# The association between BMI trajectories and the development of bronchopulmonary dysplasia among preterm infants born at less than 30 weeks of gestational age

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## ABSTRACT

**Importance:** Preterm growth assessment focuses predominantly on weight gain, but the association of changes in body mass index (BMI) on bronchopulmonary dysplasia (BPD) is unknown.

**Objective**s: Determine the association between changes in BMI *z* score (ΔBMI) from birth to 36 weeks corrected gestational age (CGA) and BPD among preterm infants born at <30 weeks gestational age (GA).

**Method:** Multicenter retrospective cohort study including infants born <30 weeks GA admitted within 1 day after delivery to 3 tertiary neonatal intensive care units from 2015-2018 and alive at ≥34 weeks corrected. Infant characteristics and outcomes were collected from the Canadian Neonatal Network database and biweekly anthropometric measurements and caloric intake from medical chart review. The primary outcome was BPD (need for respiratory support or oxygen at 36 weeks CGA). Change in BMI *z* scores (ΔBMI) were calculated from birth to 36 weeks CGA using the 2015 BMI Olsen curves and grouped into quartiles of change. Weight and length *z* scores were calculated using 2013 Fenton curves. The association of ΔBMI quartile with BPD was assessed using generalized linear mixed models adjusted for confounders.

**Results:** A total of 772 infants with a median GA at birth of 27 weeks [IQR 26; 29] were included; 391 (51%) developed BPD. Infants with BPD had similar BMI z scores to BPD-free infants at birth (median [IQR], 0.19 [-0.66; 0.95] vs 0.31 [-0.34; 0.91]; *P*=0.10), but higher BMI z scores at 36 weeks CGA (median [IQR], 0.30 [-0.35; 1.01] vs -0.01 [-0.60; 0.55]; *P*<0.01). From birth to 36 weeks CGA, the weight *z* score of infants with BPD decreased less than for BPD-free infants **(**median [IQR], -0.76 [-1.29; -0.27] **vs** -0.90 [-1.30; -0.50]**;** *P*<0.01), despite a

greater decrease in length z score (median [IQR], -1.09 [-1.78; -0.44] vs -0.97 [-1.52; -0.37]; *P*= 0.03) and similar caloric intakes (mean, 124kcal/kg/d vs 123kcal/kg/d; *P*=0.14). Higher quartiles of ΔBMI were associated with higher odds of BPD compared to the 2$^{nd}$ quartile (Q3 vs Q2, AOR [95%CI], 2.02 [1.23-3.31] and Q4 vs Q2, AOR [95%CI], 2.00 [1.20-3.34]).

**Conclusion and Relevance:** An increase in BMI z score from birth to 36 weeks CGA was associated with higher odds of BPD among infants born <30 weeks GA. This increased BMI reflects a higher weight gain but slower linear growth despite similar caloric intake, suggesting that infants with evolving BPD may require individualized growth and nutritional targets.

## RESUME

**Importance :** L'évaluation de la croissance des nouveau-nés prématurée vise principalement sur le gain pondéral mais l'association des changements de l'indice de masse corporelle (IMC) avec la dysplasie broncho-pulmonaire (DBP) est inconnue.

**Objectifs :** Déterminer l'association entre les changements du score *z* de l'IMC (ΔIMC) entre la naissance et 36 semaines d'âge gestationnel corrigé (AGC) et la DBP chez les prématurés.

**Méthode :** Étude de cohorte rétrospective multicentrique incluant des nourrissons nés à < 30 semaines d'âge gestationnel et admis durant leur premier jour de vie dans 3 unités de soins intensifs néonataux tertiaires de 2015 à 2018 et qui ont survécu ⩾ 34 semaines d'AGC. Les caractéristiques et les données de santé des nourrissons ont été recueillies à partir de la base de données du Réseau néonatal Canadien et des mesures anthropométriques bimensuelles et l'apport calorique à partir de revue des dossiers médicaux. La variable d'intérêt principale était la DBP (besoin de support respiratoire ou d'oxygène à 36 semaines AGC). Les changements du score *z* de l'IMC (ΔIMC) ont été calculés de la naissance à 36 semaines AGC à l'aide des courbes IMC d'Olsen de 2015 et regroupés en quartiles de changement. Les scores *z* de poids et de longueur ont été calculés à l'aide des courbes de Fenton de 2013. L'association du quartile ΔBMI avec la DBP a été évaluée à l'aide de modèles mixtes linéaires généralisés ajustés pour les facteurs confondants.

**Résultats :** Un total de 772 nourrissons avec un AG médian à la naissance de 27 semaines [EI 26 ; 29] ont été inclus ; 391 (51 %) ont développé la DBP. Les nourrissons atteints de DBP avaient des scores *z* d'IMC similaires à ceux des nourrissons sans DBP à la naissance (médiane [EI], 0,19 [-0,66 ; 0,95] vs 0,31 [-0,34 ; 0,91] ; $P = 0,10$), mais des scores z d'IMC plus élevés à 36

semaines AGC (médiane [EI], 0,30 [-0,35 ; 1,01] vs -0,01 [-0,60 ; 0,55] ; *P*<0,01). De la naissance à 36 semaines AGC, le score *z* du poids des nourrissons atteints de DBP a moins diminué que celui des nourrissons sans DBP (médiane [EI], -0,76 [-1,29 ; -0,27] vs -0,90 [-1,30 ; -0,50] ; P <0,01), malgré une diminution plus importante du *z* score de longueur (médiane [EI], -1,09 [-1,78 ; -0,44] vs -0,97 [-1,52 ; -0,37] ; *P*= 0,03) et des apports caloriques similaires (moyenne, 124kcal /kg/j vs 123kcal/kg/j ; *P*=0,14). Les quartiles supérieurs de ΔIMC étaient associés à une probabilité plus élevée de DBP par rapport au 2e quartile (Q3 vs Q2, RCA [IC à 95 %], 2,02 [1,23-3,31]) et (Q4 vs Q2, RCA [IC à 95 %], 2,00 [1.20-3.34]).

**Conclusion et pertinence :** Une augmentation du score *z* de l'IMC de la naissance à 36 semaines CGA était associée à un risque plus élevé de DBP chez les nourrissons nés <30 semaines AG. Cette augmentation de l'IMC reflète un gain de poids plus élevé mais une croissance linéaire plus lente malgré un apport calorique similaire, ce qui suggère que les nourrissons atteints de DBP en évolution peuvent nécessiter des objectifs de croissance et nutritionnels individualisés.

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## CONTRIBUTIONS OF AUTHORS

Ms. L. Li Ching Ng was the primary author of this thesis and the included manuscript. She performed the literature review. She conceptualized and designed the study, wrote the research proposal, ethics and grants documents, coordinated and collected data, performed statistical analysis and interpretation of data, and critically reviewed the thesis and manuscript for important intellectual content.

Ms. S. Patel assisted in the research proposal, documentation of ethics approval, coordinated the data collection, reviewed statistical analysis and interpretation of data, and critically reviewed the manuscript for important intellectual content.

Dr. Plourde was L. Li Ching Ng's co supervisor. He provided feedback on all aspects of the study and critically reviewed the manuscript and thesis and provided valuable feedback.

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Drs A. Lapointe and V. Bizgu provided support in ethics approval and access for data collection at their respective centres and reviewed and revised the manuscript.

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Dr M Beltempo was L. Li Ching Ng's primary supervisor. He was the principal investigator of this research project and provided support for research grant proposal. He conceptualized and designed the study, provided administrative and material support, provided support for ethics approval, statistical analysis, and interpretation of data, critically reviewed the manuscript and thesis for important intellectual content. He supervised the entirety of the study.

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## LIST OF ABBREVIATION

| | |
|---|---|
| ADP | Air displacement plethysmography |
| BIA | Bioimpedance analysis |
| BMI | Body mass index |
| BPD | Bronchopulmonary dysplasia |
| BW | Birth weight |
| CGA | Corrected gestational age |
| CPAP | Continuous positive airway pressure |
| DEXA | Dual-energy X-ray absorptiometry |
| ECF | Extracellular fluid |
| ELBW | Extremely low birth weight |
| FM | Fat mass |
| FFM | Fat free mass |
| GA | Gestational age |
| ICU | Intensive care unit |
| IGF | Insulin growth factor |
| IQ | Intellectual quotient |
| IUGR | Intrauterine growth restriction |
| LBM | Lean body mass |
| LBW | Low birth weight |
| LOS | Length of stay |
| MRI | Magnetic resonance imaging |

| | |
|---|---|
| MRS | Magnetic resonance spectroscopy |
| nCPAP | Nasal continuous positive airway pressure |
| NICHD | National Institute of Child Health and Human Development |
| NICU | Neonatal intensive care unit |
| nIPPV | Nasal intermittent positive pressure ventilation |
| $O_2$ | Oxygen consumption |
| PDA | Patent ductus arteriosus |
| PMA | Postmentstrual age |
| RDS | Respiratory distress syndrome |
| TNF-$\alpha$ | Tumor necrosis factor alpha |
| US | Ultrasound |
| VLBW | Very low birth weight |
| $VO_2$ | Rate of total body oxygen consumption |
| WHO | World Health Organization |
| WHOGS | World Health Organization Growth Standard |
| ΔBMI | Change in body mass index from birth to 36 weeks corrected gestational age |
| Δhc | Change in head circumference from birth to 36 weeks corrected gestational age |
| Δlt | Change in length from birth to 36 weeks corrected gestational age |
| Δwt | Change in body weight from birth to 36 weeks corrected gestational age |

# 1 CHAPTER 1: *REVIEW OF LITERATURE*

## 1.1 PREMATURITY AND BRONCHOPULMONARY DYSPLASIA

### *1.1.1 Prematurity incidence and outcomes*

Prematurity is defined as birth before 37 weeks gestational age (GA). Globally, 15 million babies are born premature every year, and it accounts for about 8% of pregnancies in Canada.[1] Prematurity accounts for two thirds of infant deaths in Canada and is associated with significant morbidity which can lead to chronic diseases in adulthood.[2,3] Prematurity can be grouped based on GA at birth: extreme preterm (<28 weeks GA), very preterm (28-31 weeks GA), moderate preterm (32-33 weeks) and late preterm (34-36 weeks GA).[1] Among preterm infants, risk of death and morbidities is inversely related to GA: the lower the GA the higher the risk of adverse outcomes.[4] Preterm infants can also be classified based on birth weight (BW): extremely low birth weight (ELBW) have BW<1000g, very low birth weight (VLBW) have BW of <1500g and low birth weight (LBW) have BW<2500g.[5] GA at birth and BW are two of the major determinants of neonatal survival and morbidity. Complications of prematurity include a range of morbidities namely pulmonary hypertension, intraventricular hemorrhage, seizures, hypoxic-ischemic encephalopathy, necrotizing enterocolitis, bronchopulmonary dysplasia, sepsis, respiratory distress syndrome and hyperbilirubinemia. [4]

### *1.1.2 Incidence of BPD*

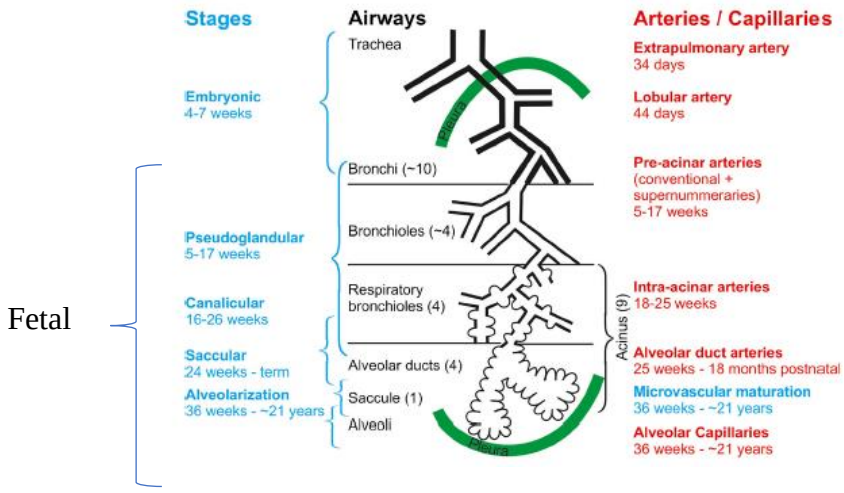
Bronchopulmonary dysplasia (BPD) is the most common complication among very preterm infants and affects about 50% of infants born under 1000 grams.[6] It is a form of chronic lung disease of prematurity where preterm infants still require supplemental oxygen or mechanical ventilator support at 36 weeks postmenstrual age (PMA).[7] Contrary to other neonatal morbidities, rates of BPD have not improved but rather have seen a rise due to the increasing

survival of extreme preterm infants.[6] GA and low weight at birth are the greatest predictors of BPD with infants born <30weeks GA being at the highest risk. A cohort study assessing neonatal outcomes of extreme preterm infants born < 29 weeks GA and at birthweights of <1500g found that the risk of BPD is inversely proportional to GA.[8] Infants born at 22 weeks GA had an 85% incidence of BPD while infants born at 28 weeks GA had a 23% incidence.[5]

### *1.1.3 Normal fetal lung development and pathophysiology of BPD*

Efficient breathing after birth is dependent on the architecture of the peripheral lung saccules, alveoli and pulmonary microvasculature.[9] Lung development is divided into 3 distinct periods: embryonic, fetal and postnatal stages. During the fetal phase (week 8 to 36 weeks GA), the pseudoglandular stage is characterised by the formation of bronchial tree and a large part of the respiratory parenchyma; the canalicular stage involves the formation of the most distal airways leading the branching morphogenesis and the saccular or terminal sac is characterised by the expansion the airspaces for gas exchange.[10] Between 23 to 28 weeks GA, the alveolization of the distal saccule and the alveolar capillary bed develop in conjunction to form the alveoli.[9] During the 3rd trimester (28 to 40 weeks GA), the peripheral saccules will undergo septation (existing airspaces are subdivided by the formation of new walls) which increases the total surface area of the lung. The peripheral lung epithelia also mature into alveolar cell type 1 and 2 which contribute to pulmonary surfactant production.[9] Pulmonary surfactant reduces the surface tension at the air and liquid interface in the lung thus improving the transition to breathing air at birth. Very preterm infants require ventilator assistance since they are still in the canalicular and saccular stage of their lung development and morphogenesis and alveolar differentiation has not yet happened.[9,11] The limited functional capacity of the lungs to breathe on its own explains why LBW infants often require supplemental oxygen or mechanical ventilation.

Figure 1.1. The 3 stages of lung development in utero[10]




The pathogenesis of BPD has a multifactorial etiology. Initially, BPD was thought to occur because of oxygen toxicity from increased production of cytotoxic oxygen free radicals which overwhelmed the antioxidants host defence mechanism and lead to overall pulmonary injury.[12] Today, it is better understood that these infants experience initial lung injury from surfactant deficiency, exposure to increased oxygen, mechanical ventilation, limited early nutrition, inflammation and potentially infection which affect pulmonary growth and repair leading to loss of functional alveolar surface needed for gas exchange.[13] Additionally, alterations to the pulmonary circulation such as delayed pulmonary vascular transition and early pulmonary hypertension have been associated with a higher risk of developing BPD.[9] Early disruption in lung vascular growth from oxidant injury caused by hyperoxia and inflammation can impair growth of the distal airspace.[14,15] Structural changes in pulmonary vasculature contribute to high pulmonary resistance due to the narrowing of the vessels and decreased vascular compliance. The decreased angiogenesis result in a limited surface area for gas exchange causing elevations in pulmonary vascular resistance especially in periods of stress.[12] Overall, BPD has a complex and heterogenous pathology which are caused by a multiple antenatal and postnatal exposures.

### *1.1.4 Clinical definition of BPD*

A clear definition of BPD is needed to identify high risk infants who would require special surveillance and medical care, to understand the incidence and implications of the disease, for parental counselling and to benchmark quality of neonatal care. Scientists have suggested several definitions for BPD over time. In 1967, Rosen and Porter were the first to describe a new form of lung disease in preterm babies which consisted of hyaline membrane disease. It is now called respiratory distress syndrome (RDS).[9] The babies required a prolonged recovery from airway and lung parenchymal injury and this was termed BPD based on airway histological features. In the past 50 years, with the advent of antenatal corticosteroids, advanced neonatal care, more effective respiratory support devices, surfactant treatment and better nutritional modalities; the characteristics features of BPD has largely evolved. The definition of BPD has been revised to reflect a new form of BPD. The classic definition of BPD referred to premature infants who required oxygen supplementation or mechanical ventilation at 28 postnatal days or 36 weeks PMA due to respiratory distress.[13] In the "old BPD", radiographic imaging and lung histology showed alternating atelectasis with hyperinflation, severe airway epithelial lesions, marked airway smooth muscle hyperplasia, extensive and diffuse fibroproliferation, hyperactive remodelling of pulmonary arteries and decreased alveolarization and surface area of the lung.[12] However, due to major changes in prevention management of BPD, these features are neither as severe or as predominant. The increasing survival of more extremely preterm infants has also contributed to this change over time of the pathogenesis of BPD. The old definition of BPD failed to account for important clinical distinctions among the very preterm infants such as lung immaturity versus lung injury and did not predict accurately the long-term pulmonary morbidity. With the "new BPD", the pathological features observed

shows milder airway injury, inflammation and fibrosis.[12 16] The "new BPD" shows less regional heterogeneity of the lung, rare airway epithelial lesions, mild airway smooth muscle thickening, rare fibroproliferative changes, fewer but dysmorphic arteries and fewer, larger, and simplified alveoli.[12] The "new BPD" happens as a result of the reparative process in alveolar and vascular compartments of the lung after injury caused by antenatal and postnatal pathogenic factors leading to reduced, enlarged, thin-walled alveoli, dysmorphic capillary configuration with airway and vascular lesions.[16] New definition for BPD have also been introduced to describe BPD over a spectrum to reflect the different level of disease severity and to predict long term pulmonary morbidity. In Canada, the consensus definition for BPD is defined as the need for oxygen or respiratory support at 36 weeks CGA. The definition varies mostly across severity of BPD classification, which is classified as mild, moderate, or severe based on the level of treatment of oxygen and the timepoint of assessment as shown in the table below.

Table 1.1. Definition of BPD and BPD severity[5]

| **I. Oxygen supplementation alone** | | |
|---|---|---|
| Oxygen supplementation at 28 days postnatal age or 36 weeks PMA | | |
| **II. Diagnostic criteria based on 2001 NICHD consensus workshop** | | |
| | **Gestation age at birth** | |
| | **<32 weeks** | **≥ 32 weeks** |
| **Timepoint of assessment** | 36 weeks PMA or discharge to home, whichever comes first | >28 days but <56 days postnatal age or discharge home, whichever comes first |
| **Grade** | Treatment with oxygen >21% for at least 28 days plus | Treatment with oxygen >21% for at least 28 days plus |
| **Mild BPD** | Breathing room air at 36 weeks PMA or discharge, whichever comes first | Breathing room air by 56 days postnatal age, whichever comes first |
| **Moderate BPD** | Need for <30% oxygen by 36 weeks PMA or discharge, whichever comes first | Need for <30% oxygen by 36 weeks PMA or discharge, whichever comes first |
| **Severe BPD** | Need for >=30% oxygen and/or positive pressure (PPV or nCPAP) by 36 weeks PMA or discharge, whichever comes first | Need for <30% oxygen and/or positive pressure (PPV or nCPAP) by 36 weeks PMA or discharge, whichever comes first |

| IIa. 2016 Revisions of NICHD criteria based on oxygen concentration (%) and type of respiratory support at 36 weeks CGA | | | | | |
|---|---|---|---|---|---|
| **Grades** | **Invasive IPPV** | **nCPAP, NIPPV*, or nasal cannula ≥3 L/min** | **Nasal cannula flow of 1 to ≥3 L/min** | **Nasal cannula flow of <1 L/min** | **Hood oxygen** |
| **I (mild)** | - | 21 | 22 to 29 | 22 to 70 | 22 to 29 |
| **II (moderate)** | 21 | 22 to 29 | ≥30 | ≥70 | ≥30 |
| **III (severe)** | >21 | ≥30 | - | - | - |
| **III. 2019 Diagnosis based on prospective NICHD study at 36 weeks CGA** | | | | | |
| **Grades** | | **Invasive IPPV** | **nCPAP or NIPPV*** | **Nasal cannula flow of >2 L/min** | **Nasal cannula flow of <2 L/min** |
| **I (mild)[17]** | | - | - | - | ≥21 |
| **II (moderate)** | | - | ≥21 | ≥21 | - |
| **III (severe)** | | ≥21 | - | - | - |

*Abbreviation: nCPAP: Nasal continuous positive airway pressure and NIPPV: Nasal intermittent positive pressure ventilation

The incidence of BPD is hard to assess given the changing definitions but it is independently associated with poor postnatal growth, neurodevelopmental impairment, and death.[18-20] With the increasing survival of very preterm infants, understanding how to best treat and prevent of this condition has become a key component of neonatal care.

