Review

Measuring body composition in the preterm infant: Evidence base and practicalities

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A R T I C L E   I N F O

S U M M A R Y

Preterm birth and body composition have demonstrable effects on growth and later health outcomes. Preterm infants reach term equivalent age with a lower proportion of lean mass and higher body fat percentage than their term equivalent counterparts. Weight and length do not give an accurate assessment of body composition. Tracking body composition rather than just weight is a fundamental part of improving nutritional outcomes. This is important given the ongoing controversies regarding the nutritional needs of preterm infants, as well as establishing suitable targets for their growth.

In this review we describe current methodologies used in the measurement of body composition of the preterm infant and the review the recent published evidence for their accuracy and utility.

Current measurement techniques employed include air displacement plethysmography, bioelectrical impedance analysis, isotope dilution techniques, MRI and a combination of manual measurements including skinfold thickness, body mass index and mid upper arm/mid-thigh circumference. These measures allow for the estimation of fat mass, fat-free mass and regional assessment of adiposity.

Some methods, such as dual-energy X-ray absorptiometry and air displacement plethysmography do allow for comparison of change in body composition over time in cohorts of preterm infants that may be studied over a longer period of time and into adult life. However, none of the currently described methods give an accurate and practically achievable method of obtaining body composition measures in preterm infants in day to day routine clinical practise, although this remains a key priority when decisions are being made about how best to feed.

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1. Introduction

Studies evaluating the growth of preterm infants show them reaching term equivalent age with less fat-free mass (FFM) and a higher percentage total body fat than their term born counterparts, due to a relative paucity of lean mass [1]. They also appear to have differences in the relative amount and distribution of their visceral adipose tissue [2]. This is likely to have an adverse impact on cardiovascular outcomes and increase the risk of metabolic disease in adult life, as both body size and composition in early life are known to impact on the risk of non-communicable disease in adulthood

[3]. Not all changes in body composition persist into later life and long term follow up of body composition in preterm infants remains important [4]. With increased survival of preterm infants there is an increasing emphasis on nutritional outcomes, body composition and long-term health.

The assessment of body composition is of interest in all age groups and several models exist for describing body composition (Fig. 1), all of which look to simplify a complex process, and as such have their own pitfalls and strengths. Similarly, a multitude of methods exist for assessing body composition, each of which have their own assumptions, advantages and inadequacies.

The first values for the body composition of preterm infants come from post-mortem chemical analysis, with 191 infants analysed to date using this method [6]. Uncertainty regarding gestational age and confounding pathology associated with abnormal patterns of growth has limited these data [6,7]. These early

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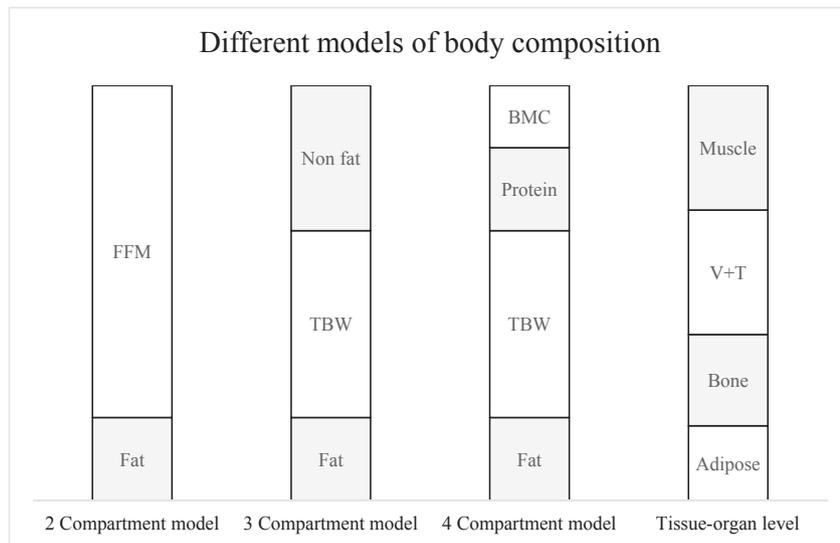
Fig. 1. A graphical demonstration of different models of body composition based on body compartments, adapted from Ellis [5]. Abbreviations: Fat-free mass (FFM), Total body water (TBW), Non-fat solids (Non-fat), Bone mineral content (BMC), Visceral organs and other tissues (V + T), Muscle (skeletal muscle).

composition studies gave an indication of fat accretion and water content of the fetus through pregnancy [6,8]. Later work, using isotope dilution described the body water content of both small and appropriate for gestational age preterm infants at birth, with authors describing an initial total body water (TBW) as 844—908 ml/kg of lean body mass reducing to around 782 ml/kg by term [9,10].

