severity of neonatal illnesses,[3] estimates of the prevalence of body weight more than two standard deviations below normal for corrected age range from 36% to 44%.[4-5] Among VLBW infants, poor growth during infancy is associated with adverse neurodevelopmental outcomes, but excessive "catch up" growth could lead to obesity,[6] increasing the risk of cardiovascular,[7-11] metabolic,[12] and other adverse health outcomes.[13-17] Thus there is a lack of agreement among clinicians about the optimal growth pattern for VLBW infants.[18] Further, among VLBW infants, optimal patterns of growth might differ across subgroups defined by fetal or neonatal morbidities.

Two morbidities known to influence growth of VLBW infants are bronchopulmonary dysplasia (BPD) and fetal growth restriction (FGR) defined as birthweight <10% of expected for gestational age. BPD, which develops in approximately 30% of VLBW,[19] is associated with higher nutritional demands due to early growth failure and increased work of breathing.[20] While FGR is associated with low weight for age during infancy, it also has been associated with a higher risk of being overweight at 11 years of age.[21] Further, accelerated growth during the first three months of life may increase risk of later metabolic disturbances in FGR individuals.[22]

The purpose of this study was to describe rates of poor and excessive growth among VLBW infants in the first years of life and compare rates for infants with and without FGR and with and without BPD.

METHODS

Study Participants

As neonates, study participants were hospitalized in either of two large level 3 neonatal intensive units affiliated with Wake Forest School of Medicine, one at Wake Forest Baptist Health and the other at Novant Health Forsyth Medical Center. Between January 2002 and December 2011, 2853 infants with birth weight ≤ 1500 grams were admitted to these units and survived to discharge. Of the survivors, 2572 (90%) were followed in the NICU Follow Up Clinic and 1149 (45%) returned for follow up at 18 months corrected age and had complete data on age, weight and length in the database. Measurements were obtained by physicians, pediatric nurse practitioners, or a nurse with special expertise in neonatal follow-up. Weights were obtained using a calibrated scale with the infant nude; lengths were obtained supine with the infant's head held in place by the parent or an assistant, the legs fully extended at the knee, and the ankle in a neutral position. Data were stored in an electronic database and retrieved for the current analysis. Clinically significant BPD was defined as an oxygen requirement at 36 weeks corrected age in those infants <32 weeks at birth.[23] FGR was defined as birthweight <10% for gestational age based on Fenton growth curves.[24]

Statistical Analyses

To derive weight, height, and body mass index (BMI) percentiles and z-scores, we used the SAS macro from the Center for Disease Control.[25] Z-scores for a child's sex and age are based on the World Health Organizations growth charts for children <24 months of age. Fenton growth charts were used for birth growth parameters.[24]

For group comparisons, we used chi-square tests for categorical variables and student's two-sample t-test for continuous variables. Linear regression was used to evaluate the associations between BPD, FGR, and growth outcomes, adjusting for maternal age, sex, and race. SAS version 9.4 (SAS Institute, Inc, Cary, NC) was used to perform the statistical analyses.

RESULTS

Demographic data are presented in Table 1. The mean (±SD) GA for the total cohort was 27.4 (±2.5) and mean birthweight was 943.2 (±257.4) grams. Of the cohort, 50% were female. Infants with BPD had lower GA and birthweight, were more likely to be male, and had younger mothers. Infants with FGR had lower birthweight, higher GA, were more likely to be female, and had younger mothers. Marital status was not associated with either BPD or FGR.

Table 2 examines anthropometric measures and z-scores of VLBW infants based on term reference data of the World Health Organization. Female VLBW infants at 18 months corrected age were closer to their term counterparts with an average weight-for-age z-score of -0.3 and an average BMI-for-age z-score of 0.82 as compared to the males who had an average weight-for-age z-score of -0.39 and an average BMI-for-age z-score of 1.77. Average length-for-age z-scores for females at 18 months corrected age were also higher than their male counterparts with z-scores of -0.81 and -1.27 respectively.

Table 3 compares growth data by BPD and FGR. Weight was less in BPD infants at 18 months corrected age with an average weight-for-age z-score of -0.73 as compared to an average weight-for-age z-score of -0.45 in those VLBW infants without BPD (p=0.002). Average BMI-for-age z-scores were not different among infants with and without BPD (1.76 versus 2.3; p=0.34) nor did the groups differ in the proportion with weight-for-age and BMI-for-age z-scores >2.

Comparing infants with and without fetal growth restriction, weight-for-age z-score at 18 months corrected age was lower among those with FGR (-1.36 versus -0.48; p<0.0001) as was average height-for-age z-score (-2.37 versus -1.63; p=0.0009). However, BMI-for-age z-scores were not significantly different between the two groups (1.24 versus 2.16; p=0.11). No FGR infants had weight-for-age z-score >2 whereas 3.5% of non-FGR infants had weight-for-age z-score >2. No differences were found between the two groups in the proportion with BMI-for-age z-score >2.