### *1.1.5 Neonatal and postnatal risk factors of BPD*

Perinatal risk factors of BPD include GA, intrauterine growth restriction (IUGR), being male, chorioamnionitis (inconsistently), race, ethnicity, smoking and possibly genetic predisposition.[9,21,22] Patterns of lung disease during the first 2 weeks after birth are also thought to be predictive of BPD. Infants with highest risk of BPD often either experience respiratory failure leading to substantial and prolonged need for respiratory support, or some initially show of improvement in their lung disease which is then followed by pulmonary decompensation needing mechanical ventilation.[9] This respiratory decompensation is often precipitated by one of the following: a late surfactant deficiency, sepsis, increase in inflammatory proteins and/or patent ductus arteriosus.[9] Approximately 50% of infants with pulmonary deterioration and 70% of

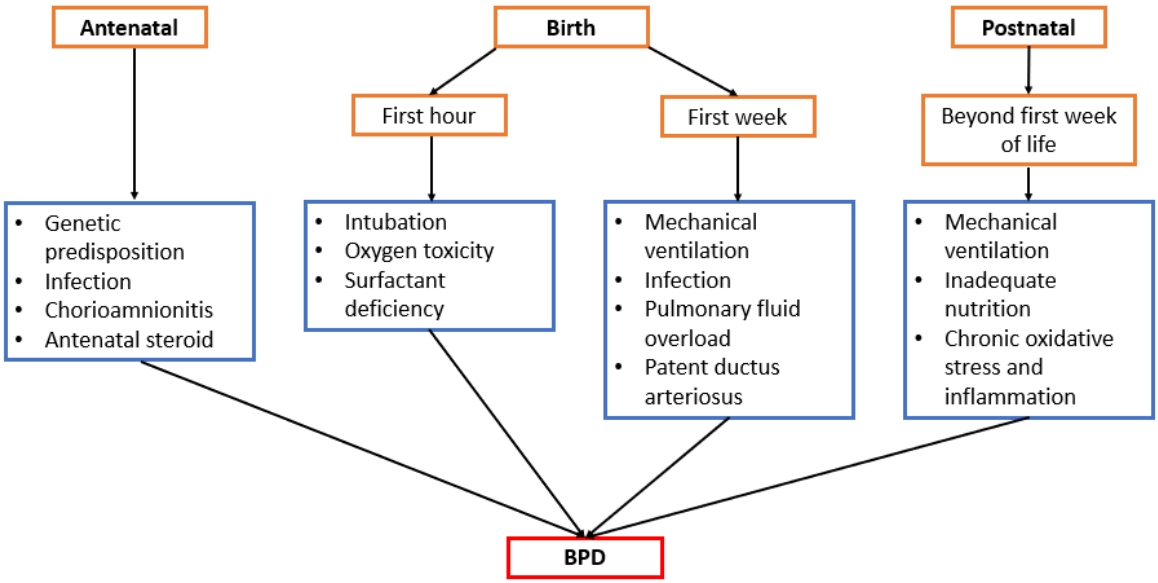
infants with early persistent pulmonary deterioration will develop BPD.[9] Other postnatal risk factors include prolonged mechanical ventilation, initial fluid management and diuresis and inadequate nutrition in the first 2 weeks of life. The role of nutritional deficit in the first 2 weeks of life in the development of BPD will be discussed later in this thesis.

Mechanical ventilation is both a treatment and a cause for BPD. It is a life-saving intervention which is used to achieve optimal oxygen saturation for brain development. Mechanical ventilation is a form of respiratory support which was previously used liberally in preterm infants. Very preterm infants have a high chest wall compliance, weak respiratory muscles, incomplete surfactant production and under-expression of their transepithelial sodium channels which all together hinders the successful transition from in utero to postnatal breathing.[6] Therefore, a majority of very preterm infants will require respiratory support due to early respiratory distress. Respiratory support can range from non-invasive support such as CPAP and NIPPV to invasive mechanical ventilation via endotracheal tube. However, mechanical ventilation is now known to cause trauma on under-developed lungs.[7] Therefore, prolonged mechanical ventilation (invasive and non-invasive) is also the most significant postnatal contributor of BPD. While the underdeveloped lung can support gas exchange, its developing structures are fragile and easily prone to injury. In the most immature infants, even a minimal exposure to oxygen and mechanical ventilation could be enough to contribute to the BPD.[12] To decrease the inflammation on the lungs, neonatologists now use less invasive forms of ventilation while striking a balance between adequate oxygenation and preventing lung damage.

Evidence suggests that inspiration of high oxygen concentration above room air is a major contributor to BPD and is toxic to the immature lungs, but the precise dose and duration of oxygen is not known.[7] Oxygen free radicals are highly reactive and can cause oxidative damage

to the lung and trigger an inflammation cascade. Wu et al., reported that "Early pulmonary changes due to oxygen toxicity include atelectasis, edema, alveolar hemorrhage, inflammation, fibrin, deposition, thickening of alveolar membrane. Continuous high oxygen exposure causes influx or polymorphonuclear leukocytes containing proteolytic enzymes which causes inflammation reaction and cytotoxic damage.".[7] Additionally, mechanical ventilation also contributes to barotrauma and volutrauma. The pressure used to inflate the lungs is often five-fold greater than the physiologic pressure of the normal lung.[7] The over distension of the airways and irregular aeration of the alveoli result in a cascade of reaction which lead to alveolar shear stress, disruption of alveolarization, pulmonary air leak and release of damaging cytokines and other biological substances.[7] Volutrauma which is due to the high tidal volume ventilation, on the other hand causes lung injury by stretching the alveolar wall and capillaries leading to the over-distension of the lung. The combination of oxygen free radicals, barotrauma, volume trauma coupled with other factors like infection or pulmonary edema triggers inflammation.[7] Studies have shown that infants who develop BPD were found to have high concentration of proinflammatory and chemotactic factors in the tracheobronchial aspirate such as leukotriene B4, interleukin-1B, interleukin-8, soluble ICAM-1, anaphylatoxin C5a, platelet aggregation factors and prostaglandin.[7] Pulmonary inflammation affects normal alveolization and angiogenesis which may lead to further remodeling of the developing lung causing ongoing bronchoconstriction, vasoconstriction, edema, neutrophils chemotaxis and mucus production.[7] Recommendations suggests avoiding intubation within the first minutes of life where possible and favor non-invasive respiratory support such as nasal continuous positive airway pressure (nCPAP), nasal intermittent positive pressure ventilation (nIPPV) and high flow nasal cannulae.[9]

Figure 1.2. Summary of risk factors for BPD




### *1.1.6 Short- and long-term complications of BPD*

BPD has been associated with an increased risk of childhood mortality and increased risk of long term respiratory complications, pulmonary hypertension, growth failure, feeding difficulties and neurodevelopmental delay.[23,24] Poor neurological outcome can carry significant long-term impacts where children with BPD were found to have a low average IQ, more academic difficulties, delayed speech and language development, visual–motor integration impairments, and behavioral problems.[24] BPD can also increase economical and societal cost, with parents of children with BPD often being unable to resume work due to considerable medical care required by their infant.[25] A US 2009-2015 study found that preterm infants with BPD had a significantly longer hospital stays than those without and incurred higher total cost (mean [SD] $799,499 [$535,528] vs. $588,949 [$377,137], respectively, $P < 0.001$) during their neonatal intensive care unit (NICU) admission.[26] While assessing adult age outcome of infants

with BPD, a study compared ex preterm with BPD to term subjects and found that while the two groups had similar health-related quality of life, the infants with BPD had a lower education level, higher rates of unemployment, greater health care needs and prescription drug utilization.[27]

## 1.2 POSTNATAL GROWTH IN VERY PRETERM INFANTS

Achieving adequate postnatal growth is one of the most important determinants of long-term morbidity for very preterm infants. Several studies and systematic reviews have suggested improved survival and long-term neurodevelopmental outcome with early postnatal growth. [28,29] The definition of optimal growth for very preterm infants remains a challenge but several assessment tools are used to estimate postnatal growth. Preterm growth curves and calculated daily reference weight gain are the methods used to assess and monitor preterm growth.[30] Calculation of growth velocity in g/kg/day over several days together with assessment of size relative to published growth curve ensure the most comprehensive growth assessment.[31]

### *1.2.1 Preterm growth curves*

Several preterm growth charts have been validated over the years, but the most updated and commonly used chart include the revised Fenton 2013 growth chart, the Olsen 2010 growth chart, and the INTERGROWTH 2015 growth chart. The growth curves are an essential part of neonatal care and are used to direct both nutritional and medical management. The Fenton 2013 or Olsen 2010 intrauterine growth curve are used for infants born ≤ 36 6/7 weeks GA and the World Health Organization (WHO) growth standards for infants born ≥ 37 0/7 weeks GA.[32] The WHO curve describes infant growth from low-risk pregnancies growing under ideal conditions and health outcomes (low infant mortality, low prevalence of underweight, stunting, wasting, access to safe water, low altitude of <1500m and existence of exclusive breastfeeding support and international feeding recommendations). Preterm growth curves describe mostly in utero

growth of both high and low risk pregnancies. Both extrauterine and intrauterine curves have been developed since the 1960s but today, intrauterine charts are favoured in the NICU. Preterm growth curves now include a larger cohort, younger GA, more ethnically diverse population and reflect changes in growth pattern from both nutrition and other neonatal care practices. The table below provides a comparison of most used neonatal growth curves/standard or references.

Table 1.2. Comparison of most used neonatal growth curves

| Chart | Characteristic | Advantages | Disadvantages |
|---|---|---|---|
| **Fenton 2013**[33] | Sample size: 3,986,456<br>GA: 22 -50 weeks<br>Based on estimates of intrauterine size and for preterm infants<br>Assess weight, length, and head circumference | Large multiethnic cohort<br>Includes extreme GA<br>Includes smoothed transition from preterm and WHO estimates<br>Most robust cohort for extreme prematurity | Does not reflect adaptation to extrauterine life |
| **Olsen 2010**[34] | Sample size: 257,855<br>GA: 23-41 weeks<br>Based on intrauterine growth and for preterm infants<br>Assess weight, length, head circumference | Includes extreme GA<br>Includes assessment of body proportionality with BMI curve | Does not reflect adaptation to extrauterine life<br>United States only based cohort<br>Include preterm period only |
| **Olsen 2015 BMI**[35] | Sample size: 391,681<br>GA: 22-42 weeks<br>Based on intrauterine growth and for preterm infants<br>Assess body proportionality | Includes extreme GA<br>Compared different measures of body proportionality | Does not reflect adaptation to extrauterine life<br>United States only based cohort<br>Include preterm period only |
| **INTERGROWTH 2015**[28] | Sample size: 224<br>GA: 28-64 weeks, however data is more robust as of 33 weeks<br>Based on prospective data from healthy low risk pregnancies | Prospective multicentre, multiethnic data<br>Tracked cohort of healthy preterm babies | Data followed only low risk pregnancies, therefore low rate of premature birth<br>Less robust data for extreme prematurity |

| | | | |
|---|---|---|---|
| | Assess weight, length, and head circumference | | |
| **WHO** 2006[32] | Sample size: 8440<br>GA: As of 37 weeks, follows 0-2years old<br>Data based on term infants' growth from low-risk pregnancies and under ideal living conditions<br>Assess weight, length, head circumference, and weight for length ratio | Large multiethnic cohort<br>Includes assessment of body proportionality | Not suitable assess growth for preterm infants<br>Need to use corrected age for preterm infants |

The most common preterm growth curve used is the Fenton 2013 growth standard. The Fenton 2013 curve was first developed in 2003 based on the 1976 Babson and Benda "fetal-infant growth graph".[31] The aim was to develop an updated growth curve that included preterm infants born as early as 22 weeks using a much larger sample size than previous. The 2003 curve was developed out of a combination of population-based cohorts from Kramer et al. (2001), Niklasson et al. (1991), Beeby et al. (1996), and 2000 CDC curves.[31,36-38] The curve was then validated against the Babson and Benda's chart as well as the National Institute of Child Health and Human Development Neonatal Research Network (NICHD) growth curves.[31] The Fenton growth curve tracks weight, length and head circumference of preterm infants from 22-50 weeks GA. All anthropometric measures are classified based on percentiles ($3^{rd}$, $10^{th}$, $50^{th}$, $90^{th}$ and $97^{th}$) and due to different growth patterns observed in sex; different curves were developed for males and females.[33] Percentiles can be converted in corresponding *z* scores for each anthropometric parameter. A *z* score is a numerical measurement which is used to "describe the number of standard deviations (SD) which are greater (positive *z* score) and smaller (negative *z* score) compared to the median" in a normal distribution curve.[39] The use of *z* score is used to compare the growth parameters of preterm infants based on the population's normal distribution of intrauterine growth curve in order to determine whether their size or growth rate falls above or

below the normal range. The use of *z* scores is superior to percentiles as it can categorize and better quantify infants who are outliers and may fall well beyond the normal range of the 3rd and 97th percentile.[37] For example, rather than being at the 0th percentile, an infant would have numerical value of -3.0 SD which means that he would be 3 SD below the median population. The *z* score used within the Fenton growth standards uses *z* scores derived by "summarizing growth charts as LMS parameters (Lambda for the skew, Mu for the median, and Sigma for the generalized coefficient of variation)." Since the curves were based on multiple cohort studies; different methodologies, inclusion and exclusion criteria were used in each study, but infants included were from developed countries with a universal healthcare system. In the 2003 curves, the data included infants born from 1963 to 1996 and some studies included all births while others used only healthy singleton births.[31] The Fenton curve is based on a combination of fetal-infant curve at birth followed by longitudinal charts of term infants in the post-term period. The initial part of the curves is based on the size of fetuses at birth and therefore does not track initial changes in weight changes from the diuresis period post birth. Fenton's rationale for using postnatal curves rather than curves based on actual growth pattern of LBW infants was to avoid variations in medical and nutritional care which would likely impact growth and the need for catch up growth. Despite the use of different cohorts, there was consistency in the head circumference and length data across the cohorts adding to the reliability and generalizability of the curves. The strength of the Fenton curve compared to other preterm curves is the inclusion of a large sample size especially in the more extreme GA and therefore added more confidence in the extreme percentiles. In 2013, a weight gain validation study by Fenton et al. found that around 36 to 40 weeks, there were differences in weight gain velocities between the observed cohort and the fetal-infants growth reference curves which prompted for the use of smoothing

techniques for the curves using the WHO data between the pre and post-term period[33]. Rigorous validation studies using fetal-infant growth reference, World Health Organization Growth Standard (WHOGS) and NICHD cohort were done.[33] Postnatal weight gains collected in three North American NICUs for infants born < 40 weeks was compared to fetal-infant growth reference while the WHOGS was used for infants born after 40 weeks. Fenton at al. revised the chart in 2013 to better harmonize the transition period between the pre-term and post-term period.[33] The data from the 2003 curve were maintained in the 2013 curve. The revised curve included a cohort of 3,986,456 infants from Germany, United States, Italy, Australia, Scotland, and Canada born between 1991 to 2007.[32] Included infants were born as early as 20 weeks up until 50 weeks GA. The following studies were included: Voight (2010), Olsen (2010), Kramer (2001), Roberts (1999), Bonellie (2008), Bertino (2010) and WHO (2006).[34,36,40-43] Most studies excluded multiple births, still births and major congenital anomalies. Cubic splines were used to interpolate smooth values between the chosen GA points and LMS (Lambda for the skew, Mu for the median, and Sigma for the generalized coefficient of variation) values (measures of skewness, median and standard deviation) were computed from the interpolated cubic splines at weekly intervals.[33,44] An iterative least squares method was used to derive the LMS parameters to produce the final percentile curves. The curve was validated against the 2003 Fenton curve and was designed to be equivalent to the WHO growth chart at 50 weeks GA. There was a remarkable close fit for all 3 anthropometric measures across the 6 countries, especially at the $50^{th}$ percentile.

The ideal validation method for growth curves would be to follow a cohort of healthy preterm infants, but data from fetal growth pattern and healthy terms infants were used when merging the pre-term and post-term period to avoid bias from illness acquired through

prematurity. Term versus premature infants differ but most notably in their growth pattern. Cordova et al. suggested that classifying poor growth using the fetal reference was more effective in identifying infants at the greatest risk for adverse neurodevelopmental outcomes in infancy and childhood compared with the healthy preterm reference.[45] Growth treated as a trajectory (change in *z* score) has been shown to have better predictive ability for long-term outcomes than cross sectional assessments of growth.[35] However, the use of fetal size studies probably inserts bias, but while imperfect, it is also the best available data at present to estimate appropriate size for gestational age in preterm infants. This has been an area of contention in neonatology given prematurity is not normal and therefore it may be unrealistic to expect similar growth rates in preterm infants as in healthy term infants. This is particularly important to consider when assessing growth of infants who experience significant postnatal failure from severe morbidities acquired due to prematurity. Several morbidities such as bronchopulmonary dysplasia, intrauterine growth restriction, necrotizing enterocolitis, short bowel syndrome, late onset sepsis and patent ductus arteriosus are known to be independents factors for postnatal growth failure.[46] Currently, there is no recommendations as to whether these infants should follow the same growth trajectory as healthy preterm infants. Based on studies that have demonstrated improved neurodevelopmental outcome with higher weight gain and nutritional intakes, clinicians tend to agree that catch up weight gain is required for infants who experience failure to thrive in the NICU. But there are no guidelines on definitions of appropriate catch-up weight gain, how to quantify catch-up growth velocity, whether it is feasible and even beneficial in the presence of significant neonatal morbidities which are known to impede growth. One of the challenges of building neonatal growth curve is the evolving nature of medical and nutritional care over time. Evidence to support early parenteral nutrition support, early

breastmilk introduction, improved fortifier composition and improved mode of ventilation have improved growth rates in the NICU over the last 50 years. Fenton points out that growth rate throughout gestation is dynamic and that ideal growth in premature remains difficult to define. Therefore, while preterm growth charts are powerful tools to monitor growth, it was not made for preterm infants with severe morbidity who may deviate from the norm and these outliers may benefit from a more individualized growth pattern. Our understanding of what constitutes optimal growth pattern for very preterm infants are constantly evolving as more data becomes available and neonatal care continues to improve.

### *1.2.2 Assessing growth: length and BMI*

Tracking of length using standardized reference growth curves are an integral part of the pediatric medical health assessment.[45] Length is typically assessed based on comparison with standard reference growth charts and length velocity calculation. Stunting is defined by the WHO as a length/height for age $\leq 2$ standard deviations below the WHOGS median. A similar definition is used in preterm infants using preterm growth charts. The use of *z* scores or standard deviations are most commonly used to describe growth patterns, and some have suggested that the use of *z* scores are a better metric compared to traditional growth percentiles.[47] Stunting within the first 1000 days from conception until the age of two is a strong marker of health as it can contribute to adverse consequences which include poor cognition and educational performance, low adult wages, lost productivity and, when accompanied by excessive weight gain later in childhood, an increased risk of nutrition-related chronic diseases in adult life.[48,49]

In preterm infants, optimization of growth parameters is highly relevant given brain and somatic growth are correlated with higher weight gain and subsequently improved neurodevelopmental outcome.[50] Linear growth is often described as the best measure for lean

body mass (LBM) accretion, organ growth and differentiation and nutritional adequacy in the neonatal period.[47,51] However, postnatal linear growth restriction defined as a decline in length *z* score from birth to discharge is highly prevalent in the NICU. Several studies comparing term and preterm infants at discharge have reported consistently that preterm infants are significantly shorter than their term counterpart at term age.[29,52] However, little is known on the full impact of linear growth failure; it is seldom reported as a benchmark for adequate growth in NICUs and few interventions have addressed this problem. Additionally, length is often less reported due to the logistical difficulties of measuring the unstable preterm infant and the lack of proper equipment used to measure the infant. Measuring tapes rather than an infantometer (length board) are often used in the NICU and this can add significant inaccuracies in the measurement and the misdiagnosis of body proportionality.[53,54] Consistency in the timing and technique of serial measurements are often lacking even though several studies have managed to show that length is a good indicator of growth and can be accurately measured with high reproducibility.[55,56] There is overwhelming evidence that linear growth restriction is associated with worse neurodevelopmental outcome, but other neonatal outcomes have not been assessed. Despite a LBW, infants who had higher length *z* scores at discharge correlated with a higher Bayley III language score by 24 months.[47,50,57] Moreover, improved linear growth velocity between term to 4 months was associated with lower odds of IQ <85 at 18 months.[47,50,57] Another study including 2403 preterm infants found that a difference between observed length growth and expected length growth ≤ -0.5 z score was associated with higher odds for 2 year non optimal neurodevelopment outcome.[58] Additionally, neonatal stunting based on fetal references has been shown to be associated with low developmental scores across several domains at 7 years of corrected age.[58]

Currently, weight and head circumference are overwhelmingly used as an indicator for appropriate growth and nutritional status. Given the paucity of data to address linear growth restriction; clinicians tend to assume stunting happens because of lack of nutrition. Surprisingly, the pathogenesis of linear growth restriction in the NICU is poorly understood. Linear growth failure is often attributed to nutritional inadequacy, but very preterm infants often experience events making them more susceptible to worse linear growth outcome. The use of steroids, diuretics, fluid restriction, periods of increased work of breathing, stress-induced growth suppression, feeding intolerance and hypermetabolic needs can also contribute to linear growth restriction which are especially present for very preterm infants with BPD.[51,59] Yet, similar weight gain velocities are used to guide nutrition support in very preterm infants with or without evolving BPD despite potentially different linear growth potential. This combination of higher weight gain but linear growth restriction may lead to disproportionate growth and neonatal experts have described the nutritional dilemma that comes with trying to optimize weight gain for improved neurodevelopment but at the expense of developing an increased fat mass.[50,60] This change in body composition with higher propensity for increased fat mass percentage may not be benign but evidence is scarce to encourage proportional growth in the NICU.

### *1.2.3 Use of BMI and body composition in preterm infants*

BMI is used as the metric to classify relative lack and excess of adiposity to length. BMI is a calculated ratio of weight in kilograms to the square of height in meters ($kg/m^2$). Weight-for-length ratio or BMI are often used in clinical practice to approximate body fat since they are simple, non-invasive, and inexpensive metric. In neonates or children, the BMI classifications are based on age and gender matched normative data. Overweight is defined as weight-for-length ratio or BMI above the $85^{th}$ percentile while obesity is defined as weight-for-length ratio or BMI

of above the 95th percentile depending on the age of the child. However, the use of BMI to assess body fat is contentious. It has been criticized in adults as a measure of excess weight rather than excess body fat. BMI cannot distinguish between excess fat, muscle, bone mass, the distribution of fat (visceral versus subcutaneous) but also does not account for ethnicity which may influence the interpretation of BMI.[61] It is recommended that when BMI is used as a health outcome predictor, it should be used with other biological markers or anthropometric measures.

