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Comparing apples with apples: it is time for standardized reporting of neonatal nutrition and growth studies

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The ultimate goal of neonatal nutrition care is optimal growth, neurodevelopment, and long-term health for preterm babies. International consensus is that increased energy and protein intakes in the neonatal period improve growth and neurodevelopment, but after more than 100 y of research the optimum intakes of energy and protein remain unknown. We suggest an important factor contributing to the lack of progress is the lack of a standardized approach to reporting nutritional intake data and growth in the neonatal literature. We reviewed randomized controlled trials and observational studies documented in MEDLINE and the Web of Science from 2008 to 2015 that compared approximately 3 vs. 4 g.kg^{-1}.d^{-1} protein for preterm babies in the first month after birth. Consistency might be expected in the calculation of nutritional intake and assessment of growth outcomes in this relatively narrow scope of neonatal nutrition research. Twenty-two studies were reviewed. There was substantial variation in methods used to estimate and calculate nutritional intakes and in the approaches used in reporting these intakes and measures of infant growth. Such variability makes comparisons amongst studies difficult and meta-analysis unreliable. We propose the StRONNG Checklist—*St*andardized *R*eporting *O*f *N*eonatal *N*utrition and *G*rowth to address these issues.

For preterm babies, nutrition in early life is now recognized as a key determinant of improving neonatal outcomes: survival; optimal growth; neurodevelopment, and long-term health (1). Ever since the "gavage" feeding of preterm babies began in the late 19th century and nutritional intake could be determined by neonatal staff rather than the baby, we have faced the dilemma of the nutrition required to achieve these goals (2).

Early 20th century metabolic studies estimated the energy and protein requirements of late preterm babies, but despite over 1,000 publications on neonatal nutrition and growth, a 2014 review of clinical trials on parenteral nutrition for extremely preterm babies concluded that the "cardinal unresolved questions are the optimal protein and energy intakes and the growth velocity that is predictive of optimal long-term health (3)." There is broad consensus that the target for growth of the preterm baby should be to match intrauterine growth of the normal human fetus. To achieve this, we need to know, first, what this growth looks like in terms of not only weight but also other measures of growth, including body composition, and, secondly, the nutritional requirements needed for this growth to be realized. This review will consider these critical questions and will propose that a standardized approach to reporting data will aid progress toward answering these unresolved questions.

The many different approaches taken to reporting nutritional intake data and growth in the neonatal literature make addressing these questions through interpretation of the data difficult. To investigate the variability in reporting, we identified and reviewed recent randomized controlled trials and observational studies documented in MEDLINE and the Web of Science from 2008 to 2015 that compared approximately 3 vs. 4 g.kg^{-1}.d^{-1} protein for preterm babies in the first month after birth. Consistency might be expected in the calculation of nutritional intake and assessment of growth outcomes in this relatively narrow scope of research. Twenty-two studies were reviewed. Many of the studies did not cite the reference for the breast-milk nutrient composition data used to calculate nutritional intakes or, in some cases, even what these figures were (**Table 1**). Where composition data were provided, there was a range of different figures for the composition of breast milk and intravenous nutrition and intakes were presented in a variety of ways (**Table 1**). Assessment of growth also was undertaken over varied time periods, using different growth references and several methods of calculating growth (**Table 2** and **Supplementary Table S1** online). It is difficult to find even two studies where the same references or methods have been used to determine nutritional intake or growth outcomes (**Tables 1** and **2**; **Supplementary Table S1** online). These differences make the body of neonatal nutrition research

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Table 1. Nutritional intakes, energy, and protein figures used for breast-milk composition and their references for 22 randomized and observational studies from 2008–15 of ~3 vs. 4 g.kg^{-1}.d^{-1} protein in first month after birth, by reverse chronological order