Ex-utero the preterm infant has a pattern of weight gain that drops off from their term counterparts [11—13] and reaches term equivalent age lighter and with a lower proportion of lean tissue than their term equivalent [1]. Their decreased stature, weight and head circumference persists until at least school age, although many show later catch-up [14]. Current guidance suggests that preterm infants should continue to grow at the same rate as their intrauterine counterparts and that "*in-utero growth*" should be used as a reference [15,16]. However, published growth data from preterm infants demonstrates a drop in weight standard deviation scores from birth to term equivalent age [12,13]. There is also evidence to support improved outcomes and better weight gain in preterm infants who receive higher amounts of nutrition closer to or in line with current recommendations [17,18], including lower rates of retinopathy of prematurity and bronchopulmonary dysplasia, and improved neurocognitive outcomes [19,20]. Data is conflicting and still lacking regarding the optimum nutrition and amino acid composition required to achieve optimal growth [21,22].

Growth patterns are not always linear and weight gain is not always the best marker of outcome; for example breast feeding of preterm infants is associated with better neurodevelopmental outcomes, despite breastfed infants exhibiting slower rates of growth than formula fed preterm infants [23,24]. Multiple studies have demonstrated an association between prematurity, poor initial extrauterine growth, an increased risk of obesity and increased blood pressure later in life [23]. Insulin resistance, altered lipid profiles and suboptimal metabolic outcomes including diabetes in adult life have also been associated with prematurity [23,25].

In summary therefore, the optimum pattern of growth remains unclear, with pitfalls apparent for rapid early growth as well as growth failure. Importantly though, there is evidence that quality of growth in terms of body composition, is as important as quantity. Understanding how to asses body composition in preterm infants

is therefore key to ascertaining the appropriate nutritional interventions required for optimal growth and later outcomes.

In this article we will describe the current methodology available for assessing body composition for preterm infants, the evidence base for this and the practicalities of employing the different methods.

We carried out a literature search in order to identify the current literature regarding the assessment of body composition in preterm infants (see Supplementary Table 1).

2. Body composition analysis in preterm infants

Body composition analysis can be considered as direct and indirect. Indirect methods measure a property within the body, such as bioelectrical impedance or density, with body composition values derived from these. Direct methods measure components of body composition directly, such as total body water or chemical composition analysis. The advantages, disadvantages and evidence behind these are summarized in Table 1 and the evidence table (Table 2) and described in more detail below.

2.1. Indirect methods

2.1.1. Body mass index (BMI) and ponderal index

Body mass index (weight/length^2) has been applied to preterm infants to estimate body composition. It is simple to perform and can be derived from conventionally and commonly used measures. Validated gender specific reference curves have been produced for infants of differing gestational age [26]. These are potentially useful in determining disproportionate growth failure [26]. However, BMI does not reflect the degree of adiposity that newborn infants display, and this extends to other commonly used weight/length indices including ponderal index (weight/length^3) [27,28]. Therefore, despite the relatively easy application of BMI, its addition does not currently contribute to body composition assessment in preterm infants. BMI may have some use as a composite measure although it is no more than a calculated parameter from weight and height and exact conclusions regarding body composition cannot be made.

Table 1
Comparative advantages and disadvantages of a selection of methods of body composition assessment.