Several studies have demonstrated that at term corrected age premature infants have a different body composition than infants born term; preterm infants were more likely to a have lower weight, LBM percentage and bone mineral content but a higher percent of body fat.[52,62-64] Moreover, a meta analysis showed that despite preterm infants being significantly lighter and shorter, they had significantly less fat-free mass by a mean difference of 460g at the same gestational age suggesting a propensity for a higher fat mass despite being overall proportionately smaller compared to their term counterparts.[62] The optimal body composition in growing preterm infants is unknown but there has been a growing concern among neonatal experts that rapid weight gains relative to height results in disproportionate postnatal growth. Goals of nutrition care for very premature infants is primarily based on achievement of similar in utero growth rates both quantitatively and qualitatively.[62] Premature growth charts provide a quantitative measure for growth, but quality of growth is harder to assess. Weight gain is the dominant indicator to adjust nutrition support however, weight unlike body composition assessment does not distinguish body compartment.

Many have encouraged body composition assessment due to concern over long term outcomes such as metabolic syndrome and obesity in ex preterm infants. Longitudinal studies assessing adult age outcomes of prematurity found that LBW was associated with an increased

risk of obesity while premature birth was associated with hypertension, cardiovascular disease, and type 2 diabetes. [65,66] The altered fat distribution observed in preterm infants shows intra-abdominal adiposity which is associated with increased risk of type 2 diabetes.[64] Rapid weight gain in infancy has been associated with childhood obesity in the post term period rather than during prematurity.[67,68] Impact of body composition on neonatal health outcome is less known. Ramel et al. found that gain in fat-free mass compared to fat mass before discharge correlated with better cognitive and motor outcomes than with weight gain alone.[57] It is unclear why infants who are born premature have a propensity for increased fat deposition compared to LBM. Macro and micronutrient intake, hormonal influence, and medication interaction such as corticosteroids could play a role in the quality of growth. Currently, use of body composition is not widely adopted and target goals for body composition assessment is currently lacking in the NICU.

### *1.2.4 Methods of body composition assessment in premature infants*

Body composition assessment is not routinely used especially in very preterm infants. Different tools are however available to measure body composition in preterm infants.[69] The most common are air displacement plethysmography (ADP), bioimpedance analysis (BIA), skinfold measurements, ultrasound (US), dual energy X-ray absorptiometry (DEXA), magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS).

A device called the Pea Pod uses ADP and is currently the only device validated using deuterium dilution to assess body composition in neonate.[70] The infant is placed in the chamber for 2 minutes and weight, length and body volume are quantified.[71] ADP is rapid, non-invasive, provides immediate results and accounts for changes in body water.[70] Studies assessing ADP report excellent accuracy for term infants but in preterm infants, ADP overestimated low fat free mass (FFM) density and underestimated high FFM density with an overall moderate accuracy

and reliability.[69,72] Currently, the validity of estimates provided in VLBW infants remains unclear.[70] While the Pea Pod results are unaffected by moving and crying infants, it cannot fit an oxygen tank and rely on estimated thoracic-lung volume to calculate body composition making it unfit for critically ill neonates.[72,73] Irremovable items such as tubes need to be removed prior, making it less practical in clinical setting. This technique is best suited for healthy term infants rather than preterm infants especially if unstable.

BIA uses electrical current to differentiate body compartment by using the assumption that LBM produces less resistance because of its high fluid content, while adipose tissue and bone yield a larger resistance because of lower fluid content.[69,74] In the first 2 weeks of life, BIA is not accurate but improves significantly afterwards.[69] The consensus is that BIA does not outperform anthropometric measurements for whole body composition or FFM prediction.[74-76] There were large error range at every age and simple measures such as length and weight provided as good estimates of percent body composition as BIA.[74] A stable fluid status is needed since electrical conductivity is used, which can be challenging in critically ill preterm infants. In children with BPD, BIA could not precisely evaluate body composition as it overestimated fat mass and underestimated fat free mass.[77] Normal physiologic changes in body composition from initial higher body fluid content to normal LBM accretion depending on GA make it hard to standardize BIA equations which have been deemed inappropriate for the growing infant.[69,78]

Skinfold assessment is used to assess adiposity using predictive equations for whole body fat mass and percent body fat. Most equations developed showed an overall low accuracy; they tend to overestimate low FM values and underestimate high FM values.[69] One equation by Dauncey et al. was developed using term and preterm infants and is considered the most accurate skin fold assessment method.[79] The equation requires a combination of subscapular and triceps

skinfold and 9 body measures but has yet to be validated in the neonatal period. A small study in preterm infants comparing ADP and skinfold measures suggest the mid upper arm circumference and suprailia skinfold analysis may measure adiposity.[69,80] While inexpensive, several measures are required which can be hard especially on very preterm infants with a fragile skin. It is also influenced by fluid status and more validation studies are required.[69]

US uses high-frequency sound waves to produce images on adipose tissue and lean muscle mass thickness which can be compared to standard whole-body FM and FFM.[69] Only one study was done in preterm infants; calf cross sectional area was assessed and correlated with whole body FM when compared to DEXA scan.[81] No precision or validation studies have been done on the use of ultrasound. While ultrasound cannot be currently recommended as the standard of care to assess body composition in preterm infants, it is a promising tool given its limited use of ionizing radiation and easy accessibility in clinical setting. Currently, more standard protocols and comparative references for body composition are needed.[69]

DEXA is the most used methods to assess body composition and bone mineral density in preterm infants. It can assess whole and regional body composition distinguishing between fat mass, lean mass, % fat mass, % lean mass and bone mineral content however it cannot demarcate the distribution of fat.[82,83] It cannot differentiate between subcutaneous and visceral fat mass and reports suggest that visceral fat is likely overestimated in preterm infant using DEXA.[63] Most studies reported adequate reliability and satisfactory to excellent intraclass coefficients for total body compartment fat mass but more modest correlations for body fat in the trunk region.[82,84] These same studies have reported less accuracy in preterm infants than in term infants. The main limitation of DEXA scan is that it requires the use of x-rays and therefore repeated measures are often avoided to limit exposure to radiation.[82] There is a lack of standard for neonatal body

composition and therefore some studies have used piglet models as reference which may have significant differences in body composition compared to a preterm infant.[85]

MRI and MRS compare data on adipose tissue distribution from previously published cohort. MRI is non-invasive, radiation free and enables the direct quantification of individual adipose tissue compartments.[64] This method requires that the infant be still and sleeping in supine position to take serial imaging. Oxygen saturation and heart rate of the infant need to be monitored which requires a neonatologist; thus, this technique is limited to infants who are stable and can maintain a supine position for the whole duration of the exam.[69] While MRI is readily available in hospitals, it is less commonly used for the purpose of body composition assessment.

From this review, methods of assessing body composition are promising but not always validated especially for very preterm infants. DEXA scan is often the most used and cited methodology to calculate body composition in preterm infant, but there is currently no agreed upon gold standard method for body composition assessment in preterm infants. Availability of equipment and the logistics to perform these techniques are resource intensive. In an era of stretched healthcare resources, techniques that are easily adopted in clinical setting are needed. Anthropometric measurements are routinely done in the NICU, they are easily collected, non-invasive and cost efficient. Body proportionality index such as BMI uses routine measures available and can be used as a proxy for body composition.[86] Proportionality index is already used in the WHOGS for term infants for detection of excessive or insufficient weight gain in comparison to length. This is especially important for infants who may fall outside the traditional growth patterns e.g., infants with IUGR, SGA or disease conditions which impact growth potential such as BPD.

### *1.2.5 The Olsen 2015 BMI growth curve*

In 2015 Olsen et al. developed a BMI preterm curve to assess disproportionate growth failure and suggested that BMI could be used as a proxy for body composition in the NICU.[35] The Olsen 2015 BMI curves were based on previous work which validated the use of ponderal index (weight/length$^3$) from the Lubchenco fetal growth charts to assess body proportionality in preterm infants[86]. There were significant levels of discordance between ponderal index categories at discharge with 22.1% of infants being misclassified as inappropriate for length and 22.5% for age.[86] Since ponderal index was not an accurate measure of body proportionality in preterm infants, 6 different weight to length ratios were assessed. The ratios assessed included: weight/length, weight/length$^2$ (BMI), weight/length$^{1/2}$, weight/natural log of length, weight/length$^3$ (ponderal index) and weight/length$^n$ where "n" was defined as Benn's Index (a gestational age-specific regression coefficient designed to have a low correlation with length).[35]

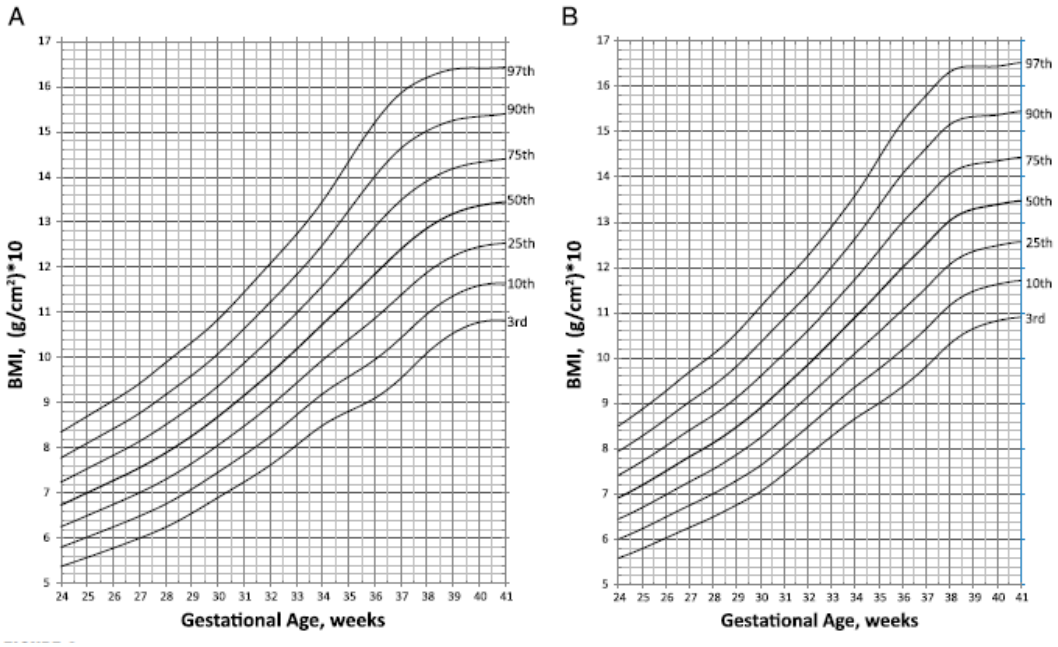
Data from 391681 infants born in the United States was used. These infants were born from 1998 to 2006 at 22 to 42 weeks GA in 33 states within the Pediatrix Medical Group.[35] After excluding for missing sex at birth, multiple births, congenital anomalies, mortality before discharge and infants who were extreme outliers (infants with weight, length and head circumference >2 times above the 75$^{th}$ percentile or below the 25$^{th}$ percentile), 254454 singleton infants were included in the analysis. GA was determined by best estimate of neonatologist based on obstetric history, obstetric examinations, prenatal ultrasound and postnatal physical examinations.[35] This dataset had been previously validated to publish previous weight, length and head circumference intrauterine growth curve.[34,35] The ideal weight for length ratio in preterm infants was defined as a measure that would be most highly correlated with weight and uncorrelated (or $r \sim 0$) with length.[35] BMI and weight/length$^n$ were the only two ratios which

met the above definition. BMI had the best correlation with disproportionate growth across most gestational ages and between genders.

Other studies have also showed consistent results to Olsen et al.[63] Ferguson et al.'s who used the same dataset found that ponderal index had a better correlation to body proportionality but when the data was stratified by GA, BMI was the most appropriate measure since it correlated better with length across GA but was uncorrelated with length within GA.[87] BMI also correlated positively with weight and BMI was proposed as proportionality index in preterm infants.[87] Cooke et al. found that both global fat mass and percent global fat mass increased linearly with BMI.[63] Increase in BMI over time which happened as result of changes in both global fat mass and central fat mass, reflected an increase in visceral fat mass which has been linked with increased insulin resistance.[63] Ramel et al. reviewed the accuracy of anthropometric measures among 218 infants born between 30 and $36^{6}$ weeks using ADP. While no weight for length ratios accurately reflected % body fat, BMI remained the most highly correlated despite large prediction errors.[88] Goswami et al. compared body composition in 389 preterm infants using DEXA scan, he similarly found that BMI increased linearly with percent fat mass, fat mass, fat free mass, and bone mineral content.[82] Conversely, the INTERGROWTH-$21^{st}$ project, used ADP to assess body composition and anthropometric ratios (weight/length, BMI and ponderal index) in 1019 newborns including 91 preterm infants.[70] They reported that weight/length was the best measure to predict newborn FM and FFM.[70] This study was done in predominantly term infants where weight/length is known be the ideal measure of proportionality.[70] This is consistent with the WHOGS which also suggest weight for length as the better measure of proportionate growth in term infants.

Two gender specific BMI curves were built based on the Lambda Mu Sigma method which estimates 3 equivalent degrees of freedom parameters: a Box-Cox power transformation of skewness, median and coefficient of variation.[35] After model fit, the point estimates at 22, 23 and 42 weeks were removed from the final curve due to poor sample size and the curve was validated for mean *z* scores of 1, mean standard deviations of 1, and appropriate distribution of typical infant size classification of SGA, AGA and LGA (9.6%, 80.6% and 9.8% respectively).

Figure 1.3. The Olsen 2015 BMI growth curve (A. Girl and B. Boy)[35]




The main strength of the curve included the large, racially diverse, and contemporary set of birth data used to build a validated gender specific BMI-for-age percentile tables and intrauterine growth curve. BMI assessment allows for quantification of proportionality of growth which is hard to assess visually and can help to individualize nutrition support. For example, an SGA infant with a high length *z* score would require a different nutrition than an SGA infant who is below the 10$^{th}$ percentile for both weight and length.

The use of BMI curves however has limitations. Unlike BMI/weight-to-length ratio in adult or pediatric population which has been associated with poorer health outcome at extremes of BMI measures; to our knowledge the preterm BMI curve has not been associated with any neonatal outcome. Few studies have looked at the impact of BMI in very preterm infants on metabolic syndrome and obesity later on in life, but none have assessed the association of health outcomes during the NICU period.[65,66 89] BMI is often criticized for not being a sensitive index for percentage body fat and LBM in all age groups. Percentage body fat and especially central adiposity is generally accepted as a better marker of risk of insulin resistance, dyslipidemia and other metabolic syndrome in both children and adults.[64]

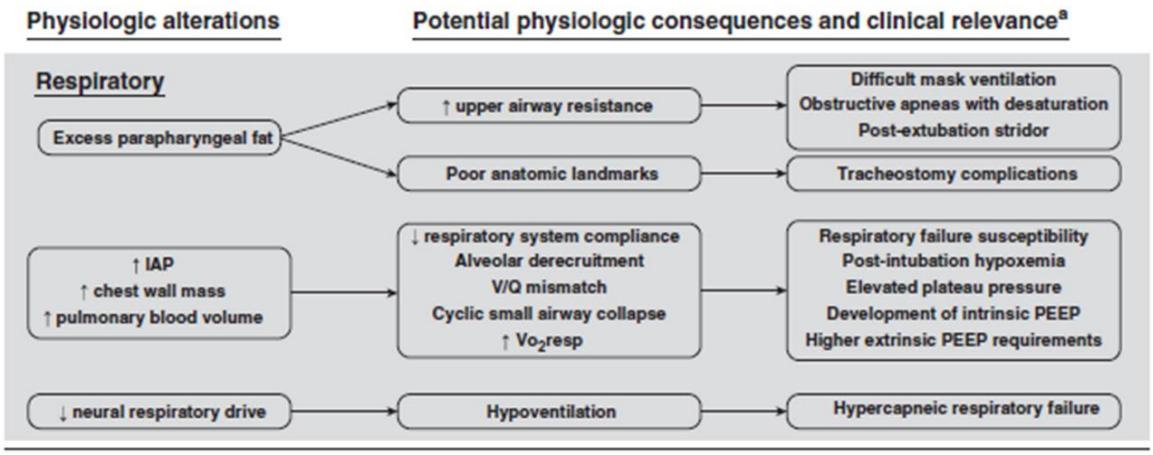
While BMI is not a perfect measure of body composition, several studies mentioned above have validated that BMI is an acceptable proxy for body composition for preterm infants especially in clinical setting where more sophisticated methods may be limited or not feasible. BMI should not be used to target ideal growth in preterm infants but rather it represents the best available estimate of body proportionality and needs to be used in conjunction with other anthropometric or measures to better understand the determinant of body composition.[35]

### *1.2.6 Adiposity and respiratory outcome*

Preterm infants appear to have a propensity towards higher fat mass deposition by term age corrected compared to term infants. These changes in body composition suggest a higher fat mass and lower LBM. In adult literature, higher adiposity may impact lung function and provision of mechanical ventilation. In adult, BMI was a risk factor for increased length of stay and longer duration of ventilation dependence. [90]

Adult patients with a high BMI which generally reflect higher fat mass, experience more hypoxemia and hypercarbia compared to those with a normal BMI. [91] Excess facial fat can compromise the ventilation mask fit. Parapharyngeal fat can contribute to airway narrowing and collapse which increases airway resistance.[91] [92] The increased thoracic wall weight and abdominal fat mass on pulmonary compliance can decrease functional residual capacity and arterial oxygenation which can increase the risk of atelectasis.[93] Excess abdominal fat increases abdominal pressure and displaces the diaphragm upwards which increases chest wall mass and raises pleural pressure.[91,92,94] Persistent hypoxemia after extubation is observed in patient with high BMI compared to healthy BMI who have a full resolution.[91]

Figure 1.4. Physiological alterations and consequences of adiposity on respiratory function [91]




Oxygenation also increases with increasing BMI due the increasing need in oxygen consumption and work of breathing. Kress et al. found that at rest, oxygen consumption is 1.5 times higher in obese patients than in non obese while, Chlif et al. showed that obese patients had a spontaneous breath rate of 15 to 21 breaths per minute versus 10 to 12 in non obese.[95,96] Naimark et al. found that total respiratory compliance can be decreased by two-thirds of the normal value in obese adults.[97] The decreased chest compliance was associated with the

accumulation fat in and around the ribs, diaphragm and abdomen which restricts the movement of the thoracic cavity. During ventilation, patient with high BMI have poorly ventilated lower lung zone which typically have a good perfusion distribution in healthy BMI adults.[91,94] The mechanism responsible for underventilation is due to airway closure and alveolar collapse.[91,94] Increased adiposity can increase ventilation inhomogeneity and gas trapping which can lead to severe exacerbations of obstructive lung disease with concomitantly increased hypoxia, desaturation and dyspnea.[92] These mechanisms have been described in adults but not in prematurity; however, increasing adiposity and BMI over time may have similar impact.

Moreover, adipose tissue is widely considered as pro-inflammatory since it secretes adipocyte-derived factors known as adipokines.[92] Expression of adiponectin which is an abundant anti inflammatory adipokine is significantly decreased in obese patients while leptin which is a pro-inflammatory adipokine is increased.[92] Leptin also known as the satiety hormone, is primarily known to help regulate metabolism, hunger response and immune function. In the neonatal period, leptin has also been found to have an important role in ventilatory drive, surfactant production and neonatal lung development.[98] Some mice studies have shown that leptin deficient mice suffered from respiratory depression with alveolar hypoventilation and chronic hypercapnia.[99,100] Chen et al. showed that leptin promoted fetal growth and fetal lung maturity while upregulating the expression of surfactant proteins.[101] In adult, a high serum leptin concentration is inversely associated with reduced lung function with increasing BMI. While leptin is not fully understood, it is involved in the pathogenesis of airway disease. Increase systemic circulation of pro-inflammatory adipokines and cytokines observed in obese patients increases airway inflammation.[92] While studies appear conflicting, there is mounting evidence that adipose tissue contributes to chronic inflammation which is associated with airway disease

and abnormal lung function.[92] Other inflammatory mediators that are increased with adiposity include tumor necrosis factor alpha (TNF-**α**), interleukins 8 and 6 and high-sensitivity C-reactive protein. [92] These mediators may have an impact on growth given higher levels of TNF-**α** were found in children with growth hormone deficiency.[102] More studies are required to understand how adiposity may impact growth and respiratory function in prematurity.

In the 1990s, postnatal steroid such as dexamethasone or hydrocortisone were used liberally especially in very preterm infants to induce lung maturation, decrease inflammation, and ease the wean of ventilation. Studies have consistently shown that steroids acutely improves lung mechanics, gas exchange and reduce inflammatory cells.[6,9] However, due to long term adverse effect on neurological outcome, head growth, bone and mineral metabolism and growth failure, corticosteroid is now reserved for infants who cannot be weaned off the ventilator. Observational studies in preterm infants exposed to dexamethasone or hydrocortisone showed decreased absolute growth velocities in weigh, length, and head circumference during and shortly after exposure. [103-105]. There was also a persistent lag in linear growth even by 4-month CGA.[103] Systemic steroids are thought to decrease levels of insulin-like growth factor(IGF)-1 and IGF binding protein 3 which are involved in growth.[106] It is also known to impair glucose and fat use, increase proteolysis and decrease calcium and phosphate absorption.[106] Weight and length parameters decreased by at least 10% on both steroids and decrease in head circumference in the hydrocortisone group. Similar studies also found that dexamethasone affected absolute length, but not weight. [104 107] No significant differences were observed in body composition and by 6 months CGA, the infants did not show catch-up linear growth despite no longer being on steroids. Routine use of high dose or prolonged use of postnatal steroid is strongly discouraged and the adverse side effects of systemic steroids may outweigh the benefits.[6]

## 1.3 GROWTH IN PRETERM INFANTS WITH EVOLVING BPD

### *1.3.1 Determinants of growth in preterm infants*

LBW infants have low nutritional reserves and high metabolic demands for growth. Meeting adequate nutritional needs and optimizing growth of very preterm infants rapidly after birth and throughout their time in the NICU are integral part of goals of care. Goals for postnatal growth which are based on preterm growth curves, are uniform for all infants independent of their specific health conditions. However, preterm infants who develop BPD are particularly vulnerable to postnatal growth failure. They experience episodic increased work of breathing causing hypermetabolic states and high growth demands that are hard to meet with fluid restriction. There is also growth suppression from chronic stress, use of steroids and diuretics, prolonged need restricted fluid intake (which can limit nutrition) and feeding intolerance[7,51].