	Breast-milk composition per 100 ml			
Author	Energy (kcal)	Protein (g)	Reference	Energy intake and protein intake reported as: Data are mean intake kcal.kg^{-1}.d^{-1} and g.kg^{-1}.d^{-1} unless otherwise stated
Morgan 2014 (58)	66 *transitional* 69 *mature*	1.9; 1.5	(59)	Total and parenteral intake by week for each of the first 4 weeks; Cumulative total and parenteral non protein energy day 1 to 28
Olsen 2014 (60)	66.4	1.62	(61)	Total intake day 1 to 28; Cumulative energy and protein deficit day 1 to 28
Moltu 2014 (43)	71	1.3	Norwegian Food Composition database 2013 (Norwegian Food Safety Authority, Ullevålsveien, Norway)	Total intake day 1 to 28
Bolisetty 2014 (62)	Not specified	Not specified	Not cited	Total intake on days 1, 3, 7, 14, and 21
Vlaardingerbroek 2013 (63)	Not specified	Not specified	Not cited	Total protein intake, and total nonprotein energy intake on days 1,4, and 6
Loui 2013 (64)	Not specified	2.4	(65)	Total intake each day for days 1 to 35, Total intake 1–7, days 8–35 and for days 1–35
Burattini 2013 (42)	Not specified	Not specified	Not cited	Nonprotein energy and amino acid intake in the first 10 d; Cumulative energy intake from birth to 36 wk postmenstrual age
Cormack 2013 (66)	65 *transitional* 72 *mature*	1.5; 1.4	NZ Food Composition database 2007 (67)	Total intake on day 1 and by week for each of the first 4 wk; Total intake in the 1st 2 wk and 30 d
Scattolin 2013 (68)	69	1.2	(69)	Parenteral protein and non-protein energy intake in the first week; Total protein intake in the 3rd week
Balasubramanian 2013 (70)	Not specified	Not specified	Not cited	Enteral energy intake in first 4 wk; Parenteral cumulative non protein energy intake in first 4 wk
Ditzenberger 2013 (71)	Not specified	Not specified	Not cited	Total intake by week for each of the first 9 wk
Senterre 2012 (23)	64	1.4	Not cited	Cumulative weekly intake for each of the first 6 wk; Cumulative energy and protein deficit for each of the first 6 wk
Biasini 2012 (72)	Not specified	0.8–1.1	Not cited	Prescribed intake from reaching full enteral feeds to discharge, transfer or >50% breastfed (not actual intake)
Moya 2012 (73)	Enteral intake not reported			Not reported
Blanco 2012 (74)	Enteral intake not reported			Parenteral energy intake on days 1, 3 and 7
Rochow 2012 (48)	80	2.4	Not cited	Total intake on days 1 to 7, from days 1–28 and at 36 wk PMA; Total intake from regain of birthweight to 36 wk PMA
Can 2012 (75)	Not specified	Not specified	Not cited	Total intake weekly for each of the first 3 wk
Miller 2012 (44)	Measured weekly but not reported		(76)	Total protein intake from study weeks 1–4
Roggero 2012 (77)	Not specified	Not specified	Not cited	Total intake in first 7 d; Cumulative parenteral energy and protein intake at 7 d
Costa-Orvay 2011 (78)	Not specified	Not specified	(79)	Prescribed intake from study weeks 1–4 (intended not actual)
Smolkin 2010 (80)	Not specified	Not specified	Not cited	Total intake while on exclusive parenteral nutrition in first month after birth; Total intake on combined parenteral and enteral nutrition in 1st month
Tan 2008 (47)	Not specified	Not specified	Not cited	Cumulative intake day 1 to 28

PMA, postmenstrual age.

challenging to interpret and meta-analysis difficult to perform. Given that many studies are of small size, meta-analysis and Individual Participant Data meta-analysis would enhance interpretation of these data. Meta-analysis would be much more robust if there were an agreed upon set of international guidelines for standardized methodology and reporting of neonatal nutrition and growth outcomes. In this review, we present further analysis of the differences,

Table 2. Methods used to assess growth of preterm infants in randomized controlled trials and observational studies of approximately 3 vs. 4 g.kg^{-1}.d^{-1} parenteral protein in first week after birth

Growth outcomes reported as:	Reference
Mean weight, length and head circumference (g, cm, cm) at:	
21 d	(68)
28 d	(43,58,60,68,70,78)
Study days 1, 14, and 28	(73)
Study day 1 and study end	(78)
Weekly from weeks 1 to 9	(71)
Day 1 and weekly from weeks 1 to 4	(75)
Weekly from 25 to 37 wk PMA	(48)
36 wk PMA	(42,47,48,58,68)
40 wk PMA	(75)
1 wk and 1 mo	(80)
Discharge, transfer or > 50% breastfed	(72)
Study end (discharge or 40 wk PMA whichever first)	(44)
Discharge	(62,80)
2 y	(42)
Cumulative gain in weight, length and head circumference (g, cm, cm)	
At 28 d	(63,70,74)
During second and third weeks	(68)
Length gain (cm per day)	(73)
From birth to 1,800 g and regain of birthweight to 1,800 g	(42)
From regain of birthweight to 36 wk PMA	(42)
Weight g/week, cm/week, cm/week from enrolment to study end (discharge or 40 wk PMA whichever first)	(44)
During the NICU stay	(80)
Growth velocity for weight, length and head circumference (g.kg^{-1}.d^{-1} or cm per week)	
Birth to 28 d	(58)[d], (60)[c], (43)[c], (70)[a], (74)[d], (63)[d]
Birth to 35 d	(64)[b]
Days 1–7, days 8–35, and for days 1–35	(64)[b]
Birth to 36 wk PMA (weight only)	(43)[c]
By week for weeks 1 to 4	(43,66),[c]
First 30 d of life (after regaining birthweight)	(66)[c]
Second week and third week after birth	(68)[d]
By week for weeks 1 to 9	(71)[d]
Full enteral feeds to discharge, transfer or > 50% breastfed	(72)[d]
Regained birthweight to 36 wk PMA	(48)[d]
First of birth to discharge home or corrected gestational age of 40 wks	(63)[d]
By week from birth to week 11	(77)[c]