Method	Measure	Assumptions	Advantages	Disadvantages
BIA/BIS	TBW (Derives FFM)	Constant values for fat content and density of fat.	Quick and relatively non-invasive. Cumulative accuracy makes useful for repeated measures.	Over-estimation of TBW. Inconsistent individual accuracy. Distribution of fat unable to be determined.
Isotope Dilution	TBW	Constant of lean tissue hydration. Tissue equilibration over given period.	Accurate measures of FFM obtainable.	Access to mass spectrometry. High associated workload. Distribution of fat unable to be determined.
ADP	Volume of subject and density	Reference figures for FM and FFM	Relatively fast and non-invasive. Accurate.	Limited data on very low weight infants. Distribution of fat unable to be determined.
DXA	Total body fat, regional body fat, bone density and FFM	Accurate and appropriate algorithms and software. Constant x-ray attenuation of FM and FFM.	Reliable and repeatable. Can give regional fat distribution as well as total FM.	Small radiation exposure. Infant must be able to tolerate scan. Can overestimate FM. Limited accuracy regarding regional fat distribution.
MRI	Volume of adipose tissue	Constant values for the fat content of adipose tissue and density of fat.	High reproducibility, accurate assessment of adipose tissue volume, assessment of regional adiposity and of intra-abdominal vs subcutaneous adiposity	Expense Not suitable for all infants due to need for transfer to scanner and time required for scan acquisition.
TOBEC	TBW	Constant values for density of fat. Geometry of subject appropriately accounted for.	Relatively non-invasive.	Limitations regarding accuracy. Distribution of fat unable to be determined.
TBK	Radioactive isotope omission (^{40}K)	Distribution of potassium within intracellular compartment of FFM		Prolonged time to obtain results. Decreasing accuracy with decreasing weight. Distribution of fat unable to be determined.

List of abbreviations: BIA- bioelectrical impedance analysis, BIS- bioelectrical impedance spectroscopy, TBW- total body water, FFM- fat-free mass, ADP- air-displacement plethysmography, DXA- dual energy x-ray absorptiometry, FM- fat mass, MRI- Magnetic resonance imaging, TOBEC- Total Body Electrical Conductivity, TBK- total body potassium.

2.1.2. Skinfold thickness

Skinfold thickness (SFT) is a relatively easy and low-cost method which attempts to assess body composition and adiposity. SFT measurement represents a well-established method of assessing subcutaneous fat, particularly in more mature infants, children and adults. It involves the tester pinching the skin at a specified location and pulling the fold away from underlying muscle. SFT callipers are then used to measure the thickness of the skin and fat held in the calliper. Measurements are taken from 4 sites [29]. The accuracy as a tool for assessing body composition has been compared against dual-energy x-ray absorptiometry (DXA) in term infants at birth and 2 and 4 months of age, showing a high degree of agreement and correlation [30]. However, the practicalities of using SFT callipers in extremely preterm infants is not without difficulty due to their size, potential fragility and underdeveloped skin.

Earlier studies have attempted to establish body fat predictive values from SFT in term infants using cadaveric analysis with known fat thickness as a reference [31]. Daly-Wolfe et al. compared (amongst other things) SFT with air displacement plethysmography (ADP) in 28 term and 28 moderately preterm infants and found the highest correlation with suprailiac SFT and body fat measurement [32].

Rodriguez et al. attempted to establish normal values in term and moderately preterm infants, but no comparison against a reference body composition method was used [33]. Other studies have used a variety of SFT measures to compare groups but with no validation measures [3]. Although this represents a relatively non-invasive method of assessment there is currently a dearth of literature regarding how the values obtained relate to fat mass (FM) or FFM.

2.1.3. Mid-upper arm circumference/Mid-thigh circumference

This method requires the examiner to measure the maximal mid-upper arm (MUAC) or mid-thigh circumference (MTC) with a non-stretch tape measure and represents a relatively quick and non-invasive procedure. This measures the entire circumference of either the mid arm or thigh including the muscle and subcutaneous fat. This method has been validated against ADP in 28 moderately preterm and 28 term infants and found to be a relatively reliable method for estimating adiposity, although with a higher correlation coefficient in term than preterm infants [32]. MUAC has also been compared to mid arm:head circumference ratio in an effort to use as a tool to assess body proportionality, however no reference measures were used to measure body composition [34]. More recently MUAC and MTC were assessed for their reproducibility and demonstration of measurable change over time in preterm infants [35]. MUAC and MTC represent easily obtainable measurements for the clinician but without well-established reference values for their relationship to FM and FFM currently offer limited utility for body composition analysis.

2.1.4. Densitometry and air displacement plethysmography

Air displacement plethysmography measures the volume of an infant by measuring the volume of air in a chamber with and without the subject present. This estimate of body volume can be used to calculate the infant's density. By using reference values for the densities of FM and FFM, it is possible to estimate the relative proportions of these in the infant. This method relies on several assumptions regarding the proportions of non-fat compartments, and the use of reference values for FM and FFM that may display some variance between individuals.