In a large multicentre cohort study comparing growth from birth to discharge and neonatal outcomes, infants who grew on the lowest quartile for velocity in weight, head circumference and length had the highest incidence of BPD compared to those in the higher quartiles.[29] Ehrenkranz et al. showed that infants who experienced the slowest growth velocity, had the highest incidence of morbidities including BPD and suggested that this happened because of undernutrition in the NICU.[29] However, nutrition data collected in this study was not robust enough to infer that nutrition was associated with those observations. There is a large body of evidence suggesting that malnutrition in preterm infants can delay somatic growth and the development of new alveoli as well as decrease diaphragmatic and intercoastal muscle strength which may contribute to the development of BPD.[108] In a retrospective study of preterm infants born < 28 weeks, Williams et al. showed that change in weight z score (△wt) and head circumference *z* score (△hc) from birth to discharge were negatively associated with the number

of days of invasive ventilation.[109] Long periods of invasive ventilation increase the circulating levels of proinflammatory cytokines which have an inhibitory impact of the growth hormone axis[110]. This sustained neonatal systemic inflammatory response is associated with poor postnatal growth, particularly poor linear growth.[110] Even in adult cohort, undernourished patients showed reduced neural drive, decreased diaphragmatic muscle mass, and stayed longer on the ventilator suggesting for the role of nutrition in prompt weaning of the ventilator.[109] Very preterm infants who experience growth failure often require longer and more aggressive form of ventilation.[6]

Postnatal growth failure described as inadequate weight gain and/or poor linear growth are strikingly common features observed in infants with BPD. While poor weight gain and malnutrition are known to be independent predictors of increased risk for BPD, the optimal growth pattern for very preterm infants with evolving BPD is not known. Linear growth and body composition is not well understood in relation to mechanical ventilation or BPD. Clinicians often provide aggressive nutrition support to these infants to compensate for their growth failure. However, in doing so, often lead to a high weight gain but faltering length resulting to an overall high body mass index (BMI). In older adults on mechanical ventilation, a higher BMI which is used as an indirect measure of body composition, has been shown to increase the need for ventilation and thus trauma on the lung.[111] While a suboptimal weight gain is detrimental, the impact of an excessive weight gain is not known. It is unclear whether in very preterm infants, a high BMI affects the need for mechanical ventilation that needs to support an excessive body mass. Current neonatal growth guidelines predominantly rely on weight gain as a standard for optimal growth with faint consideration for linear growth and body composition. Changes that occur in a disproportionate body composition is known to have an impact on the outcome of critical illness in adults, but this has never been assessed in preterm infants.

### *1.3.2 Evidence for "catch up growth" in preterm infants*

Preterm infants are often disproportionately affected by growth failure prompting clinicians to achieve "catch up growth". Catch-up growth has been defined as "a height velocity above the statistical limits of normality for age or maturity during a defined period of time, following a transient period of growth inhibition; the effect of catch-up growth is to take the child towards his/her pre-retardation growth curve."[112] The rationale for catch up growth stems from a large body of literature showing improved neurodevelopmental outcomes by 2 years old in preterm infants with higher weight gain velocity.[60] The "catch-up model" suggests that to achieve catch up growth, weight increases before length resulting in an initial rise in BMI but also by default adiposity.[112] Given sufficient time for catch up, eventually BMI normalizes as catch-up length improves. However, studies have shown that in preterm and SGA infants, there appears to be a mismatch between increased adiposity compared to linear growth and this has been associated with fat mass accumulation, increased risk of higher blood pressure, higher fasting glucose and insulin, and higher total cholesterol level.[65] These markers have been associated with increased risk of cardiovascular disease, type 2 diabetes and metabolic syndrome in longitudinal studies following ex-preterm infants. In very preterm infants, improvement in weight often occurs, but linear growth often does not improve as expected based on the "catch-up model" but rather infants maintain a higher BMI. It is possible that this is a function of insufficient time, however, preterm infants with significant morbidities such as BPD or NEC are often exposed to factors beyond lack of nutrition that can affect their linear growth such as steroid, hypoxia or inflammation. The need for catch up growth is a contentious topic but differentiating the causes for poor linear growth between nutritional and non-nutritional causes may help target the infants who really benefit from catch up growth without the added risk of

metabolic syndrome in adulthood. It is important to note that morbiditieswhere linear growth is often impaired are themselves independent risk factors for poorer neurodevelopmental outcome.

### *1.3.3 Current literature on growth and risk of BPD*

Delayed progression of nutrition to caloric and protein goals resulting in undernutrition and poor weight gain are often observed in ELBW who develop BPD. This is problematic given enough protein and calories are necessary for organ development including the lungs; any deficit would possibly result in impaired lung development which can lead to BPD.[16] Malnutrition during the first days of life can affect the pulmonary defences against hyperoxia, volutrauma and infection which can affect lung maturation and repair.[113-115] Several studies have reported that infants with BPD received significantly less nutritional intake in the first 10 to 14 days of life compared to BPD-free infants.[116 117 118 114,119] Poor nutritional intake within the first 2 weeks of life is associated with worse BPD outcomes. Studies also consistently show that infants with BPD often take more time to reach enteral nutrition goal, have longer duration of parenteral nutrition, and experience more feeding tolerance issues which may further exacerbate their nutritional status. [51,108,120] The cumulative effect of the delayed provision of adequate nutrition likely does not help the overall development of the immature lung.

### *1.3.4 Estimated energy requirements of preterm infants and BPD*

Currently, recommendations are based on caloric intake per kg of body weight in very preterm infants and do not account for disease status.[121,122] Several investigators have published on estimated energy requirements for preterm infants, with most references ranging from 60-100kcal/kg/d for ELBW and then increasing to 120-140kcal/kg/d as the infant grows.[123]

However, these recommendations are very broad. Below is the classification of nutritional requirements based on birth weight and type of nutrition support published by Zeigler et al.[124]

Table 1.3. Estimated protein and energy requirements of premature infants[124]

| **Body weight (g)** | **500-700** | **700-900** | **900-1200** | **1200-1500** | **1500-1800** |
|---|---|---|---|---|---|
| **Fetal weight gain (g/d)** | 13 | 16 | 20 | 24 | 26 |
| **Fetal weight gain (g/kg/d)** | 21 | 20 | 19 | 18 | 16 |
| **Protein (g/kg/d)** | | | | | |
| Inevitable loss | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 |
| Growth | 2.5 | 2.5 | 2.5 | 2.4 | 2.2 |
| *Required intake* | | | | | |
| Parenteral | 3.5 | 3.5 | 3.5 | 3.4 | 3.2 |
| Enteral | 4.0 | 4.0 | 4.0 | 3.9 | 3.6 |
| **Energy (kcal/kg/d)** | | | | | |
| Loss (Expenditure) | 60 | 60 | 65 | 70 | 70 |
| Growth | 29 | 32 | 36 | 38 | 39 |
| *Required intake* | | | | | |
| Parenteral | 89 | 92 | 101 | 108 | 109 |
| Enteral | 105 | 108 | 119 | 127 | 128 |
| **Protein/energy (g/100kcal)** | | | | | |
| Parenteral | 3.9 | 3.8 | 3.5 | 3.1 | 2.9 |
| Enteral | 3.8 | 3.7 | 3.4 | 3.1 | 2.8 |

Estimating energy requirements for infants with evolving BPD is a challenge due to combined effects of increased catabolic state and possible altered growth due to chronic stress and hypoxia. BPD infants often experience episodic periods of increased work of breathing, inflammatory response, and the need for repair of damaged lung and growth which contribute to an overall high energy consumption compared to an infant without BPD.[51,106] Higher energy needs has been suggested as the cause for growth failure with either a need for a higher basal

metabolic rate or an increased in energy expenditure from work of breathing. Metabolic studies in the 1990s using doubly labelled water technique in term corrected preterm infants after NICU discharge suggested that at 1 and 3 months corrected, ex preterm infants with BPD had a higher energy expenditure compared to term BPD-free infants.[120,125,126] They concluded that infants with BPD may have a higher energy needs than term born infants or stable growing VLBW infants but the period during which higher energy expenditure is sustained is not known.[120,126] Infants with BPD probably have fluctuating energy needs with periods of both hyper and hypometabolism due to their respiratory status. [127] Guidelines on interdisciplinary care for infants with BPD recognize that the needs of these children change over time and the role of nutrition is to try and match those demands.[51] Understanding nutritional needs is complex as it depends on how the lung disease affects the somatic growth and slows organ development. However, nutritional needs have been studied in mostly term corrected infants with little evidence available on very preterm infants. Cochrane guidelines published in 2006 on increased energy intake for preterm infants with (or developing) BPD were unable to provide recommendations due to lack of data even after revision in 2011.[128] Few neonatal experts suggest infants with evolving BPD may require 20 to 40% more energy compared to their age-matched healthy infants.[129] They suggest initial energy needs to be approximately 40-60kcal/kg/d in respiratory distress and then requires up to 120-150kcal/kg/d to achieve growth in chronic BPD infants.[16,129] However, this is often challenging to achieve and there is no evidence to show improved outcome with higher energy intake beyond the first 2 weeks of life.[130]

Infants with BPD also often experience chronic stress from noise in the NICU, disruption in sleep pattern, light, suboptimal developmental environment, and painful procedures. Exposure to chronic pain and stress during this crucial period of development has been associated with

growth impairment and elevated cortisol level, increase in inflammatory markers such as interleukin-6, C reactive protein and erythrocyte sedimentation rate.[106] All of the above decrease growth and suppress IGF-1 which is critical in neonatal growth. [106] The new definition of BPD and treatment modalities have also affected both nutritional and growth needs of preterm infants. However, most of the studies done on the nutritional needs and growth requirements of very preterm infants at highest risk of BPD are sparse and based on metabolic studies done in the 1990s which reflect a different standard of care and does not account for increased survival of younger gestational ages. Nutrition and our growth expectations for infants with the new BPD may differ from recommendations from studies made in the 1990s.

### *1.3.5 Nutritional strategies to reduce BPD*

Nutrition for very preterm infants plays a crucial role for growth and in preventing the development of BPD.[16,108,115,117,126,131-133] Adequate nutrition is an important factor in prenatal formation and growth of the lung as well as influence the developmental programming through epigenetic exposures. Studies suggest that provision of insufficient nutrition during critical early developmental period can alter the normal development of the lung and contribute to BPD in VLBW infants.[16] Postnatal growth failure in BPD infants is likely acquired by the cumulative effect of inadequate nutrient delivery which is among the main contributors of BPD.[6,51,108,115,131]. Optimal nutritional strategies for infants at high risk of BPD are not well defined.

Several evidence-based strategies have been put forward to help prevent the development of BPD in high-risk preterm infants as shown in the figure below. Early parenteral nutrition, protein intake of 3g/kg/d after birth, early initiation of enteral nutrition with breastmilk and introduction of calorically dense fortifiers with improved protein to energy ratio have improved both postnatal growth and BPD in very preterm infants. [16,134] Studies in adult ventilated patients

have assessed the impact of macronutrient composition (percentage of carbohydrate compared to fat) of enteral feed have on ventilation weaning. Results conflicting, but some studies have shown that higher carbohydrate content increases carbon dioxide production due to increased respiratory quotient which suggests overfeeding, lipogenesis and increased respiratory demands.[135,136] This has been associated with increased ventilatory demands and prolonged mechanical ventilation; this could increase risk of BPD if true in very preterm infants.[135,136]

Figure 1.5. Preventative nutritional strategies in infants at high risk of BPD [16]

| Intervention | |
|---|---|
| Avoid excessive fluid intake | – In the first postnatal day: 80–100 mL/kg/day<br>– After the first postnatal week: 135–150 mL/kg/day |
| Provide adequate incubator humidity | – In the first postnatal week: 60–70% |
| Maintain adequate temperature | – Abdominal skin: 36.0–36.5 °C<br>– Inspired air temperature (hood, CPAP, or ventilator): 34.0–41.0 °C, relative humidity of 100% |
| Optimize early parenteral energy intake | – In the first postnatal week: 80–100 kcal/kg/day<br>– After the first postnatal week: 120–150 kcal/kg/day |
| Optimize early parenteral amino acid intake | – Start with 1.5–2 g/kg/day after birth<br>– Increase to 3.5 g/kg/day from the first 48–72 postnatal hours |
| Optimize early parenteral fat intake | – Start with 1.0–2.0 g/kg/day within the first postnatal day<br>– Increase by 0.5–1.0 g/kg/day up to a maximum of 4.0 g/kg/day at 72–96 postnatal hours |
| Provide adequate intravenous glucose | – Limit the rate to 12 mg/kg/min (ideal limit: 8.3 mg/kg/min) |
| Optimize early parenteral calcium and phosphorus intake | – In the first postnatal week: parenteral Ca 32–80 mg/kg/day and P 31–62 mg/kg/day<br>– After the first postnatal week: parenteral Ca 100–140 mg/kg/day and P 77–108 mg/kg/day<br>– Parenteral Ca/P ratio: 1.3 (mass) or 1 (molar) |
| Provide adequate intravenous lipid soluble vitamins | – Vitamin A (retinol) 227–455 µg/kg/day or 700–1500 IU/kg/day<br>– Vitamin E (α-tocopherol) 2.8–3.5 IU/kg/day |
| Provide adequate intravenous trace elements | – Particularly zinc 400–500 µg/kg/day |
| Initiate early enteral feeding | – Initiate minimal enteral feeding (12–24 mL/kg/day) prior to 3rd postnatal day<br>– Use preferably mother's own milk or donor human milk as second choice |

## 1.4 SUMMARY OF LITERATURE REVIEW

In summary, BPD is the most common morbidity among preterm infants who are born < 30 weeks GA. Several prevention strategies have been suggested to avoid the development of BPD, with the use of non-invasive ventilation being one of the most effective methods. Growth assessment in preterm infants uses growth curve references and standard weight gain velocities which are based on intrauterine growth chart of healthy term infants. Current guidelines dominantly use weight gain as benchmark for adequate growth but does not consider that preterm infants at high risk for BPD, may experience events that limits their growth potential.

In adult literature, increase adiposity has been associated with increased ventilation requirement and prolonged mechanical ventilation which increases risk of acquired lung injury. Preterm infants often experience altered postnatal growth with a propensity towards higher fat mass compared to term infants. Growth guidelines predominantly aims for adequate weight gain without considering length which may lead to a higher BMI (increase in weight but not length) and increased adiposity over time. A higher body fat deposition over time may affect respiratory status and development of BPD. Assessment of body composition using BMI as a proxy is relatively new in the NICU, but several studies comparing different anthropometric ratios have consistently found that BMI was the best measure of body proportionality in preterm infants. To our knowledge, the use of BMI has not yet been correlated with any neonatal health outcome.

Based on current literature, a change in BMI from birth to 36 weeks, which may reflect an increase in adiposity over time may have an impact on the respiratory function and the effectiveness of providing ventilation. Our study aims to investigate the association between changes in body composition using BMI as a proxy in preterm infants born <30 weeks GA and their risk of developing BPD.

# 2 CHAPTER 2: *OBJECTIVES, HYPOTHESIS AND STUDY QUESTIONS*

## 2.1 OBJECTIVE

This study aimed to compare growth patterns of infants with and without BPD, and evaluate the association of changes in BMI *z* score from birth to 36 weeks corrected gestational age (CGA) with BPD among infants born at <30 weeks of GA.

## 2.2 HYPOTHESIS

We hypothesized that infants with the most extreme changes in BMI *z* score from birth to 36 weeks corrected would have increased odds of BPD.

## 2.3 RESEARCH QUESTIONS

1. To determine if linear growth is associated with BPD among preterm infants born <30 weeks GA
2. To determine if body composition (estimated using BMI) is associated with BPD among preterm infants born <30 weeks GA.

# 3 CHAPTER 3: *MANUSCRIPT*

# The association between BMI trajectories and bronchopulmonary dysplasia among preterm infants born at less than 30 weeks of gestational age

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## 3.1 KEY POINTS

**Question:** Are changes in body mass index (BMI) *z* score from birth to 36 weeks corrected gestational age (CGA) associated with bronchopulmonary dysplasia (BPD) in preterm infants born <30 weeks gestational age?

**Findings:** In this multicentre retrospective cohort study, increases in BMI *z* score from birth to 36 weeks CGA were associated with higher odds of BPD. Despite similar caloric intake, infants with BPD had a higher weight- but lower length-for-age, resulting in higher BMI *z* score compared to BPD-free infants.

**Meaning:** Infants with evolving BPD may require different growth and nutritional targets compared to BPD-free infants.

## 3.2 ABSTRACT

**Importance:** Preterm growth assessment focuses predominantly on weight gain, but the association of changes in body mass index (BMI) on bronchopulmonary dysplasia (BPD) is unknown.

**Objective**s: To investigate the association between change in body mass index from birth to 36 weeks gestation (ΔBMI) and bronchopulmonary dysplasia (BPD) among infants born <30 weeks gestation.

**Design:** Multicenter retrospective cohort study of preterm infants born January 1, 2015, to December 31, 2018, using data collected from the Canadian Neonatal Network database and medical charts.

**Setting:** Three tertiary neonatal intensive care units.

**Participants:** Infants born <30 weeks gestational age (GA) admitted within 1 day after delivery and alive at ≥34 weeks corrected.

**Exposure:** Quartiles of ΔBMI, calculated from birth to 36 weeks CGA.

**Main outcome and measures:** The primary outcome was BPD, defined as need for respiratory support or oxygen at 36 weeks CGA.

**Results:** Among 772 included infants, 51% developed BPD. From birth to 36 weeks CGA, the weight *z* score of infants with BPD decreased less than for BPD-free infants, despite a greater decrease in length *z* score and similar caloric intake resulting in increases in BMI *z* score (median [IQR], 0.16 [-0.64; 1.03] vs -0.29 [-1.03; 0.49]; $P<0.01$). In the adjusted analysis, higher ΔBMI

z score quartiles were associated with higher odds of BPD (Q3 vs Q2, AOR [95%CI], 2.02 [1.23-3.31] and Q4 vs Q2, AOR [95%CI], 2.00 [1.20-3.34]).

**Conclusion and Relevance:** An increase in BMI *z* score from birth to 36 weeks CGA was associated with higher odds of BPD among infants born <30 weeks GA. This increased BMI reflects a higher weight gain but slower linear growth despite similar caloric intake, suggesting that infants with evolving BPD may require individualized growth and nutritional targets.

## 3.3 INTRODUCTION

Bronchopulmonary dysplasia (BPD) is the most common morbidity among infants born <30 weeks gestational age (GA) affecting over 45% of survivors.[13,19] It is associated with higher hospital costs and long-term complications, including neurodevelopmental impairment.[12,25,51] The causes of BPD are multifactorial; a low GA, surfactant deficiency, persistent inflammation, prolonged invasive ventilation and oxidative damage are important contributing factors.[6,12,13] Optimal nutritional management of preterm infants with evolving BPD is complex due to their hypermetabolic needs associated with postnatal growth and increased work of breathing.[16,117,134] Nutritional interventions commonly focuses on achieving optimal body weight gain with less attention to linear growth and body composition.[137] Indeed, previous studies in infants with evolving BPD have focused on the association of body weight and head circumference with neurodevelopmental outcomes but seldomly on growth trajectories and body composition changes.[50,138,139]

A lower birth body mass index (BMI) *z* score, used as an indirect measure of body fat[35,70] likely reflects asymmetric fetal growth restrictions and has been associated with higher odds of BPD.[140] However, changes in BMI during hospitalization, reflecting disproportionate growth, may further contribute to BPD. A higher BMI in adults is associated with increased ventilatory needs in intensive care units.[111,141] Therefore, this study aimed to compare growth patterns of infants with and without BPD, and evaluate the association of changes in BMI *z* score from birth to 36 weeks corrected gestational age (CGA) with BPD among infants born at <30 weeks of GA. We hypothesized that infants with the most extreme changes in BMI *z* score would have increased odds of BPD.

## 3.4 METHODS

### *3.4.1 Study population and eligibility criteria*

This was a multicentre retrospective cohort study using a convenience sample of infants admitted to 3 tertiary neonatal intensive care units (NICU) between January 1, 2015, and December 31, 2018. We included infants born at $22^0$ to $29^6$ weeks GA, admitted within 1 day after birth. Infants who had major congenital anomalies, died before 34 weeks GA or had missing length measurements at birth or at 36 weeks CGA were excluded. Ethics approval was obtained from the Research Ethics Board of each participating site

### *3.4.2 Data collection*

Data on infant characteristics and outcomes were obtained from the Canadian Neonatal Network database. At each site, patient information is entered electronically by trained abstractors into a data-entry program with built-in error checking that has shown high reliability and internal consistency.[142] Gestational age was calculated hierarchically from best estimate based on date of in vitro fertilization, prenatal ultrasound, last menstrual period, obstetric and pediatric estimates. The following characteristics were extracted: use of antenatal steroids (partial or complete), multiple delivery, mode of delivery, outborn, birth GA, birth weight, small for GA status (SGA; defined as $<10^{th}$ percentile for GA and sex),[33] sex, 5 minute Apgar <7, Score of Neonatal Acute Physiology version 2 (SNAP-II) >20,[143] surfactant, mechanical ventilation, postnatal systemic steroid, necrotizing enterocolitis (NEC; defined as stage 2 or 3 NEC according to Bell's classification[144]) and patent ductus arteriosus (PDA; diagnosed based on clinical suspicion and/or echocardiography findings).

Biweekly anthropometric data (weight, length, and head circumference) and caloric intake from birth to 36 weeks CGA were collected from medical chart review. Weight and length were used

to calculate BMI (g/cm$^2$). Biweekly caloric intake (kcal/kg/d) was calculated from each infant's actual total caloric intake (parenteral and enteral) received on the days the anthropometric measurements were taken.