DISCUSSION

The major findings from this study are that at 18 months corrected age VLBW infants have weight and length-for-age z-scores lower than reference standards and BMI-for-age z-scores higher than reference standards. The relatively high BMI-for-age z-scores among VLBW infants are a direct impact from heights that are lower than reference standards. Weight-for-age z-scores were significantly lower among FGR children, as compared to non-FGR children, and weight-for-age z-scores were significantly lower among BPD children, as compared to those without BPD. However, BMI-for-age z-scores, although lower in both the BPD and FGR groups, as opposed to the non-BPD and non-FGR groups respectively, were not significantly different. Our data suggest that BMI-for-age z-scores may be the first sign of accelerated growth, manifesting as early as 18 months corrected age.

Prior studies have reported that as compared to term infants, preterm infants attain lower adult height.[26] With accelerated weight gain on a short-stature frame, weight distribution may be affected. One study found FGR children continue to gain excess abdominal fat after completion of catch-up weight gain.[27] The lower weight-for-age found among infants with BPD may be attributed to repeat hospitalizations in the first two years of life related to respiratory illness/infection which can worsen nutritional status.[28-29] It also may be related to increased caloric expenditure with increased work of breathing.[30]

With emerging evidence that premature infants are growing up to be overweight and obese adolescents and adults with cardiovascular and metabolic derangements,[31-35] it is unclear at what age their growth begins to accelerate to a level above normal. One longitudinal population-based study of extremely low gestational age infants showed a decline in weight-for-age z-scores through age 3 years, and then a significant catch-up from age 3 years through adolescence with BMI-for-age z-scores also increasing from age 3 years through adulthood.[26]

The continued evaluation of longitudinal growth during childhood through adulthood will be important to further characterize growth trajectories in VLBW infants with and without BPD and FGR, and associations with long-term cardiometabolic outcomes.

Strengths of this study include its relatively large sample of VLBW infants and consideration of two neonatal factors (BPD and FGR) that appear to influence growth outcomes. Despite its large size, the study sample was derived from a single center study, potentially limiting generalizability. Follow up ended at 18 months adjusted age, and measurements of growth derived later in childhood might lead to different conclusions. In addition, outcome data were missing for 55% of the cohort.

In summary, VLBW infants continue to show lagging growth in weight and height-for-age z-scores behind term reference standards at 18 months corrected age. However BMI-for-age z-scores are positive in both male and female VLBW infants, perhaps indicating early signs of accelerated growth. Furthermore, BMI-for-age z-scores are positive in both BPD and FGR infants as well. With shorter stature in premature infants than term counterparts as they age, BMI-for-age z-scores may be an early predictor of long term growth in VLBW infants.

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Table 1. Maternal and Infant Characteristics of the VLBW cohort (N=1149)

	Total	BPD	Non-BPD	p[§]	FGR	Non-FGR	p[§]
Gestational age (weeks) Mean (SD)	27.4(2.5)	25.6(1.8)	28.0(2.5)	<0.0001	29.1(3.1)	26.9(2.1)	<0.0001
Birthweight (grams) Mean (SD)	943.2(257.4)	758.2(209.6)	1005.2(241.6)	<0.0001	878.0(312.6)	961.8(236.2)	<0.0001
Female n(%)	573(50%)	119(41%)	454(53%)	0.0004	141(55%)	432(48%)	0.05
Race n(%)							
Caucasian	607(53%)	155(26%)	448(74%)	0.01	155(25%)	452(75%)	0.003
African American	396(35%)	86(22%)	310(78%)		83(21%)	313(79%)	
Other	131(11%)	45(35%)	85(65%)		16(12%)	115(88%)	
Unknown	15(1%)	4(27%)	11(73%)		1(7%)	14(93%)	
Maternal age (years) Mean (SD)	27.3(6.2)	26.8(6.0)	27.5(6.3)	<0.0001	27.1(6.1)	27.4(6.3)	<0.0001
Marital status n(%)							
Married	539(47%)	138(26%)	398(74%)	0.81	117(22%)	422(78%)	0.64
Not married	599(52%)	150(25%)	447(75%)		137(23%)	462(77%)	
Unknown	11(1%)	2(18%)	9(82%)		1(9%)	10(91%)	

[§] P values are derived from Student's two-sample t-test for continuous variables and Chi square test for categorical variables.

Table 2. Average anthropometric results at 18 months corrected age for VLBW infants by gender.