Other measures were: Number of babies < 10th centile at birth and discharge or study end (44), skinfold thickness measurements (cm) (71), weight centile at discharge (62) Ponderal index on day 28 (73), body mass index (78), mid arm circumference at 36 wk PMA (cm) and lower leg length gain (mm/day) (47,63), lower leg length gain in at 28 d and 36 wk PMA (mm/day) (68), dual-energy X-ray absorption scans (48), air displacement plethysmography (77), total body electrical impedance (78).
[a]Net weight gain over the time interval divided by the time interval and birth weight. [b]Net weight gain over the time interval divided by the time interval and mean of birthweight and weight at day *x*. [c]Exponential method. [d]Calculation method not reported.
PMA, postmenstrual age.

discussion of potential solutions, and a standardization checklist for neonatal nutrition research.

WHAT DO WE NEED TO KNOW?

Determining the optimal nutritional requirements of preterm babies requires an agreed reference standard for growth and other outcomes. In 1977, the recommendation of the American Academy of Pediatrics was "to achieve postnatal growth and body composition equivalent to those of normally growing, healthy human fetuses of the same gestational age" (4). Some doubt remains as to whether this is the appropriate goal; however, in the absence of an alternative based on evidence, this remains a reasonable target, albeit one that is not met by the majority of preterm babies (5).

For research to address the best means of achieving this goal, we need to know:

1. The growth that would have occurred *in utero*
2. The body composition the baby would have had if he/she had remained *in utero*
3. The nutrient intake required to achieve the first two

The Growth That Would Have Occurred *In Utero*

Babies born preterm are more likely to be growth-restricted compared with their gestational-age matched peers who remain *in utero* and are born at term (6), with up to 40% of preterm babies having some evidence of intrauterine growth restriction (7). Therefore, postnatal growth of preterm babies ideally should be monitored against a standard based on measurements of normally growing fetuses *in utero* at the same gestational age, rather than cross-sectional data from preterm births. Various methods have been developed for estimating fetal weight *in utero* with at least 35 different formulae available. These estimates have been found to be relatively accurate at predicting birth weight up to 3,500 g with 80% of estimated fetal weights within 10% of birthweight (8). Fetal head circumference and biparietal diameter can be measured by ultrasound; however, there are no reliable references for fetal length.

The INTERGROWTH 21st study (9) provides the most consistent standards for fetal growth and size at birth, using data from carefully selected and standardized participants in eight geographically defined urban populations in whom health and nutritional needs were met and adequate antenatal care was provided. Fetal growth and newborn size were measured using prespecified markers and the same methods, equipment, and selection criteria. However, as few data from babies born between 23 and 33 wk were available, the INTERGROWTH-21st curves begin at 33 wk postmenstrual age and even in the moderately preterm gestations the numbers of babies born at each gestational age is small. Thus, these charts are not suitable for the monitoring of growth in babies born at moderately preterm or earlier gestations.

Customized centile charts for intrauterine growth, adjusting for maternal size, ethnicity, and other variables such as prior birth weight, have been developed to improve the detection of

intrauterine growth restriction. There is considerable debate over whether such charts are preferable to international standards (10). Furthermore, customized charts only provide a customized fetal weight centile, ignoring the very important length and head circumference variables, and were not developed to assess birthweight or longitudinal postnatal growth. Given the importance of linear growth in preterm babies to ensure proportional growth and head circumference growth, which is correlated with brain growth (11), it is difficult to support the use of customized fetal growth charts for monitoring postnatal growth.

Comparison of Potential Growth Curves. In practice, therefore, the postnatal growth of most preterm babies is monitored using growth charts derived from cross-sectional data of babies born preterm. Two international standards commonly used for assessing the growth of preterm infants from around 23 wk postmenstrual age (PMA) and for calculation of Z-scores are the UK 1990 (12) and Fenton 2013 (13) datasets. The essential features of these datasets and INTERGROWTH 21st are summarized in **Table 3**. Both the UK 1990 and Fenton 2013 datasets have been developed based on cross-sectional data from preterm births and linked to the World Health Organization (WHO) post-term growth standard (14). The UK-WHO growth curves were designed for assessing preterm infants from 23 wk postmenstrual age to 2 y corrected age using a combination of UK 1990 and WHO data (15). The Fenton 2013 growth curves use a more recent and much larger sample of cross-sectional data of preterm births which link to the WHO growth data from birth to 10 wk post-term (16).