### *3.4.3 Standards of care*

Nutritional approaches and feedings protocols were generally similar across the sites (Supplementary Table 3.1). Parenteral nutrition was initiated after birth at 65-80 ml/kg/day and enteral feeding was initiated within 12-48 h of birth. Parenteral and enteral nutrition were adjusted by neonatologist in collaboration with trained neonatal dietitian and/or pharmacists. Typical objectives were to achieve 90-120 kcal/kg/d and 3.5-4.5 g/kg/d of protein by day 3-5, and full enteral feeding within 2-3 weeks of life. Weight was measured daily using a neonatal scale. Length and head circumference were measured at least biweekly by a trained registered nurse and nursing assistant using either an infantometer or measuring tape.

### *3.4.4 Exposure variables and outcome definitions*

Weight-, length- and head circumference-for-age *z* scores were calculated using the 2013 Fenton reference standards[33] and BMI-for-age *z* scores were calculated using the 2015 Olsen reference standards.[35,145] Length *z* scores before 23.5 weeks CGA and BMI *z* scores before 24.5 weeks CGA were based on extrapolated data as measurements fell beyond the published growth charts.[145] The main exposure variables were changes in BMI (ΔBMI), weight (Δwt), length (Δlt) and head circumference (Δhc) *z* scores from birth to 36 weeks CGA, using the closest value recorded between $34^0$ to $38^6$ weeks CGA. Missing birth length measurements were imputed for 68 infants by subtracting 0.89 cm (the mean increase in length from birth to week 2 among

infants with available data) from the first length measurement taken between 7 and 13 days of life.

The primary outcome of BPD was defined as the need for oxygen or respiratory support at 36 weeks CGA, or at time of death or NICU discharge before 36 weeks CGA. BPD severity was graded as mild, moderate and severe using standardized definitions (Supplementary Table 3.2).[19]

### *3.4.5 Statistical analyses*

Descriptive comparisons between infants with and without BPD were conducted using Pearson $\chi^2$ test for categorical variables and Wilcoxon rank-sum test for continuous variables. For both groups, growth trajectories were plotted using the median biweekly measurements (BMI, weight, length, head circumference *z* scores and caloric intake), from birth up to 14 weeks postnatally.

Since the association between ΔBMI and BPD was nonlinear, ΔBMI was categorized into quartiles. Quartile 2 (Q2) was used as the reference category since we hypothesized that the most extreme changes would have highest odds of BPD. Generalized linear mixed models including site as random effect were used to assess the association between ΔBMI quartiles and BPD; crude and adjusted odds ratios (OR) with corresponding 95% CI were reported. Two adjustment models were evaluated: the birth model included antenatal steroid exposure, GA, sex, multiple delivery, mode of delivery, SGA status and SNAP-II score >20, while the postnatal model included all birth model variables, mechanical ventilation exposure, NEC (due to possible effect of NEC on growth), and PDA (due to possible changes in fluid management due to PDA). Collinearity was assessed with variance inflation factor >5.[146] Birth weight and use of surfactant and postnatal steroids were excluded from regression models due to collinearity with GA and mechanical ventilation, respectively. Primary analyses aimed to evaluate the association of BPD

with ΔBMI, and secondary analyses evaluated associations with quartiles of Δwt, Δlt and Δhc in attempts to better understand what components of growth better correlate with BPD. Secondary analyses were not adjusted for multiple comparisons as these were conducted to generate hypotheses and should be interpreted with caution.[147] Biweekly median caloric intake was plotted based on ΔBMI quartiles and comparisons were made using the Kruskal-Wallis test.

Additional analyses were performed for exploratory purposes and should be interpreted as such. Ordinal regression models, adjusted for the same confounders as above, were used to assess association of BPD severity with ΔBMI, Δwt, Δlt and Δhc quartiles. Sensitivity analyses were conducted by stratifying GA groups (22-25$^{6}$ and 26-29$^{6}$), SGA status and postnatal systemic steroid exposure, to address the potential differences in growth trajectories of lower GA and SGA infants and the possible effects of postnatal systemic steroids on body composition. Statistical significance was set at a two-tailed *P* value <0.05. Analyses were performed in R version 3.6.1 using Tidyverse version 1.3.0.[148,149]

## 3.5 RESULTS

During the study period, 1023 infants were born <30 weeks GA at participating sites and 251 infants were excluded (29 had a major congenital anomaly, 139 died before 34 weeks GA and 83 had a missing length at birth or 36 weeks [Supplementary Figure 3.1]). Excluded infants due to a missing length at birth or 36 weeks had a higher birth weight, higher GA and were discharged/transfer prior to 36 weeks (Supplementary Table 3.3). Of the 772 infants included in the final study sample, 391 (51%) developed BPD. Among infants with BPD, 44 (12%) had mild BPD, 244 (66%) had moderate BPD and 83 (22%) had severe BPD. A total of 11 (1%) infants died, all of whom were >35 weeks CGA at time of death and met criteria for BPD.

Compared to BPD-free infants, infants with BPD had similar rates of antenatal steroid exposure, were more frequently delivered by caesarean, born at lower GA and birth weight and more frequently had a SNAP-II score >20, exposed to surfactant, mechanical ventilation, postnatal steroids, and were more often diagnosed with NEC and PDA (Table 3.1). At birth, median weight, length, and head circumference *z* scores were significantly lower for BPD infants compared to BPD-free infants but there was no significant difference in median BMI *z* score at birth. At 36 weeks CGA, there was no difference in median weight *z* scores, but length and head circumference *z* scores remained significantly lower resulting in a significantly higher BMI *z* score in BPD infants compared to BPD-free infants.

Figure 3.1 shows the anthropometric trajectories and caloric intake between BPD and BDP-free infants from birth to 14 weeks postnatal. Infants with BPD were born with similar BMI *z* scores, but lower weight and length *z* scores compared to BPD-free infants. After week 2, infants with BPD had higher biweekly BMI z scores, similar weight z scores and lower length z scores, despite similar biweekly caloric intakes.

When comparing characteristics of infants across ΔBMI quartiles, infants in Q3 and Q4 had higher rates of BPD than those in Q1 and Q2 (Supplementary Table 3.4). Compared to all other quartiles, infants in Q4 had a greater increase in ΔBMI, smaller decrease in Δwt and greater decrease in Δlt from birth to 36 weeks CGA. After adjusting for birth and postnatal variables, infants in Q3 and Q4 of ΔBMI had higher odds of BPD compared to Q2 (Table 3.2). Similarly, Q3 and Q4 of Δwt were associated with higher odds of BPD after adjustment for postnatal variables, whereas associations were non-significant between Δlt quartiles and BPD.

Biweekly caloric intake using postnatal age and CGA was compared between ΔBMI quartiles in Figure 3.2. Infants in Q4 had higher caloric intakes from 27-33 weeks CGA than those in other quartiles (unadjusted comparisons). In the ordinal regression analysis for the association of ΔBMI with BPD severity, Q3 and Q4 were associated with BPD severity compared to Q2 in all models (Supplementary Table 3.5). Sensitivity analysis based on GA group (<26 and 26-29 weeks), SGA status and postnatal systemic steroid exposure showed similar results or effect directions: Q3 and Q4 of ΔBMI were associated with higher odds of BPD compared to Q2 (Supplementary Table 3.6).

## 3.6 DISCUSSION

In this multicentre cohort of preterm infants born <30 weeks GA, an increase in BMI *z* score from birth to 36 weeks was associated with higher odds of BPD. At birth, infants who developed BPD were proportionately smaller, with lower weight and length *z* scores, compared to BPD-free infants, with no significant difference in BMI *z* score. By 36 weeks CGA, BPD infants had higher BMI *z* scores due to a combination of higher weight gain velocity but slower linear growth despite receiving similar caloric intakes as BPD-free infants.

Our findings are consistent with several studies that have shown lower birth weight, length and head circumference *z* scores are associated with the development of BPD.[132,138,150] However, our study expands on prior work by including description of changes in length and BMI *z* scores from birth to 36 weeks based on BPD status. Contrary to a recent study by Lee et al., we observed no significant difference in birth BMI *z* score between BPD and BPD-free infants, which may be explained by differences in study populations and inclusion criteria:[140] Our study excluded infants who died <34 weeks GA who may have had a lower BMI *z* score at birth which differs from Lee et al. who assessed association of birth BMI with all neonatal outcomes. Also, Lee et al. included infants based on birth weight <1500g (regardless of GA), which may have led to including more infants with growth restriction. At 36 weeks CGA, weight *z* score was similar in BPD and BPD-free groups despite a lower birth weight *z* score. Our results are consistent with a large UK study showing that infants with BPD had a smaller decrease in Δwt compared to BPD-free infants.[138] Length and head circumference *z* scores remained significantly lower in infants with BPD at 36 weeks CGA. This relative weight "catch up" in infants with BPD combined with poor linear growth may explain why these infants had higher ΔBMI despite similar caloric intake.

Based on growth trajectories, we hypothesize that the higher ΔBMI in BPD infants was due to lower weight loss in the first 2 weeks of life, a higher Δwt and lower Δlt compared to BPD-free infants. The lower initial weight loss in the BPD group is likely a reflection of differences in fluid balance and diuresis post birth which has been associated with BPD.[151-153] While fluid is predominantly contributing to ΔBMI in the first 14 days, shifts in ΔBMI from week 2 to week 14 are likely due to changes in body composition as nutrition becomes better established. Several investigators have shown that preterm infants often experience disproportionate growth with increased adiposity compared to term infants by discharge.[69,83,154] While BMI cannot distinguish between fat mass, fat-free mass, and fluid, studies have shown that a higher BMI correlates with higher fat mass in preterm infants, making BMI a reasonable proxy for body fat percentage.[154-156] This has been validated against dual-energy X-ray absorptiometry and bioimpedance analysis which are more accurate but less accessible in clinical practice.[63,69,77,157] Different anthropometric ratios of body proportionality have also been compared and BMI was consistently the best measure of disproportionate growth in preterm infants.[35,87] BMI is a validated, easy, non-invasive and cost-effective method to assess body composition in the NICU for preterm infants.[35,70,87,158]

To better understand the association of ΔBMI, we used several adjustment models and sensitivity analyses. Across all models, quartiles with an increasing ΔBMI (Q3 and Q4) were consistently associated with increasing odds of BPD. This novel finding suggests that infants at highest risk for BPD would benefit from monitoring changes in BMI *z* score as part of their growth assessment. Infants with BPD appeared to have a different growth potential even when provided with similar calories. We hypothesized that the combination of episodes of hypometabolic hypoxia, chronic inflammation and nutritional epigenetic may alter the growth and metabolism

of infants with evolving BPD.[110,159-161] Alternatively, the extent of change in BMI *z* score as early as at 2 weeks of life can be a marker of a more severe phenotype of BPD requiring a different nutritional approach. Despite similar caloric intakes, our results suggests that an excessive fat mass deposition especially combined with linear growth restriction might contribute to delayed weaning from mechanical ventilation and development of BPD. Studies in ventilated adults have shown that physiological alterations from obesity can increase upper airway resistance, alveolar de-recruitment and decreased respiratory compliance.[92,111,141,162] These lead to obstructive apneas and desaturations which can influence the need for higher ventilatory settings. This has not been studied in preterm infants, but similar changes may occur; a higher fat mass and lower lean body mass may impact ventilatory requirements. BPD-free infants had lower BMI *z* scores after postnatal week 2 but also a better linear growth which could reflect a higher percentage of lean body mass. Linear growth is generally recognized as the best indicator of lean body mass accretion, organ growth and nutritional adequacy, which together can improve muscle function involved in lung mechanics.[51,56,163] Aggressive mechanical ventilation is an independent factor for BPD and body composition may indirectly alter ventilatory needs leading to lung trauma and inflammation. It is also possible that prolonged intermittent hypoxia, inflammation, and steroid exposure in infants with BPD alter their metabolic profile in a way that predisposes them to fat mass deposition; thus, potentially making the relationship between BMI and BPD bidirectional.

Current preterm guidelines focus on achieving standard growth velocities regardless of the infant's disease status. Weight gain and head circumference are overwhelmingly used as benchmark of adequate postnatal growth. However, tracking deviations in length and BMI over time may prevent under and overfeeding. This study highlights the value of linear growth, where

measuring precise weekly lengths using an infantometer is as important as weight gain. Tracking BMI trajectory over time is a simple tool to assess qualitative growth and may help reduce risk of BPD in preterm infants. This recommendation is consistent with consensus guidelines for term corrected children with severe BPD, which emphasizes monitoring somatic growth by aiming for an ideal weight-for-length ratio at ~50%, preventing excessive weight gain and reassessing calories when weight gain crosses growth chart percentile.[51] Currently, there is no definition for excessive weight gain in preterm neonates but a positive change in BMI *z* score, where weight gain is driven by fat mass deposition or fluid accumulation may be detrimental. Optimal growth in preterm infants appears to be about striking a balance between two extremes, and monitoring changes in BMI *z* score can help achieve this balanced postnatal growth.

**Strengths and limitations**

Strengths of this study includes the analyses of each individual growth parameters (BMI, weight, length, and head circumference) at multiple time points and their association with BPD using a large multicentre cohort with a validated dataset. Caloric intake was assessed based on actual intake received at the same time points to mitigate the confounding effect of nutrition in the association with BPD. Our results were consistent across adjusted models, analysis of exposures for each 2-week period and in sensitivity analyses.

This study has limitations. Having used retrospective data, we cannot infer causality and account for errors in reporting measurements and caloric intakes that may have happened. Other nutritional components that may impact BPD such as macronutrient (protein, fat, macronutrient distribution) and fluid intake were not included. Although we adjusted for postnatal factors that can affect growth and fluid balance such as NEC and PDA, we did not have data on fluid intake

and balance. There may be residual confounding due to different clinical practices for nutrition or ventilation among centres despite statistical adjustment. Caloric intake was assessed biweekly and may not reflect the cumulative effect of energy intake on growth.

## 3.7 CONCLUSION

An increasing BMI *z* score from birth to 36 weeks was independently associated with higher odds of BPD. This positive ΔBMI from birth to 36 weeks was due to a lower weight loss in the first 2 weeks of life, a higher weight gain overtime and a slower linear growth velocity, despite no differences in caloric intake when compared to BPD-free infants. These findings suggests that infants who develop BPD may have altered metabolism and may benefit from individualized growth targets that include ΔBMI as opposed to weight gain alone. Future studies on macronutrient intake and body composition are required to better identify nutritional goals in very preterm infants with evolving lung disease.

**Data availability:** The datasets generated during and/or analysed during the current study are not publicly available due to their containing information that could compromise the privacy of research participants but are available from the corresponding author [MB] on reasonable request.

## 3.8 ARTICLE INFORMATION (ACKNOWLEDGEMENT)

Short Title: Body mass index, body composition and bronchopulmonary dysplasia

**Keywords:** Premature, body mass index, body composition, bronchopulmonary dysplasia

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**Author Contributions:** Li Ching Ng and Dr. Beltempo have full access to all the data in the study and take full responsibility for the integrity of the data and accuracy of the data analysis.

*Concept and design*: Li Ching Ng and Beltempo

*Acquisition, analysis, or interpretation of data*: Li Ching Ng, Patel, Beltempo

*Drafting of the manuscript*: Li Ching Ng and Beltempo

*Critical revision of the manuscript for important intellectual content*: All authors

*Statistical analysis*: Li Ching Ng, Patel, Beltempo

*Administrative, technical, or material support*: Lapointe, Bizgu, Beltempo

*Supervision*: Beltempo

**Conflicts of Interest Disclosures:** The authors have no conflicts of interest relevant to this article to disclose.

**Consent statement:** Patient consent was not required for this study

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## Table 3.1. Maternal and infant characteristics of full cohort, BPD and BPD-free infants

| Variable | Total (n=772) | BPD (n = 391) | BPD-free (n = 381) | *P* value |
|---|---|---|---|---|
| **Maternal variables** | | | | |
| Antenatal steroids, No. (%) | 708 (92) | 357 (92) | 351 (93) | 0.67 |
| Multiple delivery, No. (%) | 178 (23) | 94 (24) | 84 (22) | 0.57 |
| Caesarean delivery, No. (%) | 525 (68) | 280 (72) | 245 (64) | * |
| Outborn delivery, No. (%) | 86 (11) | 38 (10) | 48 (13) | 0.25 |
| **Infant variables** | | | | |
| Gestational age, median (IQR), weeks | 27 (26 to 29) | 26 (25 to 28) | 28 (27 to 29) | ** |
| Gestational age group<br>22-25 $^{6/7}$, No. (%), weeks<br>26-29 $^{6/7}$, No. (%), weeks | <br>231 (30)<br>541 (70) | <br>174 (45)<br>217 (55) | <br>57 (15)<br>324 (85) | ** |
| Birth weight, median (IQR), g | 940 (744 to 1142) | 800 (660 to 980) | 1080 (890 to 1270) | ** |
| Small for gestational age, No. (%) | 60 (8) | 44 (11) | 16 (4) | ** |
| Male sex, No. (%) | 396 (51) | 199 (51) | 197 (52) | 0.88 |
| Apgar at 5 min <7, No. (%) | 319 (42) | 193 (50) | 126 (33) | ** |
| SNAP-II score >20, No. (%) | 166 (22) | 120 (31) | 46 (12) | ** |
| Use of surfactant, No. (%) | 504 (65) | 309 (79) | 195 (51) | ** |
| Mechanical ventilation, No. (%) | 576 (75) | 349 (89) | 227 (60) | ** |
| Systemic steroids, No. (%) | 307 (40) | 244 (62) | 63 (17) | ** |
| NEC, No. (%) | 51 (7) | 37 (9) | 14 (4) | ** |
| PDA, No. (%) | 467 (61) | 321 (82) | 146 (38) | ** |
| ***Z* scores at birth** | | | | |
| BMI *z* score, median (IQR) | 0.26 (-0.56 to 0.92) | 0.19 (-0.66 to 0.95) | 0.31 (-0.34 to 0.91) | 0.10 |
| Weight *z* score, median (IQR) | 0.14 (-0.51 to 0.63) | 0.02 (-0.72 to 0.50) | 0.26 (-0.28 to 0.70) | ** |
| Length *z* score, median (IQR) | 0.02 (-0.75 to 0.61) | -0.27 (-0.95 to 0.43) | 0.22 (-0.42 to 0.81) | ** |
| Head circumference *z* score, median (IQR) | -0.13 (-0.83 to 0.55) | -0.30 (-0.96 to 0.41) | 0.04 (-0.67 to 0.68) | ** |
| ***Z* scores at 36 weeks CGA** | | | | |
| BMI *z* score, median (IQR) | 0.13 (-0.46 to 0.83) | 0.30 (-0.35 to 1.01) | -0.01 (-0.60 to 0.55) | ** |
| Weight *z* score, median (IQR) | -0.73 (-1.41 to -0.16) | -0.78 (-1.57 to -0.19) | -0.69 (-1.33 to -0.12) | 0.11 |
| Length *z* score, median (IQR) | -1.15 (-1.85 to -0.37) | -1.36 (-2.09 to -0.76) | -0.77 (-1.55 to -0.12) | ** |
| Head circumference *z* score, median (IQR) | -0.91 (-1.58 to -0.24) | -1.19 (-1.95 to -0.63) | -0.57 (-1.25 to 0.03) | ** |
| **Change from birth to 36 weeks CGA** | | | | |
| Δ BMI *z* score, median (IQR) | -0.07 (-0.89 to 0.80) | 0.16 (-0.64 to 1.03) | -0.29 (-1.03 to 0.49) | ** |
| Δ Weight *z* score, median (IQR) | -0.84 (-1.30 to -0.39) | -0.76 (-1.29 to -0.27) | -0.90 (-1.30 to -0.50) | ** |
| Δ Length *z* score, median (IQR) | -1.03 (-1.67 to -0.40) | -1.09 (-1.78 to -0.44) | -0.97 (-1.52 to -0.37) | * |
| Δ Head circumference *z* score, median (IQR) | -0.76 (-1.40 to -0.13) | -0.86 (-1.59 to -0.28) | -0.63 (-1.25 to 0.01) | ** |

*Abbreviations:* IQR: interquartile range, BMI: Body mass index, BPD: Bronchopulmonary dysplasia, SNAP-II Score: Score for neonatal acute physiology, NEC: Necrotizing enterocolitis, PDA: Patent ductus arteriosus

*P* values for comparisons between BPD and BPD-free infants derived from the $\chi^2$ test and Wilcoxon Rank Sum test, as appropriate