	N	Mean	SD		N	Mean	SD
Males				Females			
WEIGHT (kg)	576	10.73	1.48	WEIGHT (kg)	584	10.13	1.46
WEIGHT (z-score)	556	-0.39	1.22	WEIGHT (z-score)	566	-0.30	1.15
LENGTH (cm)	577	79.52	10.15	LENGTH (cm)	577	78.91	8.10
LENGTH (z-score)	556	-1.27	3.52	LENGTH (z-score)	557	-0.81	2.54
HEAD CIRC (cm)	574	47.44	3.72	HEAD CIRC (cm)	587	46.54	4.10
HEAD CIRC (z-score)	555	-0.04	2.84	HEAD CIRC (z-score)	567	0.13	3.01
BMI (kg/m^2)	576	19.13	16.14	BMI (kg/m^2)	573	17.30	11.21
BMI (z-score)	556	1.77	9.48	BMI (z-score)	555	0.82	6.05

Table 3. Results for BPD and FGR predicting adjusted mean weight, height and BMI-for-age z-scores at 18 months corrected age

	BPD	Non-BPD	Diff between means	p	FGR	Non-FGR	Diff between means	p
N	277	829			248	863		
WEIGHT								
Kg (CL) [B]	9.98 (9.43,10.54)	10.26 (9.71,10.81)	0.28 (0.08,0.49)	0.007§	9.18 (8.63,9.72)	10.25 (9.74,10.77)	1.08 (0.88,1.28)	<0.0001§
Z-score (CL) [B]	-0.73 (-1.17,-0.28)	-0.45 (-0.90,-0.01)	0.27 (0.10,0.44)	0.002§	-1.36 (-1.80,-0.91)	-0.48 (-0.90,-0.06)	0.87 (0.71,1.04)	<0.0001§
Z-score>2, n(%)	6(2%)	24(3%)	-	0.49	0(0%)	30(3.5%)	-	0.003
HEIGHT								
Cm (CL) [B]	77.16 (73.96,80.36)	77.59 (74.42,80.76)	0.43 (-0.75,1.60)	0.48§	75.34 (72.05,78.63)	77.65 (74.54,80.76)	2.31 (1.11,3.50)	0.0002§
Z-score (CL) [B]	-1.83 (-2.98,-0.69)	-1.62 (-2.75,-0.48)	0.21 (-0.21,0.64)	0.33§	-2.37 (-3.55,-1.12)	-1.63 (-2.75,-0.52)	0.73 (0.30,1.17)	0.0009§
Z-score>2, n(%)	2(0.7%)	25(3%)	-	0.03	1(0.4%)	26(3%)	-	0.02
BMI								
BMI (CL) [B]	19.14 (13.96,24.31)	20.13 (14.99,25.26)	0.99 (-0.90,2.90)	0.30§	18.54 (13.19,23.89)	19.83 (14.77,24.90)	1.30 (-0.65,3.24)	0.19§
Z-score (CL) [B]	1.76 (-1.20,4.72)	2.3 (-0.63,5.24)	0.54 (-0.57,1.66)	0.34§	1.24 (-1.82,4.30)	2.16 (-0.73,5.05)	0.92 (-0.21,2.05)	0.11§
Z-score>2, n(%)	20(7%)	59(7%)	-	0.99	13(5%)	66(8%)	-	0.20

[§] P values are derived from linear regression analyses adjusting for maternal age, infant gender, and infant race.
[B] 95% Confidence intervals are reported

Part III

Further Analyses

As in my predictive/conceptual model, two additional neonatal comorbidities were listed that occur in a large number of very low birth weight infants that may impact long term growth – necrotizing enterocolitis (NEC) and intraventricular hemorrhage (IVH). When performing additional analyses in the VLBW cohort to examine the association between BPD or FGR and anthropometrics at 18 months corrected age, regression analysis was used and the model was further adjusted for NEC and IVH in addition to sex, race, and maternal age (Table 1). The associations that were previously seen when adjusting for demographic data are similar when we adjusted for these two neonatal comorbidities. Weight-for-age z-scores at 18 months corrected age remain significantly lower in BPD infants compared to non-BPD infants ($p=0.001$). BMI-for-age z-scores are not significantly different between the two groups ($p=0.38$). Height is also not significantly different between the two groups ($p=0.32$) in this model.

Among FGR infants, weight-for-age z-scores remain significantly less at 18 months corrected age as compared to non-FGR infants ($p<0.0001$) after adjusting for NEC, IVH, sex, race, and maternal age. The same is true for height-for-age z-score ($p=0.001$), however BMI-for-age z-score is not significantly different (0.09) between FGR and non-FGR infants at 18 months corrected age.

When evaluating anthropometric outcomes in NEC versus non-NEC infants while adjusting for sex, race, maternal age, BPD, and IVH (Table 2), we see that weight-for-age z-scores are not significantly different between NEC and non-NEC infants at 18 months corrected age ($p=0.37$). The same is true for height-for-age z-scores ($p=0.31$) and BMI-for-age z-scores ($p=0.92$) in NEC versus non-NEC infants.