For weight, the UK-WHO, INTERGROWTH 21st and Fenton 2013 data sets are similar. The slightly lower Fenton 2013 curves may be explained by the Fenton data being derived from actual PMA in weeks and days and the UK–1990 for completed weeks. Thus, fewer babies would be classified as small-for-gestational-age (SGA) between 24 and 34 wk PMA compared with the WHO curves. The Fenton dataset for weight is over 400 times larger than the UK-WHO dataset which includes few data for births from 32–35 wk PMA. From approximately 38–42 wk, the slope of the INTERGROWTH-21st and UK-WHO curves dip in comparison with Fenton 2013 reflecting the slower growth *in utero* that occurs just prior to term (17). The Fenton data have been statistically smoothed as they link to WHO data around 40 wk to avoid this dip. Given that the slowing of intrauterine growth prior to term is a feature of the birth-related maturational and hormonal changes, (18) there is no good reason why babies born preterm should follow this dip in growth trajectory and a smoothed transition is perhaps more appropriate for both clinical practice and research purposes (13).

The more striking difference for length and head circumference amongst the Fenton 2013, INTERGROWTH-21st and UK-1990 curves may be contributed to by a substantially larger sample, especially at lower gestations (12,13) in the Fenton dataset (e.g., for babies <30 wk gestation n = 12,000 vs. 146 in the UK-WHO), more accurate estimation of gestational age at birth and more contemporary data in the Fenton dataset.

Use of SD (Z-Scores or ΔZ-Scores). Z-scores express an anthropometric value such as weight, length, or head circumference for age or weight for height as a number of SDs below or above the reference population mean or median value. The Z-score is widely recognized as the best system for presentation and analysis of anthropometric data (19).

The recommended formula for calculating the Z-score is the Lambda Mu Sigma method using data from an appropriate published dataset (20). A negative Z-score change indicates a decline in growth status, a positive Z-score change is an increase in growth status, or a Z-score change of zero is a stable or unchanged growth status. Therefore, Z-score change rather than Z-score alone is preferable to evaluate the effect of nutrition interventions on growth (21). The potential effect of the choice of dataset on the evaluation of growth is demonstrated in **Figure 1** comparing Z-scores for the same lengths calculated with the UK-WHO vs. Fenton 2013 dataset. Linear growth in this case would be considered appropriate if using the UK-WHO data but faltering if using the Fenton 2013 dataset.

However, if z-scores are used to report growth, it is important to be cognisant of the entry criteria for babies to be enrolled in the study. Studies in extremely preterm babies often use either a GA criterion, a birthweight criterion or both (below a certain GA AND/OR below a certain birthweight). If a GA criterion alone is used, one would expect the z score distribution to approximate normality; however, if birthweight alone or a combined criterion are used, this may not be the case as smaller, more mature babies will be included and larger, less mature babies will not, skewing the z-score distribution.

It also is important to note the normal contraction of the extracellular fluid space after birth means that some downward tracking of z-score between birth and a later time point is expected. This has led some researchers to report change in growth from the nadir in weight, or from regain in birthweight, or from birth. However, unless babies are weighed daily to delineate accurately the day of maximum weight loss or of regain in birthweight, these approaches will lead to further inaccuracies. Further, postnatal weight loss and duration of poor growth immediately after birth is minimized with optimal nutrition. Some researchers report growth from birth, while others report growth from the day birthweight is regained (**Table 2**). Therefore, for consistency of reporting, we recommend reporting growth from birth, a clearly defined, consistent time-point, with the understanding that for weight loss of ECF fluid should be borne in mind.

Choice of a Reference Dataset. For consistency in attribution of SGA status, determination of Z-scores, and assessment of Z-score change over time, an agreed international dataset would be of great value. Given that INTERGROWTH-21st does not have data prior to 33 wk, and small numbers at 33 and 34 wk, and that the UK-WHO data are older and also based on much smaller numbers, beginning at 24 wk when there are increasing numbers of survivors at gestations below that, the

Table 3. Comparison of three international datasets for assessing the growth of preterm infants