*Legend*: * indicates *P* value <0.05

** indicates *P* value <0.01

**Table 3.2. Regression results for quartiles of *z* score change and BPD**

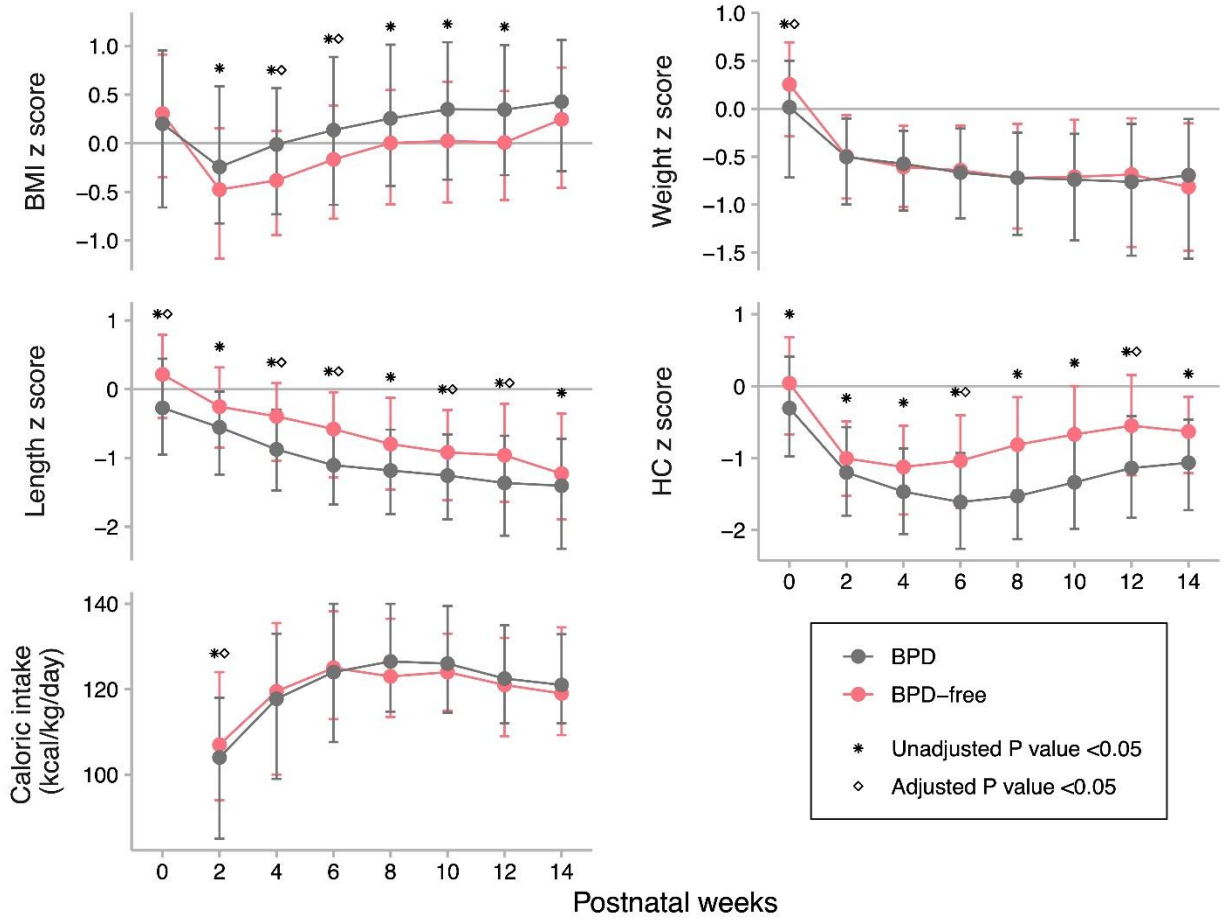
| Quartiles of *z* score change | n/N (%) | Odds ratio (95% CI) | | |
|---|---|---|---|---|
| | | Crude | Birth model | Postnatal model |
| **△BMI** | | | | |
| Q1 [-4.42,-0.89] | 80/193 (41) | 1.09 (0.72-1.65) | 1.16 (0.72-1.86) | 1.36 (0.83, 2.24) |
| Q2 (-0.89,-0.07] | 78/193 (40) | [Reference] | [Reference] | [Reference] |
| Q3 (-0.07,0.80] | 110/193 (57) | **1.89 (1.25-2.86)** | **1.81 (1.13-2.88)** | **2.02 (1.23, 3.31)** |
| Q4 (0.80,4.73] | 123/193 (64) | **2.30 (1.51-3.50)** | **1.66 (1.03-2.69)** | **2.00 (1.20, 3.34)** |
| **△Weight** | | | | |
| Q1 [-4.08,-1.30] | 94/193 (49) | **1.57 (1.03-2.39)** | 1.30 (0.81-2.09) | 1.14 (0.69, 1.88) |
| Q2 (-1.30,-0.84] | 81/193 (42) | [Reference] | [Reference] | [Reference] |
| Q3 (-0.84,-0.39] | 92/193 (48) | 1.04 (0.68-1.58) | 1.24 (0.77-1.99) | 1.21 (0.73, 2.01) |
| Q4 (-0.39,1.55] | 124/193 (64) | **1.94 (1.26-2.98)** | 1.57 (0.96-2.56) | **1.97 (1.16, 3.35)** |
| **△Length** | | | | |
| Q1 [-5.02,-1.67] | 112/193 (58) | **1.71 (1.12-2.61)** | 1.15 (0.71-1.86) | 0.91 (0.54, 1.51) |
| Q2 (-1.67,-1.03] | 96/193 (50) | [Reference] | [Reference] | [Reference] |
| Q3 (-1.03,-0.40] | 91/193 (47) | 0.85 (0.56-1.29) | 0.81 (0.51-1.28) | 0.67 (0.41, 1.11) |
| Q4 (-0.40,2.84] | 92/193 (48) | 0.86 (0.57-1.31) | 0.91 (0.57-1.46) | 0.79 (0.48, 1.31) |
| **△Head circumference** | | | | |
| Q1 [-4.81,-1.40] | 120/188 (64) | **2.07 (1.35-3.17)** | **1.84 (1.13-2.98)** | 1.58 (0.95, 2.61) |
| Q2 (-1.40,-0.77] | 89/187 (48) | [Reference] | [Reference] | [Reference] |
| Q3 (-0.77,-0.13] | 95/187 (51) | 1.09 (0.71-1.65) | 1.14 (0.71-1.84) | 1.17 (0.71, 1.92) |
| Q4 (-0.13,3.89] | 75/187 (40) | 0.67 (0.44-1.03) | 0.72 (0.45-1.17) | 0.77 (0.46, 1.29) |

Estimates derived from generalized linear mixed models including site as random effect

Birth model adjustment variables: antenatal steroids, multiple delivery, cesarian delivery, GA at birth, SGA status, sex, SNAP-II score >20

Postnatal model adjustment variables: all variables from birth model + mechanical ventilation during admission + necrotizing enterocolitis + patent ductus arteriosus

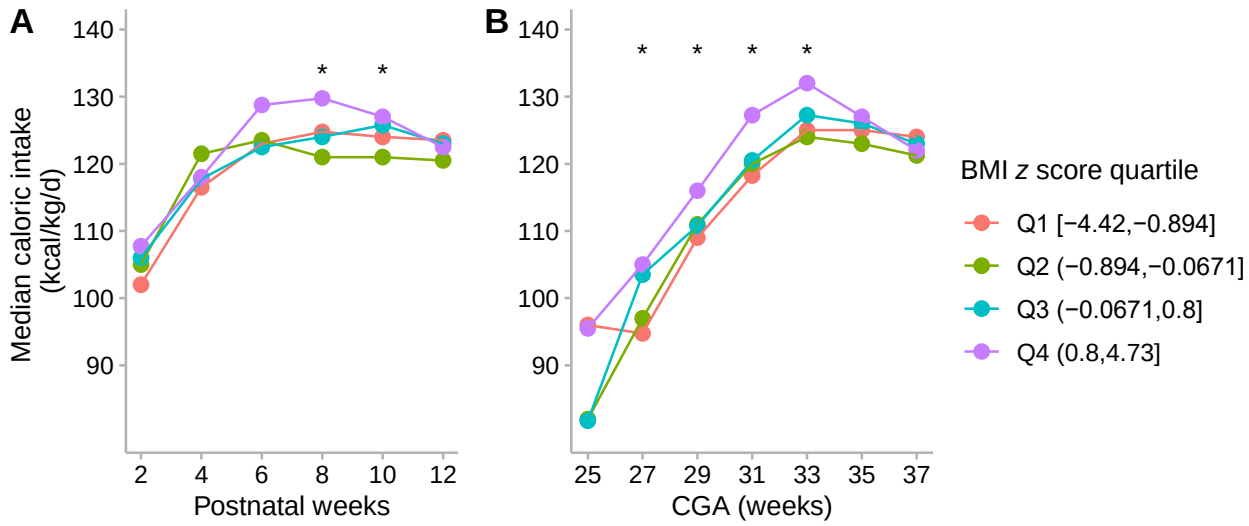
**Figure 3.1. Trajectories of *z* scores and caloric intake between BPD and BPD-free infants**




*Abbreviations*: BMI: body mass index, HC: head circumference

Legend: Points and error bars represent median [IQR]. Unadjusted *P* values derived from the Wilcoxon Rank Sum test. Adjusted *P* values derived from generalized linear mixed models including site as random effect and patient confounders (antenatal steroids, multiple delivery, cesarian delivery, GA at birth, SGA status, sex, SNAP-II score >20 and mechanical ventilation during admission, NEC, and PDA)

**Figure 3.2. Median caloric intake by △BMI *z* score quartiles from birth to 36 weeks CGA**




Legend: * indicates *P* value <0.05 from Kruskal-Wallis test

**Supplementary Table 3.1. Summary of feeding protocols of participating sites**

| Criteria | Site 1 | Site 2 | Site 3 |
|---|---|---|---|
| Timing of initiation of feeds (within) | 12-24 h of life | 24-48 h of life | 24 h of life |
| Number of days of trophic feeds | 1-3 | 2-3 | 1 |
| Average volume of trophic feeds (ml/kg/day) | 10-16 | 5-15 | 16-24 |
| Daily feeding increase (ml/kg/day) | 1-3 | 1-3 | 2 |
| Average estimated time to reach >120 ml/kg/d in enteral feeds based on protocol | 8-15 days | 9-14 days | 7-10 days |
| Use of pasteurized human milk | Yes | No | Yes |
| Timing of milk fortification | At TFI of 100 ml/kg/d | At TFI of 90-120 ml/kg/d | Reached 25 ml of feed/d |
| Recommended feeding volume for removal of central line and parenteral nutrition (ml/kg/day) | 120 | 100-120 | 120 |
| Goal enteral fluid intake (ml/kg/d) | 150-160 | 150 | 170 |

**Standards of care:**

Total fluid intake (TFI) was initiated between 65-80 ml/kg/d and increased by 20 ml/kg/d based on clinical status until achieving 150-170 ml/kg/d. Total parenteral nutrition (TPN) was initiated shortly after birth and enteral nutrition (EN) was started within 24-48hrs. Different feeding protocols were used across the participating centres. Trophic feeding was initiated for 1-4 days depending on birth weight and clinical status using expressed breastmilk, pasteurized donor milk or commercial preterm formula. Typical nutritional goal intake was 90-120 kcal/kg/d and 3.5-4.5 g/kg/d of protein depending on the infant's weight. TPN was discontinued once EN reached 100-120 ml/kg/d and feeds were fortified to 81 kcal/100 ml at TFI of 90-120 ml/kg/d EN using powder or liquid human milk fortifier.

**Supplementary Table 3.2. Definitions for BPD severity from the Canadian Neonatal Network database**

| BPD severity | Respiratory support at time of classification [a] | Oxygen | Flow rate |
|---|---|---|---|
| **No BPD** | None | 21% | None |
| **Mild** | Headbox or incubator | >21% | Any amount |
| | Nasal cannula | 100% | <0.1L/min |
| | Nasal cannula blended air/oxygen | 21-99% | <1.5L/min |
| **Moderate** | Nasal cannula | 100% | ≥100cc/min |
| | Nasal cannula blended air/oxygen | 21-29% | ≥1.5L/min |
| | CPAP, SIPAP, NIPPV, NIHFV | 21-29% | |
| **Severe** | Nasal cannula blended oxygen | ≥30% | ≥1.5L/min |
| | CPAP, SIPAP, NIPPV, NIHFV | ≥30% | |
| | Mechanical ventilation (intubated) | 21-100% | |

[a] At 36 weeks CGA or at discharge if infant was discharged prior to 36 weeks CGA

*Abbreviations* : CGA: Corrected gestational age, CNN: Canadian Neonatal Network, BPD: Bronchopulmonary dysplasia, CPAP: Continuous positive airway pressure, SIPAP: Synchronized inspiratory positive airway pressure, NIPPV: Nasal intermittent positive pressure ventilation, NIHFV: Nasal high frequency ventilation

**Supplementary Table 3.3. Characteristics of infants excluded for missing length at 36 weeks CGA**

| Variable | Included infants (n=772) | Excluded for missing length (n = 83) | *P* value |
|---|---|---|---|
| **Maternal variables** | | | |
| Antenatal steroids, No. (%) | 708 (92) | 72 (87) | 0.12 |
| Multiple delivery, No. (%) | 178 (23) | 25 (30) | 0.19 |
| Caesarean delivery, No. (%) | 525 (68) | 53 (64) | 0.51 |
| Outborn delivery, No. (%) | 86 (11) | 15 (18) | 0.09 |
| **Infant variables** | | | |
| Gestational age, median (IQR), weeks | 27 (26 to 29) | 28 (27 to 29) | ** |
| Gestational age group<br>22-25 $^{6/7}$, No. (%), weeks<br>26-29 $^{6/7}$, No. (%), weeks | <br>231 (30)<br>541 (70) | <br>14 (17)<br>69 (83) | * |
| Birth weight, median (IQR), g | 940 (744 to 1142) | 1150 (960 to 1295) | ** |
| Small for gestational age, No. (%) | 60 (8) | 3 (4) | 0.25 |
| Male sex, No. (%) | 396 (51) | 49 (59) | 0.22 |
| Apgar at 5 min <7, No. (%) | 319 (42) | 21 (26) | * |
| SNAP-II score >20, No. (%) | 166 (22) | 9 (11) | * |
| Use of surfactant, No. (%) | 504 (65) | 41 (49) | ** |
| Mechanical ventilation, No. (%) | 576 (75) | 47 (57) | ** |
| Systemic steroids, No. (%) | 307 (40) | 18 (22) | ** |
| NEC, No. (%) | 51 (7) | 6 (7) | 1 |
| PDA, No. (%) | 467 (61) | 33 (40) | ** |
| Length of stay, median (IQR), days | 92 (70 to 118) | 46 (31 to 79) | ** |
| Corrected age at discharge/transfer, median (IQR), weeks | 40 (38 to 43) | 35 (33 to 39) | ** |
| **Outcomes** | | | |
| BPD, No. (%) | 391 (51) | 28 (34) | * |
| Mortality, No. (%) | 11 (1) | 4 (5) | 0.05 |

*Abbreviations:* BPD: Bronchopulmonary dysplasia, SNAP-II Score: Score for neonatal acute physiology, NEC: Necrotizing enterocolitis, PDA: Patent ductus arteriosus

*P* values for comparisons between groups derived from the $\chi^2$ test and Wilcoxon Rank Sum test, as appropriate

*Legend:* * indicates *P* value <0.05

** indicates *P* value <0.01

**Supplementary Table 3.4. Maternal and neonatal characteristics and outcomes across △ BMI quartiles from birth to 36 weeks**

| Variables | △BMI quartiles | | | | |
|---|---|---|---|---|---|
| | **Q1 [-4.42,-0.89]** | **Q2 (-0.89,-0.07]** | **Q3 (-0.07,0.80]** | **Q4 (0.80,4.73]** | ***P* value** |
| | N=193 | N=193 | N=193 | N=193 | |
| **Maternal variables** | | | | | |
| Antenatal steroids, No. (%) | 175 (92) | 177 (93) | 179 (93) | 177 (92) | 0.93 |
| Multiple delivery, No. (%) | 39 (20) | 48 (25) | 46 (24) | 45 (23) | 0.73 |
| Caesarean delivery No. (%) | 122 (63) | 126 (65) | 140 (73) | 137 (71) | 0.13 |
| Outborn delivery, No. (%) | 26 (13) | 25 (13) | 17 (9) | 18 (9) | 0.33 |
| **Infant variables** | | | | | |
| Gestational age, median (IQR), weeks | 28 (26;29) | 28 (26;29) | 27 (26;29) | 27 (25;28) | ** |
| Gestational age group<br>22-25 $^{6/7}$ weeks, No. (%)<br>26-29 $^{6/7}$ weeks, No. (%) | <br>49 (25)<br>144 (75) | <br>57 (30)<br>136 (70) | <br>53 (27)<br>140 (73) | <br>72 (37)<br>121 (63) | 0.06 |
| Birth weight, median (IQR), g | 1050 (860;1290) | 1030 (790;1240) | 900 (740;1080) | 785 (650;980) | ** |
| Small for gestational age, No.(%) | 8 (4) | 5 (3) | 20 (10) | 27 (14) | ** |
| Male sex, No. (%) | 93 (48) | 97 (50) | 103 (53) | 103 (53) | 0.68 |
| Apgar at 5 min < 7, No. (%) | 83 (43) | 83 (44) | 78 (40) | 75 (39) | 0.72 |
| SNAP-II score > 20, No. (%) | 50 (26) | 37 (19) | 34 (18) | 45 (24) | 0.18 |
| Use of surfactant, No. (%) | 122 (63) | 129 (67) | 118 (61) | 135 (70) | 0.27 |
| Mechanical ventilation, No. (%) | 139 (72) | 148 (77) | 140 (73) | 149 (77) | 0.14 |
| Systemic steroids, No. (%) | 63 (33) | 70 (36) | 82 (42) | 92 (48) | * |
| NEC, No. (%) | 10 (5) | 11 (6) | 12 (6) | 18 (9) | 0.35 |
| PDA, No. (%) | 99 (51) | 115 (60) | 124 (64) | 129 (67) | * |
| ***Z* scores at birth** | | | | | |
| BMI *z* score, median (IQR) | 1.23 (0.61;1.85) | 0.45 (-0.13;0.88) | -0.03 (-0.63;0.47) | -0.67 (-1.28;0.03) | ** |
| Weight *z* score, median (IQR) | 0.55 (0.05;1.01) | 0.21 (-0.24;0.68) | -0.01 (-0.75;0.48) | -0.34 (-0.98;0.21) | ** |
| Length *z* score, median (IQR) | -0.21 (-0.93;0.48) | 0.06 (-0.44;0.62) | 0.09 (-0.76;0.65) | 0.04 (-0.79;0.71) | * |
| Head circumference *z* score, median (IQR) | 0.26 (-0.56;0.89) | -0.12 (-0.68;0.52) | -0.25 (-0.84;0.47) | -0.42 (-1.23;0.16) | ** |
| ***Z* scores at 36 weeks CGA** | | | | | |
| BMI *z* score, median (IQR) | -0.37 (-0.99;0.17) | -0.01 (-0.59;0.48) | 0.35 (-0.33;0.86) | 0.90 (0.13;1.56) | ** |

| | | | | | |
|---|---|---|---|---|---|
| Weight *z* score, median (IQR) | -0.88 (-1.43;-0.28) | -0.81 (-1.34;-0.26) | -0.72 (-1.55;-0.19) | -0.56 (-1.23;0.07) | * |
| Length *z* score, median (IQR) | -0.55 (-1.41;0.20) | -0.90 (-1.55;-0.23) | -1.35 (-2.03;-0.62) | -1.60 (-2.17;-0.96) | ** |
| Head circumference *z* score, median (IQR) | -0.79 (-1.38;-0.17) | -0.75 (-1.55;-0.10) | -1.06 (-1.77;-0.29) | -1.04 (-1.58;-0.43) | * |
| **Change from birth to 36 weeks CGA** | | | | | |
| Δ BMI *z* score, median (IQR) | -1.49 (-2.04;-1.13) | -0.41 (-0.63;-0.25) | 0.36 (0.12;0.53) | 1.41 (1.03;1.81) | ** |
| Δ Weight *z* score, median (IQR) | -1.30 (-1.80;-0.93) | -0.93 (-1.42;-0.58) | -0.74 (-1.11;-0.40) | -0.32 (-0.69;0.06) | ** |
| Δ Length *z* score, median (IQR) | -0.39 (-0.95;0.22) | -0.91 (-1.49;-0.36) | -1.24 (-1.80;-0.71) | -1.48 (-2.10;-0.98) | ** |
| Δ Head circumference *z* score, median (IQR) | -1.05 (-1.63;-0.45) | -0.76 (-1.31;-0.09) | -0.71 (-1.42;-0.14) | -0.56 (-1.18;0.14) | ** |
| **Outcomes** | | | | | |
| BPD, No. (%) | 80 (41) | 78 (40) | 110 (57) | 123 (64) | ** |
| BPD grade, No. (%) | | | | | |
| Mild | 13 (7) | 8 (4) | 9 (5) | 14 (7) | |
| Moderate | 52 (26) | 46 (24) | 75 (39) | 71 (37) | |
| Severe | 13 (7) | 19 (10) | 22 (11) | 29 (15) | |
| Unspecified | 2 (1) | 5 (2) | 4 (2) | 9 (5) | 0.48 |
| Mortality, No. (%) | 1 (1) | 3 (2) | 4 (2) | 3 (2) | 0.71 |

*Abbreviations:* IQR: interquartile range, BMI: Body mass index, BPD: Bronchopulmonary dysplasia, SNAP-II Score: Score for neonatal acute physiology, NEC: Necrotizing enterocolitis, PDA: Patent ductus arteriosus

*P* value calculated for comparison by using the $\chi^2$ test for categorical data and Kruskal Wallis test for continuous data

*Legend:* * indicates *P* value <0.05

** indicates *P* value <0.01

**Supplementary Table 3.5. Ordinal regression results for quartiles of *z* scores changes and BPD severity**

| Quartile of *z* scores changes | OR (95% CI) | | |
|---|---|---|---|
| | Crude | Birth model | Postnatal model |
| **△BMI** | | | |
| Q1 [-4.42,-0.89] | 1.00 (0.67, 1.49) | 0.99 (0.64, 1.52) | 1.10 (0.71, 1.73) |
| Q2 (-0.89,-0.07] | [Reference] | [Reference] | [Reference] |
| Q3 (-0.07,0.80] | **1.88 (1.27, 2.79)** | **1.71 (1.13, 2.61)** | **1.85 (1.20, 2.86)** |
| Q4 (0.80,4.73] | **2.33 (1.57, 3.46)** | **1.62 (1.06, 2.48)** | **1.93 (1.24, 3.01)** |
| **△Weight** | | | |
| Q1 [-4.08,-1.30] | 1.24 (0.84, 1.84) | 1.04 (0.68, 1.59) | 0.90 (0.58, 1.40) |
| Q2 (-1.30,-0.84] | [Reference] | [Reference] | [Reference] |
| Q3 (-0.84,-0.39] | 1.26 (0.85, 1.86) | 1.48 (0.98, 2.26) | 1.42 (0.92, 2.20) |
| Q4 (-0.39,1.55] | **2.38 (1.62, 3.51)** | **1.94 (1.29, 2.93)** | **2.22 (1.45, 3.44)** |
| **△Length** | | | |
| Q1 [-5.02,-1.67] | 1.35 (0.92, 1.98) | 0.92 (0.61, 1.39) | 0.78 (0.51, 1.19) |
| Q2 (-1.67,-1.03] | [Reference] | [Reference] | [Reference] |
| Q3 (-1.03,-0.40] | 0.97 (0.66, 1.43) | 0.98 (0.65, 1.48) | 0.86 (0.56, 1.32) |
| Q4 (-0.40,2.84] | 0.92 (0.62, 1.35) | 0.95 (0.63, 1.43) | 0.85 (0.55, 1.32) |
| **△Head circumference** | | | |
| Q1 [-4.81,-1.40] | **1.84 (1.25, 2.71)** | 1.51 (1.00, 2.27) | 1.35 (0.89, 2.06) |
| Q2 (-1.40,-0.77] | [Reference] | [Reference] | [Reference] |
| Q3 (-0.77,-0.13] | 1.08 (0.73, 1.59) | 1.15 (0.76, 1.74) | 1.15 (0.75, 1.77) |
| Q4 (-0.13,3.89] | 0.81 (0.54, 1.21) | 0.97 (0.63, 1.48) | 1.01 (0.64, 1.59) |