The same regression model was used to compare IVH versus non-IVH infants while adjusting for sex, race, maternal age, BPD, and NEC. Weight-for-age z-scores do not significantly differ (p=0.39) between IVH and non-IVH infants and the same is true for height-for-age z-scores (p=0.59) and BMI-for-age z-scores (p=0.64).

Based on these findings, it does not appear that NEC and IVH significantly impact the associations that we have already seen between BPD or FGR and anthropometrics at 18 months corrected age. Speculation as to why this may be is that in infants with NEC closer attention to nutrition and growth may occur with often times multiple subspecialists following the child, including pediatric surgery and programs for speech therapy or intestinal rehabilitation. Also, they may remain on parenteral nutrition for longer periods of time than infants with BPD alone or those with FGR alone due to the inability to feed enterally. Receiving prolonged parenteral nutrition allows for tighter control of the provision of glucose, lipids, and proteins and therefore growth can be more highly regulated during the neonatal period. In infants with intraventricular hemorrhage alone, though metabolic processes are occurring surrounding the hemorrhage and remodeling of brain parenchyma in the setting of inflammatory markers, the IVH itself does not appear to impact growth beyond the neonatal period.

Future Research Direction:

The primary focus of this research study was to 1) evaluate growth in VLBW infants at 18 months corrected age as they compare to reference standards, 2) assess growth in VLBW infants at 18 months corrected age in those with and without BPD, and 3) assess growth in VLBW infants at 18 months corrected age in those with and without fetal growth restriction. With growing evidence, as discussed in Part 1, of long term cardiac and metabolic derangements associated with early abnormal growth patterns, this study helps characterize growth during the first 18 months of life in not only VLBW infants, but also in those with BPD and FGR. As is discussed in Part 2, BMI-for-age z-scores may be an early predictor of abnormal or accelerated

growth in VLBW infants. In both male and female VLBW infants, weight-for-age z-scores and height-for-age z-scores remain negative, but BMI-for-age z-scores are positive in both genders, and in males, almost 2 standard deviations above the mean. Further studies are needed to look at longitudinal growth from infancy through adulthood. If evidence proves that BMI-for-age z-scores are an early predictor of obesity and adverse cardiometabolic outcomes, then pediatricians and NICU Follow Up clinics would have a duty to provide education and anticipatory guidance to parents during clinic visits. Furthermore, gender and neonatal comorbidities may affect growth and ultimately BMI-for-age z-scores in VLBW infants. In the BPD and FGR infants, though weight-for-age z-scores were significantly less in BPD and FGR infants as compared to non-BPD and non-FGR infants, the BMI-for-age z-scores were not significantly different between the two groups. BPD and FGR may be additional risk factors for abnormal growth in VLBW infants. Changes in BMI-for-age z-scores may also predict adverse cardiometabolic outcomes. In one study, each increment in BMI-for-age z-score gain during the first 6 postnatal months and 2 to 3 years of age corresponded with 0.7 and 1.5 mmHg higher SBP, respectively.[1] In another study, adults that were born preterm had higher body fat percentages and were more likely to have metabolic syndrome as compared to controls born at term.[2] Not only is prematurity associated with long-term cardiovascular outcomes, but fetal growth restriction in addition to prematurity is associated with these outcomes. Young adults born VLBW who also had FGR in utero had higher indices of central body fat and higher BP by young adulthood.[3] A Finnish study supported this finding showing FGR preterm infants were more likely to have elevated blood pressure levels than term or non-FGR preterm participants, though the elevated BP levels were not evident until well into adulthood (~ 41 years).[4]

Plan for Future Studies:

I am currently collaborating with a team of researchers interested in early growth and later cardiometabolic outcomes. This team is comprised of a neonatology colleague with an

interest in long-term follow up of premature infants and an epidemiologist interested in perinatal exposures. Using data collected in a cohort of adolescents who were born prematurely with VLBW, we plan to examine the associations of early growth with cardiometabolic outcomes including adiposity at age 14 years. Our aim is to identify patterns of growth and biomarkers that are associated with overweight or obesity in adolescence. These data will inform hypotheses to be tested in younger cohorts. Our objective will be to obtain funding for future studies in this area as the prevention of overweight and obesity in this high risk population may have even greater health implications than in the general population.

An additional path for future studies is through the ELGAN (Extremely Low Gestational Age Newborn) Research group, a multicenter study of which Wake Forest is a member. The ELGAN research group is following a cohort of infants born 2002-2004 and plans to follow them through adulthood. As a member of this team, I have access to data on early life exposures including growth parameters at age 12 months, 24 months, and 9 years, placental pathology, markers of inflammation, maternal BMI, and BMI measurements of the children.