Growth curves	Fenton 2013 (13)		UK-WHO (12)		INTERGROWTH (9)
Aim	Growth reference		Growth reference		International prescriptive growth standard
Method	Systematic review, selection and meta-analysis of 6 data sets.		Pooled birth data from 5 data sets.		Multicentre, multi-ethnic, multicounty population-based prospective study.
Years of data collection	1991 to 2007		1983 to1993		2009 to 2014
Age range					
Weight	22+ to 50 wk		23 to 42 wk		33 to 43 wk
Length	23+ to 50 wk		26 to 42 wk		33 to 43 wk
Head circumference	23+ to 50 wk		23 to 42 wk		33 to 43 wk
Age accuracy	Actual age		Completed weeks		Completed weeks
Method to assess gestational age	Mainly early ultrasound, some maternal dates and clinician assessment		Mixed—clinician assessment, maternal dates confirmed by early ultrasound and not specified		Reliable ultrasound estimate of gestational age using crown–rump length before 14 wk of gestation or biparietal diameter if antenatal care started between 14 wk and 24 wk or less of gestation
Location	Germany, United States, Canada, Australia, Scotland, Italy		United Kingdom—mainly East Anglia and excluded "non-white" participants		Eight study sites: Brazil, Italy, Oman, United Kingdom, United States of America, China, India and Kenya
Participant selection	No		No		Yes—strict individual eligibility criteria for a population at low risk of impaired fetal growth.
Measurement standardization	No		No		Newborn anthropometric measures obtained within 12 h of birth by identically trained anthropometric teams using standardized methods and the same equipment at all sites.
Sample size	<37 wk	<30 wk	<37 wk	<30 wk	33 to <37 wk
Weight	3,986,456	34,639	9,443	1,435	1022
Length	175,573	12,000	985	146	1014
Head circumference	175,573	12,000	1,841	679	1016
Centile lines	3rd, 10th, 50th, 90th, and 97th		0.4th, 2nd, 9th, 25th, 50th, 75th, 91st, 98th, 99.6th		3rd, 10th, 50th, 90th, and 97th
Least mean squares tables for term and preterm infants	Available from author		Available from www.growthcharts.rcpch.ac.uk.		Available from www.intergrowth21.org.uk/
Additional features	Z-score and percentile calculator available from www.ucalgary.ca/fenton.		Neonatal and Infant Close Monitoring growth chart		Global standards and Z- scores for length at birth, with information related to their use.

Fenton 2013 dataset may be the best currently available option. It also has the benefit of smoothing at term gestations to avoid a dip at this time.

Recommendations:

- Measure growth from birth, rather than from a nadir or from the time when birthweight was regained
- Growth reference for preterm infants—Fenton 2013
- Growth reported as Z-scores and Z-score change to indicate growth status alterations over time

Reporting of Weight Velocity. Currently, there is no standardized approach to the calculation of growth velocity, generally reported as weight gain in $g.kg^{-1}.d^{-1}$. Thirteen of the 22 studies in Table 2 reported Z-scores and seven reported Z-score change rather than weight gain. Fourteen studies reported weight velocity in $g.kg^{-1}.d^{-1}$ but seven did not specify how this was calculated.

Seven specified how weight velocity was calculated but used three different methods:

1. Net weight gain over the time interval divided by the time interval and birth weight
2. Net weight gain over the time interval divided by the time interval and the mean of birth weight and weight at day *x*
3. Exponential method for calculation of weight velocity reported by Patel (22)

The difference between these methods has been estimated to be 42% over 39 d (23). Researchers should state the method used when reporting weight gain. Patel's method is validated to assess the growth of ELBW and VLBW infants and provides a simple-to-use and consistent approach (13).

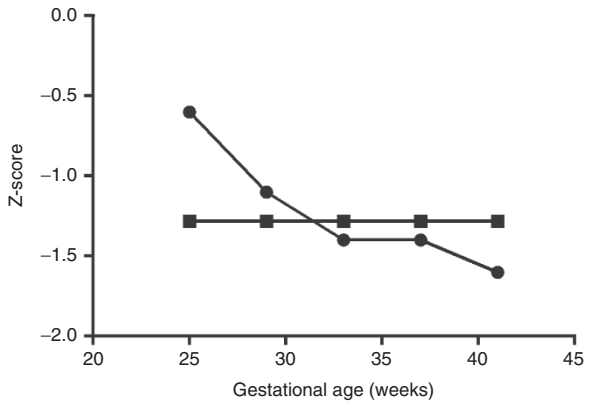

Figure 1. Comparison of Z-score change between the UK-WHO and Fenton 2013 datasets. Linear growth would be considered appropriate with the UK-WHO data (squares: no change in z-score) but faltering with the Fenton 2013 dataset (circles: a decrease of ~1 z-score). Differences below 30 wk postmenstrual age (PMA) are likely due to more recent data with better estimation of gestational age and a substantially larger sample size in the Fenton data (<30 wk PMA 12,000 vs. 146 in UK-WHO). Differences near term are likely to be due to the smoothing of the Fenton charts from prenatal growth to postnatal growth data, taking account of the slowing of intrauterine growth near term that one would not expect to see in preterm babies at the same corrected gestational age.