Birth model adjustment variables: antenatal steroids, multiple delivery, cesarian delivery, GA at birth, SGA status, sex, SNAP-II score >20

Postnatal model adjustment variables: all variables from birth model + mechanical ventilation during admission + necrotizing enterocolitis + patent ductus arteriosus

**Supplementary Table 3.6. Stratified analyses for association of BPD with quartiles of △ BMI**

## S3.6a. GA groups

| Quartiles of △BMI | n/N (%) | OR (95% CI) | | |
|---|---|---|---|---|
| | | Crude | Birth model | Postnatal model |
| **22-25 $^{6/7}$ weeks GA** | | | | |
| Q1 [-4.42,-0.89] | 34/49 (69) | 0.84 (0.35, 2.00) | 0.93 (0.36, 2.40) | 1.01 (0.39, 2.65) |
| Q2 (-0.89,-0.07) | 41/57 (72) | [Reference] | [Reference] | [Reference] |
| Q3 (-0.07,0.80] | 38/53 (72) | 0.95 (0.41, 2.25) | 0.97 (0.38, 2.43) | 1.07 (0.42, 2.73) |
| Q4 (0.80,4.73] | 61/72 (85) | 1.58 (0.64, 3.94) | 1.36 (0.52, 3.60) | 1.53 (0.57, 4.11) |
| **26-29 $^{6/7}$ weeks GA** | | | | |
| Q1 [-4.42,-0.89] | 46/144 (32) | 1.39 (0.82, 2.37) | 1.34 (0.76, 2.35) | 1.62 (0.88, 2.96) |
| Q2 (-0.89,-0.07) | 37/136 (27) | [Reference] | [Reference] | [Reference] |
| Q3 (-0.07,0.80] | 72/140 (51) | **2.77 (1.66, 4.63)** | **2.34 (1.35, 4.07)** | **2.72 (1.49, 4.95)** |
| Q4 (0.80,4.73] | 62/121 (51) | **2.64 (1.55, 4.50)** | **1.92 (1.07, 3.44)** | **2.39 (1.27, 4.51)** |

Estimates derived from generalized linear mixed models including site as random effect

Birth model adjustment variables: antenatal steroids, multiple delivery, cesarian delivery, GA at birth, SGA status, sex, SNAP-II score >20

Postnatal model adjustment variables: all variables from birth model + mechanical ventilation during admission + necrotizing enterocolitis + patent ductus arteriosus

## S3.6b. SGA status

| Quartiles of △BMI | n/N (%) | OR (95% CI) | | |
|---|---|---|---|---|
| | | Crude | Birth model | Postnatal model |
| **SGA** | | | | |
| Q1 [-4.42,-0.89] | 4/8 (50) | 0.67 (0.07, 6.41) | 1.06 (0.06, 17.70) | 5.70 (0.21, 153.98) |
| Q2 (-0.89,-0.07) | 3/5 (60) | [Reference] | [Reference] | [Reference] |
| Q3 (-0.07,0.80] | 15/20 (75) | 2.00 (0.26, 15.62) | 2.92 (0.24, 36.11) | 14.31 (0.78, 262.73) |
| Q4 (0.80,4.73] | 22/27 (81) | 2.93 (0.38, 22.46) | 3.68 (0.32, 41.79) | 9.22 (0.67, 126.39) |
| **Not SGA** | | | | |
| Q1 [-4.42,-0.89] | 76/185 (41) | 1.08 (0.71, 1.65) | 1.15 (0.71, 1.85) | 1.32 (0.79, 2.19) |
| Q2 (-0.89,-0.07) | 75/188 (40) | [Reference] | [Reference] | [Reference] |
| Q3 (-0.07,0.80] | 95/173 (55) | **1.76 (1.15, 2.70)** | **1.70 (1.05, 2.75)** | **1.85 (1.12, 3.06)** |
| Q4 (0.80,4.73] | 101/166 (61) | **2.01 (1.29, 3.11)** | 1.56 (0.94, 2.56) | **1.84 (1.08, 3.14)** |

Estimates derived from generalized linear mixed models including site as random effect

Birth model adjustment variables: antenatal steroids, multiple delivery, cesarian delivery, GA at birth, sex, SNAP-II score >20

Postnatal model adjustment variables: all variables from birth model + mechanical ventilation during admission + necrotizing enterocolitis + patent ductus arteriosus

### S3.6c. Postnatal systemic steroid exposure

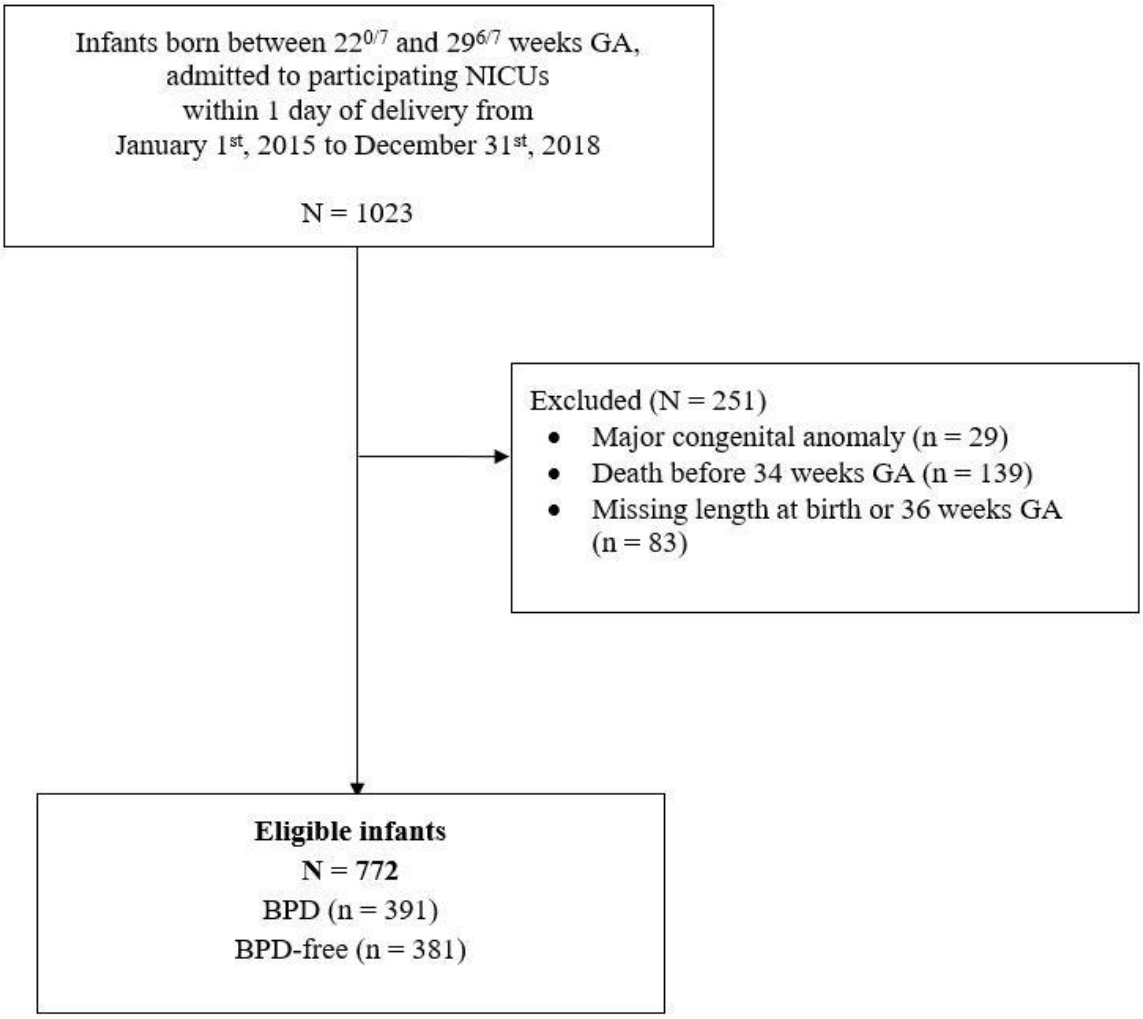
| Quartiles of △BMI | n/N (%) | OR (95% CI) | | |
|---|---|---|---|---|
| | | Crude | Birth model | Postnatal model |
| **Received systemic steroids** | | | | |
| Q1 [-4.42,-0.89] | 44/63 (70) | 0.81 (0.38, 1.75) | 0.93 (0.41, 2.12) | 0.93 (0.40, 2.15) |
| Q2 (-0.89,-0.07) | 51/70 (73) | [Reference] | [Reference] | [Reference] |
| Q3 (-0.07,0.80] | 67/82 (82) | 1.55 (0.71, 3.37) | 1.57 (0.68, 3.62) | 1.68 (0.72, 3.92) |
| Q4 (0.80,4.73] | 82/92 (89) | **2.67 (1.12, 6.33)** | 2.30 (0.91, 5.80) | 2.45 (0.97, 6.24) |
| **No systemic steroids** | | | | |
| Q1 [-4.42,-0.89] | 36/130 (28) | 1.68 (0.92, 3.06) | 1.57 (0.84, 2.94) | **1.98 (1.02, 3.84)** |
| Q2 (-0.89,-0.07) | 27/123 (22) | [Reference] | [Reference] | [Reference] |
| Q3 (-0.07,0.80] | 43/111 (39) | **2.29 (1.26, 4.16)** | **2.34 (1.26, 4.34)** | **2.59 (1.34, 5.00)** |
| Q4 (0.80,4.73] | 41/101 (41) | **2.18 (1.20, 3.99)** | 1.89 (1.00, 3.58) | **2.34 (1.19, 4.60)** |

Estimates derived from generalized linear mixed models including site as random effect

Birth model adjustment variables: antenatal steroids, multiple delivery, cesarian delivery, GA at birth, SGA status, sex, SNAP-II score >20

Postnatal model adjustment variables: all variables from birth model + mechanical ventilation during admission+ necrotizing enterocolitis + patent ductus arteriosus

**Supplementary Figure 3.1. Study patient flowchart**



# 4 CHAPTER 4: *EXTENDED DISCUSSION*

Infants with BPD had a significantly higher △BMI compared to BPD-free infants despite receiving similar caloric intake. At birth, BMI *z* score was similar suggesting both groups had possibly similar body composition. By 36 weeks CGA, there was no difference in weight-, a significantly lower length- and higher BMI *z* scores in BPD group compared to BPD-free infants despite similar caloric intake. Caloric deficit which is often suggested among the causes for BPD was unlikely a factor in the differences in growth trajectories. The higher △BMI possibly suggests an increase in fat mass deposition and/or fluid accumulation. The sustained lower △ BMI in the BPD-free group suggests a leaner body composition which has been associated with improved organ development and muscle mass.[51,92,162] Based on CGA, during most of the admission, infants in the lower quartiles of △lt received relatively similar caloric intakes as those in the higher quartiles (Figure 6.1). Conversely, higher quartiles of △wt received significantly higher caloric intakes compared to lower quartiles, suggesting higher caloric intake resulted in higher weight gain but not improved linear growth. Studies on patterns of catch-up linear growth suggest that after a period of improved weight gain and temporary increase in BMI, length will typically improve and BMI normalize if catch-up length is achieved.[49,112] However, this was not observed, rather, no catch-up △lt and△hc was observed. While△lt showed no association with BPD, Q1 of △hc was significantly associated with BPD suggesting infants with the slowest head growth velocity were at higher risk of developing BPD by 36 weeks CGA. It is unclear whether catch-up weight especially in BPD infants lead to improved body composition or outcomes, especially in periods of poor respiratory status.

## 4.1 WHY DID INFANTS WITH BPD SHOW A HIGHER △BMI Z SCORE?

Below are hypothesized physiologic changes that may have contributed to considerably different growth patterns observed between BPD and BPD-free infants despite similar calories.

### *4.1.1 Altered metabolic process in chronic hypoxia*

Preterm infants who develop BPD experience intermittent hypoxia due to their immature respiratory control and challenges in matching ventilation to their respiratory needs. Hypoxia is defined as "reduced oxygen in the environment or in an organism". [160] Chronic intermittent hypoxia triggers oxidative stress but also increases the degradation of hypoxia-inducible factors (HIF)-2α which inhibits the transcription of antioxidant enzyme superoxide dismutase.[164] Proinflammatory state in preterm infants have been described to impair growth and cardiovascular regulation.[164] Hypoxic episodes can contribute to decreased pressor and heart rate response thus affecting basal metabolic rate.[164] This has been observed more prominently in preterm infants with BPD and has been investigated in rat model studies. Investigators exposed rat pups to 3 different conditions: room air (control), dispersed or clustered intermittent hypoxic environments for day 0 to 7 after birth.[161] The rat pups were then placed in room air for up to 8 weeks postnatal. Rat pups in intermittent hypoxic environments had a significantly lower body weight compared to those in room air but as of week 4 postnatal, there was no more difference in body weight between the animal groups.[161] This suggests that during periods of decreased oxygenation, weight gain is potentially impaired but can recover once oxygenation is improved. Poor respiratory status likely impacts energy metabolism which limits lean body mass accretion and organ growth. Our results are not matched with hypoxic events, but we also observed that BPD and BPD-free infants initially had weight differences which overtime recovered by 36

weeks CGA. This possibly suggests that weight unlike other growth markers such as length, has the capacity to recover as lung maturation and periods of hypoxia improve. However, while weight catch up is possible in BPD infants, the quality of the weight gain needs to be distinguished; accumulation of fluid weight or excessive fat mass may be detrimental.

Chronic stress and inflammation, a hallmark of BPD, has been associated with delayed growth in preterm infants.[6,9,12,138,165] While all preterm infants experience stress and inflammation acutely after birth, infants with BPD experience prolonged period of stress which can further compound their growth trajectory.[110,159160]Infants who were exposed to high CRP in the first week of life had a lower weight *z* score however infants who had an elevated CRP and IL-6 between 7 to 14 days of life were shorter at discharge.[159] Systemic inflammation in the first week of life mostly affected weight whereas prolonged inflammation impacted length and head circumference.[159] Similarly, we observed that infants with BPD who likely experienced more prolonged inflammation had lower linear and head circumference growth.

Postnatal corticosteroid often used in very preterm infants have shown decreased growth velocities both during and after treatment.[103-105] Postnatal steroid is known to enhance lipid metabolism but increases protein catabolism.[166,167] A study found that ferrets who received corticosteroids had a suppressed central airway with a shorter length but a relative higher weight compared to body length.[168] This could explain the changes in body composition with increase fat mass accretion and decrease lean body mass with sustained corticosteroid use in infants with BPD. This can alter metabolic rate given lean mass is metabolically more active than fat mass. Studies on mechanism of steroids and body composition remains sparse and conflicting. Our sensitivity analysis showed that infants without steroids exposure had higher odds for BPD in Q3 and Q4 of △BMI, thus steroid was not the only contributor for changes in body composition.

### *4.1.2 Relationship between chronic hypoxia and stunting*

BPD infants had a lower length *z* score at birth and a slower linear growth velocity than BPD-free infants despite similar caloric intake. A large cross-sectional study of 964 299 children aged 0 to 59 months found that children who lived at high altitude and experienced lower oxygen saturation chronically had a systematically lower linear growth trajectory.[169] This suggests that current WHO growth guidelines may not be suitable for children living at high altitudes. Indeed, populations living above 1500m above sea level are excluded from data used to build growth curves due to evidence of impaired growth in children living at high altitudes.[169] Even after adjusting for dietary adequacy, common disease exposure (e.g. diarrhea, fever and cough), maternal age and education level, household wealth and access to water and sanitation; lower linear growth velocity was still observed at higher altitudes.[169] There was a negative almost linear association between altitude and height-for-age *z* score despite ideal home environments.[169] This suggests a biological cause for stunting which is mediated by chronic hypoxia.[169] Studies in pregnancy also showed similar results; chronic hypoxia was associated with fetal growth restriction which is the leading risk factor for linear growth faltering.[169] Another cohort of 26 976 children of up to 5 year old found that irrespective of dietary and non dietary factors, children living at higher altitudes experienced higher odds of stunting.[170]

Chronic exposure to lower oxygen saturation may impact capacity for linear growth. Preterm infants at highest risk for BPD also experience intermittent chronic hypoxia which may impact their linear growth potential. Therefore, is it even feasible to achieve standard linear growth velocity in infants with evolving BPD especially in those with the sickest lungs? Inadequate nutrition is unlikely the main cause of stunting but aggressive caloric intake to achieve catch up linear growth in infants with evolving BPD may not even be physiologically

realistic. On the contrary, attempts to achieve catch up linear growth may lead to excessive fat deposition as evidenced by higher △BMI. Somatic growth may be suboptimal in presence of chronic hypoxia and may only recover once the lung function is improved.

### *4.1.3 Metabolic requirements for infants with BPD*

Nutritional requirements in very preterm infants do not account for disease state and nutritional targets are assumed to be similar across all infants. Infants with BPD may have different nutritional needs, but studies are conflicting showing no significant difference in metabolic rates.[120,126,128,130] Metabolic studies date from the 1990s to 2000s where infants received drastically different nutritional and respiratory care. In our work, infants with BDP showed catch-up weight gain on an average of ~123kcal/kg/d from week 4 to week 14 but published guidelines suggest needs of up to 150kcal/kg/d for infants with BPD. These may be overestimated possibly resulting in overfeeding.

Energy and protein deficits in very preterm infants especially in the first month of life have been associated with increased risk of BPD.[117,119] There is evidence that underfed ventilated patients have a decreased ability to respond to hypoxemia, hypercapnia and diminished ventilator weaning capacity.[171] In preterm infants, nutrition studies are often limited to the first month of life which is the period where the lung is most compromised. Requirements as the lung improves have not been assessed and based on animal studies, growth improves naturally as oxygenation and the lung function improves.[161] Aggressive nutrition is warranted in the early weeks of life but this may not be necessary for all infants in later postnatal weeks especially if lean mass accretion does not happen. Overfeeding can increase lipogenesis, increase glucose level, hepatic dysfunction and inability to wean the ventilation due to excess carbon dioxide production.[172-175]

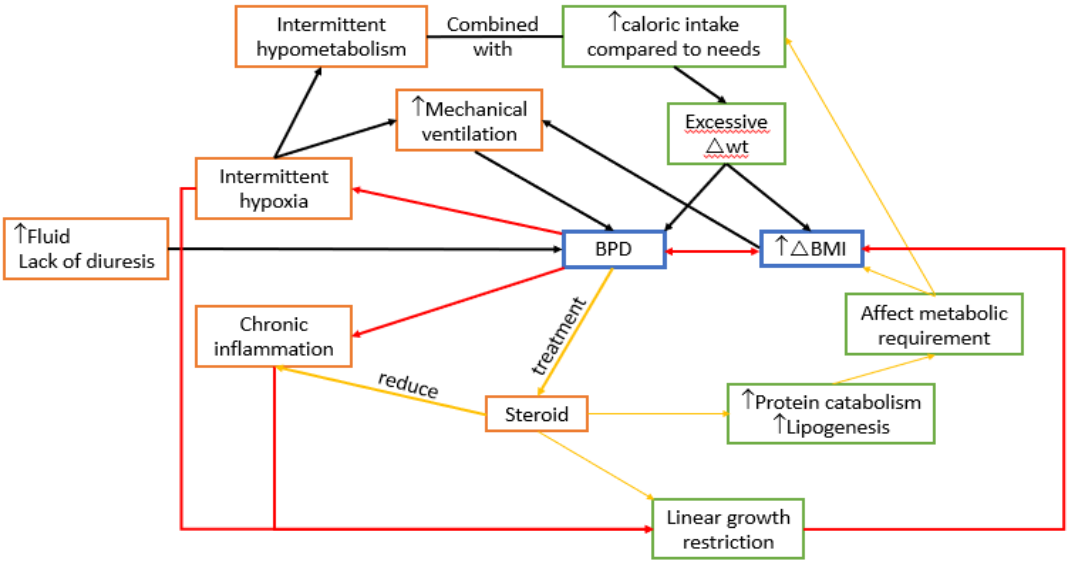
Infants with BPD likely have fluctuating energy needs depending on their lung disease status and the goal of nutritional management should attempt to match energy needs and nutrition support to avoid both under and overfeeding which can impact carbon dioxide production. If all growth parameters do not achieve catch up, individualized growth and nutritional targets considering the infants risk factors should be considered. A recent large retrospective study argued for inclusion of GA and IUGR status when assessing BMI in preterm infants.[176] Requirements for special classes of preterm infants like IUGR, SGA and BPD may warrant individualized nutritional targets given they are more vulnerable to early growth restriction and metabolic disease later.