The PEA POD infant body composition device is an ADP utility developed especially for infants. This has undergone a variety of validation studies, the earliest including validation against bovine tissue phantoms (bovine based muscle and fat constructions used as a simulating object), demonstrating reproducible and accurate measurements of body fat [36]. Given the limitations of using tissue phantoms only (no breathing movements or temperature regulation) further validation studies have been carried out on live piglets at different time points with corresponding whole body lipid chemical analysis [37]. These data showed a reasonable agreement between ADP and biochemical analysis with a mean difference of 0.66% [37].

Table 2

Table of evidence for methods of body composition analysis in preterm infants including BMI, ponderal index, skin fold thickness, mid arm/mid-thigh circumference, air displacement plethysmography, bioelectrical impedance analysis, isotope dilution, dual-energy X-ray absorptiometry, magnetic resonance imaging, total body electrical conductivity and total body potassium.

Modality	Study design	Author, year	Numbers	Accuracy measure	Conclusions	Limitations and Comments
BMI	Validate BMI growth curves	Olsen, 2015 [26]	126,988		Provides reference values for BMI in preterm infants	No validation of body composition
	Validation study (ADP as reference)	Ramel, 2017 [27]	218	$r^2 = 0.26$ for BMI prediction of % body fat	No weight/length indices reflect adiposity at birth	
Ponderal index	Validation of ponderal index against skinfold thickness	Catalano, 1992 [28]	188	$r = 0.39$ for correlation between ponderal index and est. FM	Poor correlation for ponderal index and FM	Compared against skin fold thickness only
Skin fold thickness	Validation of skinfold thickness against DXA	Schmelzle, 2002 [30]	104	$r^2 = 0.963$ correlation value for SFT vs DXA for FM	With use of equation good correlation between SFT and DXA for predicting FM	Complex formula required. Population not generalisable to preterm infants.
	SFT against predicted TBF% from previous chemical analysis	Dauncey, 1977 [31]	27	41 or 52 SFT within ± 2SD of predicted value	Unable to conclude SFT measurements correlate to correct values for TBF	Uses TBF % estimation from previous chemical analysis as reference data
	Validation study (ADP as reference)	Daly-Wolfe, 2015 [32]	11 preterm 28 term infants (for SFT and ADP measures)	Preterm infants TBF% correlation ADP vs SFT: $r = 0.42$ (tricep) $r = 0.46$ (bicep) $r = 0.59$ (subscapular) $r = 0.75$ (suprailiac)	Suprailiac skin fold thickness correlates with TBF% as measured by ADP	SFT added as a secondary measure late in the study. Small numbers
Mid arm/Mid-thigh circumference	Validation study (ADP as reference)	Daly-Wolfe, 2015 [32]	28 preterm 28 term infants	Preterm infants TBF% correlation vs ADP Mid arm $r = 0.47$ Mid-thigh $r = 0.53$	Mid-arm circumference significant covariate of TBF%	Limited numbers
	Curve development for mid arm circumference vs gestational age and head circumference	Sasanow, 1986 [34]	204 infants 25–42 weeks gestational age	Mid-arm circumference highly correlated with gestational age and birthweight	Describes correlations of mid-arm circumference	No evaluation of body composition
ADP	Validation using bovine phantoms and chemical analysis	Sainz, 2003 [36]	24 phantoms	High correlation (r=>0.99) between chemical analysis and ADP for mean percentage fat	High correlation with chemical analysis in bovine phantoms	Bovine phantoms varied from 1.4 to 10 kg.
	Validation study, using live piglets and chemical analysis	Frondas-Chauty, 2012 [37]	12 piglets	Standard error of ADP estimate (1.71) $r^2 = 0.83$	Different values recorded between repeated measures, piglets = 1.03 −15.8 kg	Decreased precision with lower FM and therefore weight, piglets anaesthetised for ADP
	Validation and comparison study vs deuterium dilution	Ma, 2004 [38]	53 term infants	$r^2 = 0.76$, 95% limits of agreement between ADP and deuterium dilution −6.84 %TBF, 6.71%TBF	Good agreement with deuterium dilution and good reliability	No trend in difference over %TBF. Tested on term infants only
	Validation study vs $H_2^{18}O$ dilution and reliability study	Roggero, 2012 [39]	57 preterm and term infants	%FM values compared to $H_2^{18}O$ dilution: Standard error of estimate 1.65 and $r^2 = 0.63$	Reliable and accurate for %FM calculation	Mean infant weight 1.89 kg
	Validation in moderately preterm infants vs isotope dilution	Forsum, 2016 [40]	14 moderately preterm infants (32–35 weeks gestational age)	Limits of agreement −6.8% to +4.8% %TBF	Less reliable in smaller infants. Further studies required.	Highly inaccurate at low body fat (gave negative body fat readings)
BIA	BIA validation analysis vs DXA for estimation of FFM	Dung, 2006 [43]	118 preterm infants mean gestational age at birth = 30 weeks	Higher correlation between weight and FFM estimated via DXA than impedance index and FFM estimated via DXA	Weight is a more effective predictor of FFM than impedance index	Weight is a stronger predictor of FFM than age or impedance index
	Validation study vs $H_2^{18}O$ dilution for assessment of TBW	Tang, 1997 [44]	28, median gestational age 30.5 weeks	High correlation between isotope dilution and BIA in estimating TBW − but dependent on model used	High correlation for TBW assessment with fitted calculations	No subsequent assessment of body composition
	Validation study (ADP as reference)	Tint, 2016 [45]	173 infants at birth and 140 at week-2	Low strength of association between FFM measured by ADP at birth and BIA $r = 0.204$	Prediction of FFM via BIA not superior to simple anthropometry in Asian population	Strengthening of association at 2 weeks, but still poor FFM predictor
	Comparison study with anthropometric measures and validation against ADP	Lingwood, 2012 [46]	77 infants	Low strength of correlation between impedance and FFM at birth, 6 weeks and 3 months	BIA improved predictions of FFM at 4.5 months as compared to anthropometry	Before 3 months of age BIA did not improve prediction of FFM
Isotope/Deuterium dilution	Validation study in piglets	Rudolph, 1988 [53]	50 piglets of varying size	Body fat and protein accurately estimated from deuterium dilution	Equilibration of deuterium by 20 minutes when injected IV	Limited to piglets only