This area of study is recognized as a priority in the field of Neonatology and as I expand on my thesis, I plan to develop a research program that will translate into evidence-based feeding and behavioral practices for former preterm infants that promote optimum health as they mature.

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Table 1. Results for BPD and FGR predicting adjusted mean weight, height and BMI-for-age z-scores at 18 months corrected age.

	BPD	Non-BPD	Diff between means	p	FGR	Non-FGR	Diff between means	p
N	277	829			248	863		
WEIGHT								
Kg (CL) [B]	9.92 (9.33,10.51)	10.22 (9.62,10.81)	0.29 (0.09,0.50)	0.005§	9.04 (8.46,9.63)	10.13 (9.58,10.69)	1.09 (0.89,1.29)	<0.0001§
Z-score (CL) [B]	-0.76 (-1.24,-0.29)	-0.48 (-0.96,-0.002)	0.28 (0.11,0.45)	0.001§	-1.46 (-1.93,-0.98)	-0.57 (-1.02,-0.12)	0.89 (0.72,1.05)	<0.0001§
Z-score>2, n(%)	6(2%)	24(3%)	-	0.49	0(0%)	30(3.5%)	-	0.003
HEIGHT								
Cm (CL) [B]	76.65 (73.26,80.05)	77.11 (73.69,80.53)	0.46 (-0.73,1.65)	0.45§	74.74 (71.22,78.25)	77.02 (73.69,80.36)	2.29 (1.08,3.50)	0.0002§
Z-score (CL) [B]	-1.97 (-3.19,-0.76)	-1.75 (-2.98,-0.52)	0.22 (-0.21,0.66)	0.32§	-2.55 (-3.82,-1.29)	-1.82 (-3.02,-0.62)	0.73 (0.29,1.17)	0.001§
Z-score>2, n(%)	2(0.7%)	25(3%)	-	0.03	1(0.4%)	26(3%)	-	0.02
BMI								
BMI (CL) [B]	19.06 (13.57,24.56)	19.99 (14.45,25.52)	0.93 (-1.00,2.86)	0.35§	18.17 (12.45,23.90)	19.58 (14.15,25.00)	1.40 (-0.57,3.37)	0.16§
Z-score (CL) [B]	1.69 (-1.45,4.84)	2.20 (-0.98,5.37)	0.50 (-0.63,1.63)	0.38§	1.01 (-2.27,4.29)	1.99 (-1.12,5.09)	0.98 (-0.16,2.12)	0.09§
Z-score>2, n(%)	20(7%)	59(7%)	-	0.99	13(5%)	66(8%)	-	0.20

[§] P values are derived from linear regression analyses adjusting for maternal age, infant gender, infant race, NEC and IVH.
[B] 95% Confidence intervals are reported

Table 2. Results for NEC and IVH predicting adjusted mean weight, height and BMI-for-age z-scores at 18 months corrected age.

	NEC	Non-NEC	Diff between means	p	IVH	Non-IVH	Diff between means	p
N	55	1089			155	989		
WEIGHT								
Kg (CL) [B]	9.95 (9.28,10.62)	10.19 (9.63,10.74)	0.24 (-0.17,0.64)	0.25§	10.14 (9.52,10.75)	10.00 (9.43,10.57)	-0.14 (-0.40,0.13)	0.31€
Z-score (CL) [B]	-0.70 (-1.24,-0.15)	-0.55 (-0.99,-0.10)	0.15 (-0.18,0.48)	0.37§	-0.57 (-1.07,-0.07)	-0.67 (-1.13,-0.21)	-0.09 (-0.31,0.12)	0.39€
Z-score>2, n(%)	1(2%)	29(3%)	-	0.70	3(2%)	27 (3%)	-	0.56
HEIGHT								
Cm (CL) [B]	76.11 (72.23,79.98)	77.65 (74.46,80.84)	1.55 (-0.78,3.87)	0.19§	77.14 (73.58,80.70)	76.62 (73.31,79.93)	-0.52 (-2.03,1.00)	0.50€
Z-score (CL) [B]	-2.08 (-3.47,-0.69)	-1.64 (-2.79,-0.50)	0.44 (-0.40,1.28)	0.31§	-1.79 (-3.07,-0.51)	-1.94 (-3.12,-0.75)	-0.15 (-0.71,0.40)	0.59€
Z-score>2, n(%)	0(0%)	27(2.5%)	-	0.24	4(3%)	23(2%)	-	0.85
BMI								
BMI (CL) [B]	19.66 (13.39,25.93)	19.39 (14.22,24.55)	-0.27 (-4.03,3.49)	0.89§	19.23 (13.46,25.00)	19.82 (14.46,25.17)	0.59 (-1.86,3.04)	0.64€
Z-score (CL) [B]	2.00 (-1.60,5.60)	1.89 (-1.07,4.84)	-0.11 (-2.28,2.06)	0.92§	1.77 (-1.54,5.08)	2.12 (-0.95,5.18)	0.34 (-1.09,1.78)	0.64€
Z-score>2, n(%)	5(9%)	74(7%)	-	0.51	13(8%)	66(7%)	-	0.43