This work does not suggest decreasing current caloric recommendations for infants at risk of BPD, but rather, a nuanced approach to growth in very preterm infant at high risk for BPD. Most very preterm infants likely require the current caloric recommendations to achieve adequate growth, however, a subset of infants with significant lung disease may have better outcome with a tailored requirement based on their short-term growth potential. Underfeeding compromises lung function but, overfeeding can be as detrimental if this results in excessive fat mass. There is no definition or biological markers to identify overfeeding in the preterm infants. In absence of indirect calorimetry to assess metabolic needs, trajectories of length-, head circumference- and $\triangle$BMI *z* scores can help inform potential for overfeeding when growth is disproportionate. In utero, it is physiologic to have increased fat mass deposition in the third trimester compared to earlier trimesters. Therefore, these metrics should not be used individually to set nutritional requirements but integrated with validated tools like preterm growth charts, standard growth velocity calculation, BMI curves, and physical assessment for best interpretation. Additionally, inclusion of a neonatal dietitian has also been shown to improve growth outcome and tailoring nutrition support.[177,178]

### *4.1.4 Fluid management in the first 2 weeks of life*

From our results, infants without BPD showed almost double the rate of weight loss at week 2 compared to infants with BPD, which is likely a reflection of fluid management and diuresis post birth. High fluid intake and lack of physiological weight loss in the first week of life has been associated with increased risk of BPD.[151-153,179-181] In extremely preterm infants with immature kidneys, fluid contraction and weight loss are limited with delayed diuresis.[179,180,182-185] Early fluid overload defined as 150-190ml/kg/d may contribute to pulmonary edema, reduced lung compliance, increased airway resistance, impaired gas exchange, and higher needs of mechanical ventilation, thus contributing to the development of BPD.[115,151-153,181,182] Changes in fluid balance after birth is considered a critical variable for respiratory function and survival among preterm infants.[115,151,152,181] A recent study assessing the association of fluid status, serum sodium and weight status has shown that compared to BPD infants, BPD free survivors had a greater percentage of weight loss in the first weeks of life, which we also observed.[152] Below is the summary of the possible interaction between BPD and △BMI

Figure 4.1. Possible mechanism between BPD and △BMI



## 4.2 NO ASSOCIATION BETWEEN Q1 OF △BMI AND BPD

Our initial hypothesis assumed that both extremes of BMI i.e., Q1 and Q4 compared to Q2 would have higher risk for BPD. This assumed Q1 which represents infants who had the most weight loss or slowest weight gain velocity during their NICU stay would be at highest risk for BPD. This hypothesis was based on evidence that poor nutritional status within the first 2-4 weeks of life is known to be a risk factor for the development of BPD. However, this was not observed in our cohort. Q1 compared to other quartiles had the highest median birth weight and GA at birth, lowest rate of SGA and PDA which are known to be the primary risk factors for the development of BPD. Surprisingly, infants in Q1 also had the highest median BMI and HC z scores at birth but experienced the highest decrease in ΔBMI. While caloric intake between Q1 versus Q4 was significantly lower, infants in Q1 theoretically reached appropriate caloric intake when adjusted to their gestational age. Caloric intake did not appear different between Q1, Q2 and Q3. This change in ΔBMI possibly points to the role of fluid rather than caloric deficit and the importance of physiologic diuresis in the first few days of life. The smaller and younger infants from Q4 likely had more immature kidneys resulting in delayed diuresis which is a major contributor in the development of BPD. This is also an important finding because clinicians often disagree over whether nutrition management should aim to bring infants back to their birth percentile or z score after the initial diuresis. Studies have suggested a physiologic transition in weight trajectory of 0.8 z score below the birth percentile by day of life 15 is appropriate.[186] BPD-free infants maintained a Δwt slightly lower than 0.8 z score which means that these infants did not regain weight above their physiologic diuresis and Q1 and Q2 were the only 2 groups that did not have a Δwt above 0.8 z score. Moreover, despite having a higher decrease in ΔBMI, infants in Q1 and Q2 had higher absolute length z scores by 36 weeks and less decrease in Δlt

compared to Q3 and Q4 suggesting these infants experienced better linear growth. Q1 and Q2 also demonstrated higher HC z scores by 36 weeks which together with better linear growth may suggest a better lean mass development which may have contributed to the lower BPD rate. This highlights the importance of length as powerful marker for growth especially for infants at risk of BPD but also targeting interventions to improve linear growth. Following this work, it would be valuable to assess whether infants in Q1 and Q2 received a different protein intake or other nutritional interventions that could explained their better linear growth.

### 4.3 ASSOCIATION OF △LENGTH AND HEAD CIRCUMFERENCE WITH BPD

Postnatal linear growth restriction is extensively described in infants with BPD however, surprisingly there was no association between △lt and BPD. While the median △lt from birth to 36 weeks CGA was significantly larger in the BPD group, even BPD-free infants experienced a decrease in △lt *z* score of almost 1SD, suggesting significant worsening of length *z* score over time. While measurement errors are possible especially the smaller the infant, the techniques within each centre were similar and the large sample size across each centre would help mitigate that effect. This highlights the question of whether postnatal linear growth is inevitable in very preterm infants or possibly is it unrealistic to use linear growth potentials based on intrauterine curve for preterm infants. The ideal growth for preterm infants remains a challenge to define and as Fenton et al. suggested, possibly following a cohort of healthy very preterm infants with no to minor comorbidities might reflect a more realistic growth trajectory. The lack of association between △lt and BPD suggests linear growth failure arises in BPD possibly more as a consequence of poor respiratory status and chronic hypoxia as explained above. Nutritional components other than calories should be considered to improve linear growth failure in preterm

infants. For example, some studies have shown promising improvement in linear growth with zinc supplementation in very preterm infants, but more research is still needed.[187-189]

For head circumference, Q1 of △hc was associated with increased odds of BPD. Head circumference is typically a reflection of brain size and total grey matter volume. In previous studies, △hc from birth to discharge has been associated with neurodevelopmental outcome at 2 years of corrected age in preterm infants.[190] Q1 represented the infants with the slowest brain growth and BPD is known to be an independent risk factor for poor neurodevelopmental outcome as well. The chronic hypoxia experienced by infants with BPD is known to affect somatic growth which could possibly also include brain growth. However, to our knowledge no known mechanism has been identified between hypoxia and head size and no other studies is known to have reported on poor head circumference growth and risk of BPD. More studies would be required to explain the results observed for head circumference and BPD.

## 4.4 SUBGROUP ANALYSIS

ΔBMI *z* score in Q3 and Q4 is associated with increased BPD compared to Q2 in the subgroups of infants with GA 26- 29+6/7 weeks, not SGA, and who did not receive systemic steroids. These associations are not statistically significant in the subgroup of the most immature patients, in SGA infants, and in those who did receive postnatal steroids. However, it is important to note that the purpose of these sensitivity analysis, were aimed to assess consistency and robustness of results and evaluate potential biases based on subgroups.[191] These sub-groups when divided by quartiles became too small to be powered to show statistical significance but were defined a priori to confirm the hypothesized effect. For all the above-mentioned 3 subgroups, while the odds ratio did not reach statistical significance, we can observe that Q3 and Q4 do show the same effect direction with higher odds ratio of BPD with increasing ΔBMI compared to Q2. The 95% CI of those groups showed high variability in the effect size, but the

overall effect direction showed a similar pattern. The effect size may have been more pronounced had the sample size within each subgroup be larger. The purpose of our subgroup analysis was to identify consistency or differences in the magnitude of the effect of ΔBMI and BPD and should be interpreted as such. As previously suggested, it is important to rely "more on the overall results of this study in assessing the effect within a subgroup than on the apparent effect observed within that subgroup".[191]

## 4.5 STRENGTH, LIMITATIONS, AND IMPACT

### *4.5.1 Strength*

This is the first study to assess the association between BPD and all parameters of growth indicators including proportionality using BMI in a large multicentre cohort with a validated dataset. To our knowledge, this is the first body of work to look at the association of BMI *z* scores throughout admission on preterm outcome using the Olsen 2015 BMI charts. Moreover, in this study, all anthropometric measurements were assessed simultaneously until 36 weeks CGA providing a comparison in growth pattern between BDP and BDP-free survivors at multiple time points. Caloric intake was also assessed based on the actual intakes that the babies received at the same time points to mitigate the confounding effect of nutrition in the association with BDP. Our results were consistent across multiple analyses to address biases including adjusted models for confounders, analysis of exposures for each 2-week period and in the sensitivity analysis.

### *4.5.2 Limitations*

This study used retrospective data. Therefore, we cannot infer causality and account for errors in measurements and caloric intakes that may have happened. 8% of the original cohort was excluded due to missing length measurement, however when sensitivity analysis was done including these infants, the results did not change the conclusion of this study. Other nutritional components that may impact BPD status such as protein and fluid intake were not accounted.

Protein intake is an essential determinant of growth in preterm infants and a key component of lean body mass accretion which affect body composition. Data on protein intake and protein energy ratio would have been an informative variable given its impact on body composition and its contribution to the development of BPD. Macronutrient distribution such as the carbohydrate versus fat content of feeds is also known to affect the respiratory quotient, carbon dioxide production and thus possibly the risk of BPD. The effect of macronutrient distribution on mechanical ventilation is conflicting in the literature but these may have differed across centres and was not accounted for.[135,136,172,192] Differences in measurement techniques and clinical practices in nutrition or ventilation management among each centre which may have impacted the results despite the use of mixed effect models. This study assessed caloric intake on one day every 2 weeks and cannot reflect the full cumulative effect of energy intake on growth. Measuring caloric intake to reflect nutritional adequacy also has limitation given the method of delivery (enteral and parenteral), may impact nutrient absorption, thermogenic effect of digestion or metabolic rate given bottle feeding may increase energy consumption versus enteral nutrition.

### *4.5.3 Impact for clinicians*

Previous literature suggests that infants with BPD who experience postnatal growth failure require catch up weight gain, but we did not observe any association between BPD and linear growth and conversely, higher quartiles of △wt showed increased association with BPD. Moreover, evidence suggests that chronic hypoxia likely affects linear growth potential and possibly nutritional needs. This raises the question whether catch-up growth is always beneficial in preterm infants at risk for BPD and is catch-up linear growth even feasible in infants with evolving BPD. Clinicians should be monitoring BMI and linear growth trend at least weekly to ensure proportional growth. Measuring length consistently and accurately using proper technique

such as an infantometer weekly, is essential to improve outcome. Measuring changes in BMI *z* score over time from birth is a valuable indicator to assess quality of growth in absence of an indirect calorimetry or more sophisticated method of body composition assessment. While most very preterm infants may grow adequately using standard growth curve and nutritional requirements, this may not be true for some who may require an individualized regimen. Clinicians should consider disease state when assessing nutritional goals and setting growth target especially in infants at high risk for moderate to severe BPD. Proportionality of growth may help improve health outcomes more than weight gain alone. With increasing survival of infants born at younger GAs, it is important to develop nutritional guidelines that are better suited for infants at high risk for BPD. The new challenge in neonatal nutrition is understanding how to achieve a more balanced approach to growth while avoiding both under and overfeeding.

### *4.5.4 Future research*

Future studies should aim to better understand the physiology of linear growth potential and determinants of changes in body composition in infants who develop BPD and how BPD may affect metabolic capacity. This study was retrospective and therefore it would be important to validate the impact of body composition with more sophisticated tools of body composition assessment and its link with ventilation management and the subsequent development of BPD. Studies on identification of normal postnatal BMI trajectories of very preterm infants including their association with other neonatal outcomes with BMI at discharge is needed. Recommendations on the threshold of △BMI *z* score over time could help clinicians monitor under and overfeeding. While BMI is an easy and practical tool to use, it uses weight which is influenced by fluid. Development of more sensitive but practical measures of body composition are required to track quality of growth. Metabolic studies assessing caloric needs of infants with

evolving BPD using current methods of ventilation need to be revised. Protein intake and protein energy ratios should be assessed to identify whether infants with BPD have different needs to improve linear growth and lean body mass accretion. Macronutrient content especially impact of carbohydrate content on respiratory quotient and subsequently weaning of mechanical ventilation which could affect risk of BPD should be assessed in very preterm infants.

# 5 CHAPTER 5: *CONCLUSION*

Increasing ΔBMI from birth to 36 weeks was independently associated with higher odds of BPD among preterm infants born <30 weeks GA. Δlt was not associated with BPD. There was no difference in BMI *z* score at birth between infants with and without BPD. Infants with BPD had a significantly lower length *z* score at birth and 36 weeks, but both BPD and BPD-free survivors experienced stunting. Despite no difference in caloric intake, stunting was more pronounced in BPD infants, but they experienced a higher Δwt and subsequently a higher ΔBMI. This change in body composition where increasing BMI *z* score over time possibly reflects increase adiposity which may contribute to the development of BPD in very preterm infants. This suggests infants with BPD may metabolize nutrition differently than BPD-free infants and benefit from individualized growth pattern focused on ΔBMI as opposed to weight gain alone.

Optimizing growth for preterm infants with BPD remains a significant challenge. This study suggests a more nuanced approached to growth especially for very preterm infants at high risk for BPD, where assessment of quality of growth through body composition assessment may provide better health outcomes than weight alone. The novel finding of this study suggests that use of standardized growth and nutritional requirement may not be appropriate for all infants but rather disease process warrants an individualized target. Revision of nutritional requirements for very preterm infants at high risk of BPD is needed.

Our study cannot provide specific targets of *z* scores to optimize growth and health outcomes, but we showed that direction of growth trajectories over time matters. Integrating simple and resource efficient tools to traditional methods such as tracking length-, and △BMI *z* scores over time can be effective proxies of body composition and improve BPD outcome.

# 6 APPENDICES

## Table 6.1. Demographics and characteristics of infants by sites

| Variable | Site A | Site B | Site C | *P* value |
|---|---|---|---|---|
| | N=230 | N=218 | N=324 | |
| **Maternal variables** | | | | |
| Antenatal steroids, No. (%) | 215 (95) | 203 (93) | 290 (90) | 0.06 |
| Multiple delivery, No. (%) | 30 (13) | 49 (22) | 99 (31) | ** |
| Caesarean delivery, No. (%) | 143 (62) | 140 (64) | 242 (75) | ** |
| Outborn delivery, No. (%) | 22 (10) | 27 (12) | 37 (11) | 0.62 |
| **Infant variables** | | | | |
| Gestational age, median (IQR), weeks | 27 (26;29) | 26 (25;28) | 28 (26;29) | ** |
| Gestational age group | | | | 0.1 |
| 22-25 $^{6/7}$, No. (%), weeks | 73 (32) | 74 (34) | 84 (26) | |
| 26-29 $^{6/7}$, No. (%), weeks | 157 (68) | 144 (66) | 240 (74) | |
| Birth weight, median (IQR), g | 950 (760 to 1180) | 885 (720 to 1108) | 950 (758 to 1140) | 0.09 |
| Small for gestational age, No. (%) | 16 (7) | 12 (6) | 32 (10) | 0.15 |
| Male sex, No. (%) | 130 (57) | 105 (48) | 161 (50) | 0.16 |
| Apgar at 5 min <7, No. (%) | 56 (24) | 121 (56) | 142 (44) | ** |
| SNAP-II score >20, No. (%) | 35 (15) | 63 (29) | 68 (22) | ** |
| Use of surfactant, No. (%) | 163 (71) | 135 (62) | 206 (64) | 0.1 |
| Mechanical ventilation, No. (%) | 175 (76) | 163 (75) | 238 (73) | 0.78 |
| Systemic steroids, No. (%) | 91 (40) | 94 (43) | 122 (38) | 0.44 |
| NEC, No. (%) | 12 (5) | 12 (6) | 27 (8) | 0.26 |
| PDA, No. (%) | 112 (49) | 134 (61) | 221 (68) | ** |
| ***Z* scores at birth** | | | | |
| BMI *z* score, median (IQR) | 0.04 (-0.65 to 0.73) | 0.31 (-0.44 to 0.94) | 0.38 (-0.48 to 1.09) | * |
| Weight *z* score, median (IQR) | 0.08 (-0.56 to 0.55) | 0.23 (-0.45 to 0.74) | 0.11 (-0.54 to 0.61) | 0.17 |
| Length *z* score, median (IQR) | 0.10 (-0.48 to 0.60) | 0.03 (-0.76 to 0.84) | -0.14 (-0.86 to 0.53) | 0.04 |
| Head circumference *z* score, median (IQR) | -0.02 (-0.65 to 0.55) | -0.25 (-0.89 to 0.47) | -0.19 (-0.99 to 0.57) | 0.12 |
| ***Z* scores at 36 weeks CGA** | | | | |
| BMI *z* score, median (IQR) | -0.42 (-0.93 to 0.11) | 0.26 (-0.35 to 0.78) | 0.48 (-0.04 to 1.16) | ** |
| Weight *z* score, median (IQR) | -1.28 (-1.78 to -0.69) | -0.60 (-1.16 to -0.16) | -0.46 (-1.10 to 0.11) | ** |
| Length *z* score, median (IQR) | -1.29 (-2.06 to -0.55) | -0.99 (-1.81 to -0.25) | -1.15 (-1.78 to -0.37) | * |
| Head circumference *z* score, median (IQR) | -0.91 (-1.64 to -0.25) | -1.18 (-1.78 to -0.48) | -0.74 (-1.45 to -0.07) | ** |
| **Change from birth to 36 weeks CGA** | | | | |

| | | | | |
|---|---|---|---|---|
| Δ BMI *z* score, median (IQR) | -0.41 (-1.17 to 0.38) | -0.05 (-0.96 to 0.81) | 0.20 (-0.49 to 1.05) | ** |
| Δ Weight *z* score, median (IQR) | -1.22 (-1.65 to -0.87) | -0.81 (-1.26 to -0.38) | -0.58 (-0.93 to -0.17) | ** |
| Δ Length *z* score, median (IQR) | -1.29 (-1.93 to -0.65) | -1.03 (-1.70 to -0.36) | -0.82 (-1.38 to -0.35) | ** |
| Δ Head circumference *z* score, median (IQR) | -0.84 (-1.47 to -0.23) | -0.91 (-1.47 to -0.30) | -0.63 (-1.19 to 0.12) | ** |
| **Outcomes** | | | | |
| BPD, No. (%) | 75 (33) | 127 (58) | 189 (58) | ** |
| Mortality, No. (%) | 2 (1) | 5 (2) | 4 (1) | 0.47 |

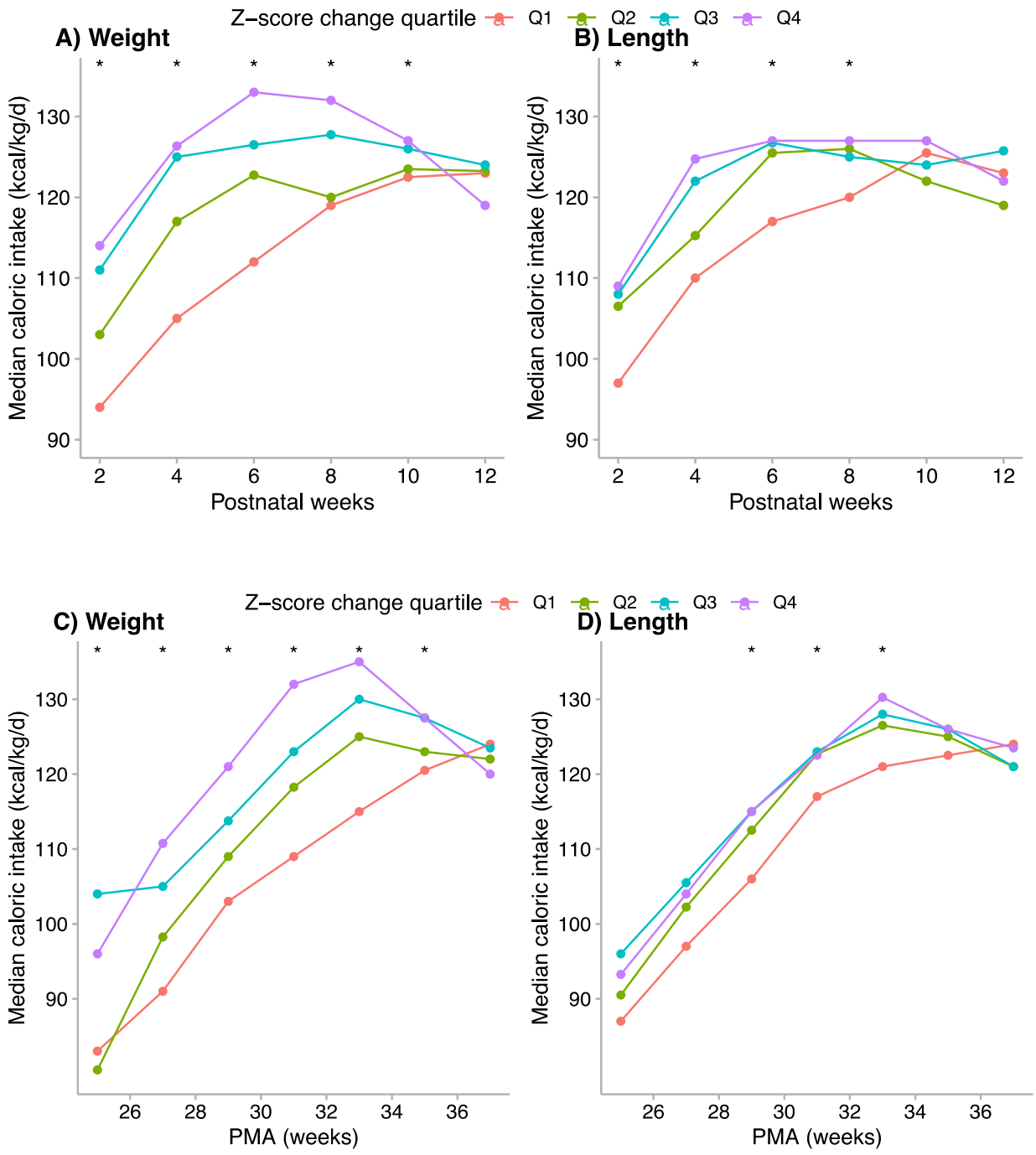
*Abbreviations:* BPD: Bronchopulmonary dysplasia, SNAP-II Score: Score for neonatal acute physiology, NEC: Necrotizing enterocolitis, PDA: Patent ductus arteriosus

*P* values for comparisons between groups derived from the $\chi^2$ test and Wilcoxon Rank Sum test, as appropriate

*Legend:* * indicates *P* value <0.05

** indicates *P* value <0.01

**Figure 6.1. Median caloric intake by △wt and △lt *z* scores quartiles from birth to 36 weeks CGA based on postnatal weeks and postmenstrual age**




Legend: * indicates *P* value <0.05 from Kruskal-Wallis test

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