Table 4. Recent consensus recommended parenteral and enteral energy and protein intakes

Parenteral nutrition recommended intake		Birthweight	Energy kcal. $kg^{-1}.d^{-1}$	Protein $g.kg^{-1}.d^{-1}$
2005	ESPGHAN (81)		110–120	1.5–4
2005	International panel of experts (82)	ELBW	105–115	3.5–4
		VLBW	90–100	3.2–3.8
Enteral nutrition recommended intake				
2010	ESPGHAN (83)	ELBW	110–135	4–4.5
		VLBW	110–135	3.5–4
2014	International panel of experts (84)	VLBW	110 and 130	3.5–4.5

ELBW, extremely low birthweight (<1,000 g); ESPGHAN, European Society of Paediatric Gastroenterology, Hepatology and Nutrition; VLBW, very low birthweight (<1,500 g).

Recommendation:

- Exponential method for calculation of weight velocity (22)

The Body Composition the Baby Would Have Had If He/She Had Remained *In Utero*

Growth patterns in early postnatal life and body composition have important consequences for metabolic and cardiovascular health in later life (24,25). At term-corrected age, preterm babies are significantly shorter, lighter, and have smaller head circumferences than those born at full-term (6,26). Several studies now have demonstrated that very preterm babies also have a different body composition at term-corrected age when compared with babies born at term (6,27,28), with substantially less lean body mass (mean difference, 460 g) but a similar fat mass (6). Thus, they also have a higher per cent fat mass. Both body size and composition relate to the risk of noncommunicable diseases in later life (29); therefore, understanding how the growth of preterm infants can be modified to aim for a body composition at term-corrected age that is similar to that of babies born at term may be important for optimizing lifelong health (30,31).

Body composition and particularly changes in lean body mass are difficult to measure accurately in very small preterm babies. Several indirect *in vivo* techniques have been evaluated including bioelectrical impedance analysis, dual-energy x-ray absorptiometry, MRI and use of stable isotopes, such as deuterium oxide dilution (32). Issues of complexity, expense, and ease of use that are beyond the scope of this article mean that none of these is practical for routine measurement of preterm babies. However, recently, it has become possible to measure fat or lean body mass routinely in the neonatal intensive care unit using air displacement plethysmography (ADP) (33); this now is standard practice in some neonatal units, although infants need to be free from significant interventions such as CPAP or ventilation. With ADP, measurements of infant mass and volume, determined by air displacement, are used to estimate whole-body density (i.e., mass/volume). Published reference models for the densities of lean body mass and fat mass from multi-component studies and standard assumptions about the densities of fat and lean tissue are used to derive the fraction of fat in body weight (34).

However, even ADP is not available in most units, meaning that weight gain is therefore often used as a proxy for growth, with much less consideration paid to length and head growth. It is relatively easy to improve the postnatal weight gain of preterm babies with additional energy in the form of glucose polymers or fat added to enteral feeds, but this may only increase fat mass rather than the intended increase in lean body mass (35,36). At present, simple anthropometric measurements using all three growth parameters and not just weight are the most reliable and readily available growth parameters for preterm babies (37).

Recommendation:

- Weight, length, and head circumference reported weekly
- Raw data for lean body mass, fat mass, and other measurements should be reported.
- In future, an agreed upon lean body/ fat mass index would be useful

The Nutrient Intake Required To Achieve the Growth and Body Composition That Would Have Occurred If the Baby Had Remained *In Utero*

Recommended Energy and Protein Intakes. The primary modifiable influence on postnatal growth is nutrition, although other factors such as disease, environment, and genetics also play a role (38,39). Research to date has focused on the energy and protein intake required to achieve intrauterine growth and

Table 5. Standardized reporting of neonatal nutrition and growth outcomes (StRoNNG checklist)