[§] P values are derived from linear regression analyses adjusting for maternal age, infant gender, infant race, BPD and IVH.
[€] P values are derived from linear regression analyses adjusting for maternal age, infant gender, infant race, BPD, and NEC.
[B] 95% Confidence intervals are reported

Wake Forest School of Medicine

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EDUCATION:

2013-present	Wake Forest University-Division of Public Health Sciences Winston-Salem, NC Anticipated Degree: MS in Clinical and Population Translational Sciences Anticipated Graduation date: Fall 2016
2002-2006	University of North Carolina-Chapel Hill, School of Medicine Chapel Hill, NC Degree: Doctor of Medicine, M.D.
1996-2000	University of North Carolina at Wilmington Wilmington, NC Degree: Bachelor of Science in Biology, *Cum Laude* *University Honors and Honors in Biology* Minor: French

POSTDOCTORAL TRAINING:

2009-2012	Fellowship in Neonatal-Perinatal Medicine Ann and Robert H. Lurie Children's Hospital of Chicago, formerly Children's Memorial Hospital Northwestern University Chicago, IL
2006-2009	Pediatric Residency Training UNC Hospitals, University of North Carolina-Chapel Hill Chapel Hill, NC

PROFESSIONAL LICENSURE:

2012-Present	North Carolina Medical Board License Number 2012-01102

SPECIALTY CERTIFICATION:

October 2009	American Board of Pediatrics – General Pediatrics
April 2014	American Board of Pediatrics – Neonatal-Perinatal Medicine

ACADEMIC APPOINTMENTS:

2012-present	Assistant Professor in Pediatrics/Neonatal-Perinatal Medicine Wake Forest School of Medicine

EMPLOYMENT:

2003 Spring	Research Assistant, University of North Carolina-Chapel Hill School of Medicine
2001-2002	Research Technician, University of North Carolina-Chapel Hill Pharmacology Department
2000-2001	Research Analyst, Coastal AHEC, Wilmington, North Carolina Research Department

INSTITUTIONAL SERVICE:

2013-present	Medical Director, NICU Follow Up Clinic, Amos Cottage Wake Forest Baptist Health

2016-present	Co-Director, Comprehensive Infant Clinic (combined Neonatal Neurology Follow Up Clinic) Wake Forest Baptist Health

Hospital Committees:

2016-present	Information Services Technology, Inpatient Advisory Council
2015-present	Brenner Children's Hospital Morbidity/Mortality Committee
2015-present	Clinical Competency Committee, Neonatal-Perinatal Fellowship
2015-present	Faculty Credentialing Committee
2014-present	NICU Service Line Registry/Database Committee
2014	Root Cause Analysis Review
2013-present	Care Coordination for Babies with Extended Stays (CCBES), Member
2012-present	Point-of-Care Test Committee, member
2009-2012	Central Line-Associated Blood Stream Infection Quality improvement working group, member Children's Memorial Hospital, Chicago IL

Review Committees:

2014	Peer Review for a publication submitted to American Journal of Perinatology

PROFESSIONAL MEMBERSHIPS AND SERVICE:

2006-Present	American Academy of Pediatrics
2002-2014	American Medical Association
2002-2007	North Carolina Medical Society
2002-2007	Durham-Orange County Medical Society
2002-2006	Christian Medical/Dental Association

HONORS AND AWARDS:

2012-2014	Translational Science Institute Research Academy, Cohort 3 Wake Forest University Baptist Medical Center
2011	Second-Year Fellow Research Award Research Scholars Day Northwestern University
2009	Research Merit Award Thomas F. Boat Evening of Scholarship University of North Carolina-Chapel Hill
1998	Study Abroad institutional grant, UNC-Wilmington University of Paris, Sorbonne

PROFESSIONAL INTERESTS:

Research Interests:	Growth after NICU Discharge in Former Very-Low Birth Weight Infants, Care Coordination in Infants with Chronic Needs and Complex Medical Conditions.
Clinical Interests:	Chronic lung disease/Bronchopulmonary dysplasia Pulmonary Hypertension Reduction of Central Line-Associated Blood Stream Infections (CLABSI) Post-discharge growth in former preterm infants

Research in Progress:

Growth Outcomes at 18 Months Corrected Age in Very Low Birth Weight Infants

Single center retrospective cohort study evaluating growth parameters at 18 months of age in very low birth weight infants <1500 grams born over a 10 year period. Primary Investigator: Jennifer Check, MD. Study in progress.