Parameter	Suggested standard
Nutrition calculations	Specify all figures used for calculations
	Enteral protein: 4 kcal.g^{-1}
	Enteral carbohydrate: 4 kcall.g^{-1}
	Enteral fat: 9 kcall.g^{-1}
	Parenteral amino acid: 4 kcall.g^{-1}
	Parenteral dextrose: 3.4 kcall.g^{-1}
	Parenteral lipid: 10 kcall.g^{-1}
	Parenteral lipid with vitamins as per manufacturer (e.g., 0.88 g fat/5 ml lipid)
Conversion of amino acid to protein	100 ml amino acid solution contains 97 g protein
Conversion of amino acid to nitrogen	1 g of amino acid contains 160 mg of nitrogen
Breast-milk composition	Specify and reference figures for transitional, mature preterm or term breast milk for: Energy; Protein; Carbohydrate, and Fat; Energy and protein intakes calculated and reported using either actual breast-milk analysis figures (stating methodology) or standardized preterm transitional breast-milk composition for 14 d (65 kcal and 1.5 g protein.100 ml^{-1}) and mature breast-milk composition thereafter (72 kcal and 1.2 g protein.100 ml^{-1}) (53–57)
Assumption for the bioavailability of enteral vs parenteral nutrients	Enteral and parenteral intakes reported separately; Enteral protein and energy should be considered 100% bioavailable, and calculations should be based on administered volumes
Intake "primarily" breast milk	Volume of feeds greater than 80% breast milk
Commercial parenteral and enteral nutrition components	Brand, manufacturer and city; Specify figures used for energy, protein, carbohydrate and fat content, as specified by manufacturer
Nutritional intake macro and micronutrients	Report by week for the first 4 wk: • Mean total energy kcal.kg^{-1}.d^{-1} • Mean parenteral energy kcal.kg^{-1}.d^{-1} • Mean enteral energy kcal.kg^{-1}.d^{-1} • Mean total protein g.kg^{-1}.d^{-1} • Mean parenteral amino acid g.kg^{-1}.d^{-1} • Mean enteral protein g.kg^{-1}.d^{-1} • Do other relevant nutrients meet recommended intake?
Full enteral feeds	Defined as the first day when no further parenteral nutrition is given or 150 ml.kg^{-1}.d^{-1} enteral feeds is reached.
Growth velocity (g.kg^{-1}.d^{-1}.)	• Measure growth from birth, rather than from a nadir or from time when birthweight was regained • Weight in g.kg^{-1}.d^{-1} Growth velocity = (1,000 × ln(Wn/W1))/(Dn−D1) (22) • Length, and head circumference in cm (rounded down to the nearest mm) Measured at a minimum at birth, 28 d and 36 wk PMA or discharge
Z-scores	• Z-scores for weight, length, head circumference at birth, 28 d and 36 wk PMA or discharge • Change in Z-score for weight, length, head circumference from birth to 28 d and birth to 36 wk PMA or discharge
Dataset for calculation Z-scores	• Method of Z-scores calculation: *Lambda Mu Sigma method* (20) • Z-scores reference dataset specified • International standard—Fenton 2013
Body composition	• Raw data for lean body mass, fat mass and other measurements • An agreed lean body/fat mass index (yet to be developed)
Follow up	Growth (Z-scores) and Z-score change, body composition and neurodevelopment at 2 y corrected age

PMA, postmenstrual age.

international consensus groups have made recommendations based on this research (Table 4). These recommendations are based on studies that showed increased protein accretion with increased protein intake and that even a small deficit in protein intake impairs both lean body mass accretion and linear growth (40), although the level of evidence is not high.

In reality, many neonatal units (41) and even clinical trials (42) struggle to reach these recommendations, and therefore, it is important that actual intakes are always reported in addition to prescribed or intended intake. Similarly, it is important that the source used to calculate nutritional intakes is referenced.

Basis for the Calculation of Energy and Protein Intake

Parenteral Solutions. The nutrient composition figures used to calculate energy and amino acid intake from parenteral solutions often are not reported, with the consequence that there may be variation that is not apparent. For example, including the energy content of glycerol and added vitamins in the energy calculation for lipid gives 10 rather than 9 kcal/ g lipid; some authors use 9 kcal per g for enteral fat and 10 kcal per g for parenteral fat (43). For carbohydrate (dextrose) some authors use 3.4 kcal per g because dextrose datasheets state that 1 g of dextrose contains 3.4 kcal, whereas others use the Atwater factor of 4 kcal per gm (44).

Further inaccuracy can occur in the conversion of lipid emulsion to fat, with 5 ml lipid emulsion often considered to provide 1 g fat. However, vitamin solutions commonly added to 20% lipid emulsions are in 10% lipid; therefore, addition of 25 ml vitamins to 100 ml of 20% lipid emulsion effectively reduces the solution to a 17.5% lipid emulsion containing 0.88 g fat/5 ml and not 1 g fat/5 ml.

Recommendation: All figures used for calculations are specified and suggest:

- Enteral protein: 4 kcal.g^{-1}
- Enteral carbohydrate: 4 kcal.g^{-1}
- Enteral fat: 9 kcal.g^{-1}
- Parenteral amino acids: 4 kcal.g^{-1}
- Parenteral dextrose: 3.4 kcal.g^{-1}
- Parenteral lipid: 10 kcal.g^{-1}
- Parenteral lipid with vitamins as per manufacturer (e.g., 0.88 g fat per 5 ml lipid emulsion)

Enteral Solutions. In the 22 studies reviewed, various assumptions were made when calculating nutrient intake:

Bioavailability of Enteral vs. Parenteral Nutrients

Parenteral nutrition bypasses the usual process of eating and digestion. As the intestines consume a significant proportion of the diet for the growth and energy of the intestines themselves, the recommended intakes of parenteral nutrition are usually lower than for enteral nutrition, e.g., 3.5 to 4 g.kg^{-1}.d^{-1} parenteral vs. 4–4.5 g.kg^{-1}.d^{-1}enteral protein for ELBW babies (**Table 4**). In the first week after birth, parenteral nutrition provides the majority of nutritional intake but up to 50% may be enteral. For statistical analysis of total protein intake in the first week where a comparison with the recommended parenteral protein intake for instance is required, some researchers use a bioavailability factor to convert enteral protein intake to a parenteral equivalent to compare total intake (parenteral + enteral) with parenteral recommendations. According to some authors, this factor ranges from 81 to 87% for fortified human milk and from 86 to 94% for infant formula (45). Fanaro assumed 88% (46), but Tan *et al.* (47) and Rochow *et al.* (48) all assumed 85% absorption of enteral protein. However, stable isotope studies have shown that protein digestion and absorption is almost 100% in infants (49), but that fecal nitrogen is derived from endogenous synthesized (glycol-) proteins, sloughed-off cells and bacterial products. There is variation in the bioavailability of different nutrients, i.e., energy vs. protein vs. micronutrients, which is also affected by the nature of the enteral solution, e.g., breast milk vs. fortified breast milk vs. infant formula. In many cases, the actual bioavailability is unknown; therefore, we suggest no adjustment is made for this until there is definitive evidence of the bioavailability of specific nutrients in breast milk and other milks and nutritional supplements for preterm infants.

Loss of Enteral Feed Volume in Feeding Tubes and Via Gastric Reflux

This refers to the proportion of enteral intake that is actually available for digestion by the gut. It takes into account enteral absorption, loss of milk in feeding tubes, and gastric reflux. Some authors consider 100% of enteral feeds to be absorbed and others only 75% (including 85% bioavailability of enteral vs. parenteral nutrients) (48). There is little evidence to support this practice and it would be difficult to measure accurately the volume of feed that is digested and absorbed; therefore, it may be better just to report the total enteral volume administered.

Recommendation:

- Calculation and reporting of parenteral and enteral protein and energy intakes separately where possible
- Enteral protein and energy should be considered 100% bioavailable, and calculations should be based on administered volumes

Nutritional Composition of Breast Milk. Own mothers' breast milk is the feed of choice for preterm babies. However, the composition of breast milk is dynamic. The concentration of both energy and protein in expressed breast milk is highly variable throughout lactation and between individuals (50). The analysis of human milk can also be influenced by methods of expression and storage and pasteurization. Published studies of breast-milk composition involve non-standardized collection with varying attention to storage and processing conditions resulting in substantial variation in reported nutritional composition (50,51). Any calculation of energy and protein intake from breast milk is merely an estimation (52).

Table 1 shows the variation in breast-milk composition figures used in recent neonatal nutrition and growth studies. The energy range is from 64 to 72 kcal.100 ml^{-1}. The range for protein was even larger (0.8–2.4 g.100 ml^{-1}).

Although the precise nutritional content of the breast milk administered to each baby in each study is unknown, the use of standardized figures for breast-milk composition would improve both the comparability of studies and the likelihood of finding optimal protein and energy intakes for preterm babies.

Recommendation:

- The energy, protein, carbohydrate, and fat concentrations per 100 ml of breast milk used to calculate nutritional intakes are reported
- Energy and protein intakes are calculated and reported using either actual breastmilk analysis figures (stating the methodology used) or standardized preterm transitional breastmilk composition for 14 d (65 kcal and 1.5 g protein.100 ml^{-1}) and mature breastmilk composition thereafter (72 kcal and 1.2 g protein.100 ml^{-1}) (53–57)

We have formulated our recommendations into a the StRONNG Checklist - *St*andardized *R*eporting *O*f *N*eonatal *N*utrition and *G*rowth, which provides guidelines for standardized reporting of nutritional intakes and growth in neonatal populations (**Table 5**).

CONCLUSION

Methodological heterogeneity underlies the body of neonatal nutrition and growth literature. Before we can determine accurately the effects of nutritional interventions and whether or not the observed anthropometric or body composition differences reflect improved short- and long-term outcomes, standardization of nutritional composition, statistical methods, growth standards, and reporting of outcomes is required. This is essential to improve the quality and usefulness of clinical trials in neonatal nutrition and enable true meta-analysis of the results.

AUTHOR CONTRIBUTIONS

B.C. conceived the review and F.B. participated in its design. B.C. and F.B. drafted the manuscript and all authors contributed to and approved the final manuscript.

SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at http://www.nature.com/pr

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