Improving Care Coordination for NICU Patients to Decrease Length of Stay and Readmission Rate

Quality improvement study to evaluate patient outcomes pre- and post- implementation of a multidisciplinary care coordination team. Primary investigator: Cherrie Welch, MD, MPH. Co-investigators: Jennifer Check, MD and T. Michael O'Shea, MD, MPH. This study has completed data analyses and has been submitted for publication.

Neonatal Neurobehavior and Outcomes in Very Preterm Infants Study – Site Co-PI
A multicenter, prospective cohort study evaluating neurobehavior and developmental outcome of infants born before 30 weeks gestation. In follow-up phase.

PENUT Study – Site Co-PI
A multicenter, randomized placebo controlled phase III 940 subject trial of erythropoietin for the neuroprotection of extremely low gestational age neonates (ELGANs)

PUBLICATIONS:

Murphy LT, Skinner AC, **Check J,** Warner DD, Perrin EM. Parental perceptions of weight status in preterm compared with term infants. *Am J Perinatol.* 2016 May 2 [Epub ahead of print]

Mestan K, **Check J,** Minturn L, Yallapragada S, Farrow KN, Liu X, Su E, Porta N, Gotteiner N, Ernst LM. Placental Pathologic Changes of Maternal Vascular Underperfusion in Bronchopulmonary Dysplasia and Pulmonary Hypertension. *Placenta.* 2014 Aug; 35(8):570-4.

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Randolph GD, Stenberg L, Socolar R, Wysocki KL, Fuller S, **Check J**, Brown WD, Steiner MJ. A Modified Healthy Steps Model to Improve Resident Training in Behavioral and Developmental Care. *J Dev Behav Pediatr*. 2011 May; 32(4): 301-306. PMID: 21325967

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Carteaux P, Cohen H, **Check J**, George J, McKinley P, Lewis W, Hegwood P, Whitfield JM, McLendon D, Okuno-Jones S, Klein S, Moehring J, and McConnell C. Evaluation and Development of Potentially Better Practices for the Prevention of Brain Hemorrhage and Ischemic Brain Injury in Very Low Birth Weight Infants *Pediatrics* 2003; 111: e489-e496. PMID: 12671169.

McLendon D, **Check J**, Carteaux P, Michael L, Moehring J, Secrest JW, Clark SE, Cohen H, Klein SA, Boyle D, George JA, Okuno-Jones S, Buchanan DS, McKinley P, and Whitfield JM. Implementation of Potentially Better Practices for the Prevention of Brain Hemorrhage and Ischemic Brain Injury in Very Low Birth Weight Infants *Pediatrics* 2003; 111: e497-e503. PMID: 12671170.

Wheeler MD, Smutney OM, **Check JF**, Rusyn I, Schulte-Hermann R, Thurman RG. Impaired Ras membrane association and activation in PPAR alpha knockout mice after partial hepatectomy. *Am J Physiol Gastrointest Liver Physiol.* 2003 *284*: G302-312. PMID: 12388208.

Sherry E. Courtney, M.D., David J. Durand, M.D., Jeanette M. Asselin, R.R.T., M.S., Mark L. Hudak, M.D., Judy L. Aschner, M.D., Craig T. Shoemaker, M.D., for the Neonatal Ventilation Study Group. High-Frequency Oscillatory Ventilation versus Conventional Mechanical Ventilation for Very-Low-Birth-Weight Infants. *NEJM* 2002; 9:Vol 347:643-652. **Check, Jennifer**, New Hanover Regional Medical Center mentioned as a contributor. PMID: 12200551.

POSTER PRESENTATIONS:

Murphy LT, Skinner AC, Check J, Warner DD, Perrin EM. *Parental Perceptions of Weight Status in Preterm Compared with Term Infants.* Poster presentation for Pediatric Grand Rounds at Wake Forest School of Medicine, Winston-Salem, NC. Sept 2014.

Check J, Ernst L, Gotteiner N, Porta N, Steinhorn R, Mestan K. *Placental Growth Restriction is Associated with Pulmonary Hypertension in Extremely Low Gestational Age Infants with Bronchopulmonary Dysplasia.* Poster presentation for PAS/SPR conference, Boston, MA, May 2012. Poster presentation for Research Scholars Day, Northwestern University, April 2012.

Check J, Harvey C, Matoba N, Porta N, Gotteiner N, Mestan K. *Intrauterine Growth Restriction in BPD Infants with Pulmonary Hypertension.* Poster presentation for PAS/SPR conference, Denver, CO, May 2011. Poster presentation for Research Scholars Day, Northwestern University, May 2011.

Check J, Wysocki K, Steiner MJ, Stenberg L, Socolar R, Fuller S, Brown WD, Randolph GD. *The Impact of a Modified Healthy Steps Program on Resident Training and Quality of Behavioral and Developmental Care.* Poster presentation at Evening of Scholarship, Chapel Hill, NC, May 2009.

Check J, Kocina K, Shiloh-Malawsky Y, Greenwood R. *Case Presentations – 3 Children with anti-NMDA Receptor Limbic Encephalitis.* Poster presentation at Evening of Scholarship, Chapel Hill, NC, May 2009.

Najak Z, Check J, Covington D. *The Effects of Neonatal Intraventricular Hemorrhage Severity on Neurodevelopmental Outcome.* Poster presentation at the 7th Annual North and South Carolina Perinatal Association Meeting, Ashville, NC, October 2000.

Diehl SJ, Sulzbach S, Check JF. *Process Evaluation of the CAHEC/NHRMC Certified Nurse-Midwifery Program.* Poster presentation at the 6th Annual North and South Carolina Perinatal Association Meeting, Charlotte, NC, October 1999.

PODIUM PRESENTATIONS:

Jennifer Check, Nina Gotteiner, Xin Liu, Emily Su, Nicolas Porta, Robin Steinhorn, Karen Mestan. Fetal Growth Restriction and Pulmonary Hypertension in Premature Infants with Bronchopulmonary Dysplasia. Oral presentation to take place Feb 2013 at 37th Southeastern conference on Perinatal Research, AAP section on Perinatal Pediatrics. Key Largo, FL.

Check J, Wysocki K, Steiner MJ, Stenberg L, Socolar R, Fuller S, Brown WD, Randolph GD. *The Impact of a Modified Healthy Steps Program on Resident Training and Quality of Behavioral and Developmental Care.* Oral presentation at Evening of Scholarship, Chapel Hill, NC, May 2009.

Check, J. *Patient Education and Retention of Information in Mothers of Newborns: Does Socioeconomic Status, Race and Education Play a Role?* Oral presentation for Residency Senior Presentation and QI project. UNC Hospitals, Chapel Hill, NC, May 2009.

Check, JF and Roer, R. *Sodium Permeability of Juvenile Blue Crabs.* Oral presentation for Honors Thesis Defense. UNCW, Wilmington, NC, May 2000.

Diehl SJ, Sulzbach S, Check JF. *Process Evaluation of the CAHEC/NHRMC Certified Nurse-Midwifery Program.* Oral presentation at the Coastal AHEC/NHRMC Student Research Symposium, Wilmington, NC, August 1999.

GRADUATE STUDENTS/RESIDENTS/FELLOWS ADVISED:

2016-present	Dr. Danielle Deines, DO SOC committee: Lisa Washburn, MD, Jennifer Check, MD, Andrew South, MD Project TBD
2014-2016	Dr. Jennifer Holman, Neonatal Fellow A Quality Improvement Initiative for the Diagnosis and Management of Cardiopulmonary Events in Very Low Birth Weight Infants Close to Discharge Jennifer Holman, MD, Tinisha Lambeth, DNP, Jennifer Check, MD, Mario A. Rojas, MD, MPH

EDUCATIONAL PRESENTATIONS:

Aug 2016	Neonatal Seizures
Jan 2013-Nov 2014	Monthly Presentation for Resident Conference Wake Forest University Baptist Medical Center Brenner Children's Hospital

May 2013	Creating and Sustaining Successful Mentor/Mentee Relationships Presentation for TSI Research Academy Wake Forest University Baptist Medical Center
Feb 2016, Aug 2016, Sept 2014, March 2013	Maternal Substance Abuse, Maternal Medications and Neonatal Abstinence Syndrome Presentation for Resident Conference Wake Forest University Baptist Medical Center Brenner Children's Hospital
Oct-Dec 2012	Infants of Diabetic Mothers (IDM) Monthly Presentation for Resident Conference Wake Forest University Baptist Medical Center Brenner Children's Hospital
June 2016	PPHN versus BPD-associated Pulmonary Hypertension Neonatology Fellow Conference, Board Review Wake Forest University Baptist Medical Center
May 2016	Respiratory Diseases of the Newborn and Bronchopulmonary Dysplasia Neonatology Fellow Conference, Board Review Wake Forest University Baptist Medical Center
Nov 2015,Sept 2014, Nov 2013,Sept 2012	Respiratory Diseases of the Newborn Neonatology Fellow Conference, Board Review Wake Forest University Baptist Medical Center

COMMUNITY ACTIVITIES AND SERVICE:

2015-present	March of Dimes ambassador at Wake Forest Baptist Health
2006	Volunteer in medical clinic, New Orleans, LA Post-hurricane Katrina
2002-2006	Student Health Action Coalition Community Clinic (SHAC)
2001-2002	EMT Training, Licensed 2002-2006
2000-present	University of North Carolina at Wilmington Alumni Association member