	Dilution kinetics study	Trowbridge, 1984 [54]	13 preterm infants, 10 children 6–36 m	Urine equilibrates with 6hr plasma values at 3–5hrs	Urine sampling equivalent to plasma sampling in body water studies	Limited numbers
	Dilution kinetics study	Tang, 1993 [55]	13 infants	Equilibration time variable and correlated with weight. loss after birth	In 1st week of life equilibration time variable and influenced by fluid state	Noted plateau phase did not occur (isotope declines after maximal level)
	Dilution kinetics study	Hartnoll, 2000 [9]	42 infants	Fat content of appropriate for gestational age infants = 7%	Described higher %TBW in small for gestational age perterm infants (p = 0.019)	
DXA	Validation study against chemical analysis	Brunton, 1993 [52]	20 piglets	DXA overestimated FM in small piglets by >200% (p=<0.01)	DXA overestimates FM in small piglets (mean weight 1.6 kg)	This effect decreases but is still present in larger piglets (mean weight 5.9 kg)
	Validation study against chemical analysis	Picaud, 1996 [58]	13 piglets	High accuracy of DXA for estimation of body weight and bone mineral content		
	Validation study against reference values from chemical analysis	Venkataraman, 1992 [56]	28 term infants	Over estimation of %TBF compared to reference values	Authors concluded better nutritional status may account for higher TBF% values	Chemical analysis reports on subjects with a lighter mean body weight.
	Validation study against chemical analysis (piglets only)	Rigo, 1998 [57]	8 piglets 106 infants	With correction equation developed DXA FM estimation and correlated to chemical FM r^2 = 0.99	Normative DXA data for body composition of preterm and term infants provided	DXA inaccurate without correction equations in small infants
	Reliability study and cross validation study with SFT and circumference measures	Godang, 2010 [59]	207 term infants	Reliability correlation coefficients 0.85 to 0.97 for FM prediction	Authors conclude good repeatability outcomes for DXA including FM.	Wide limits of agreement on Bland–Altmann plot for FM estimation between DXA scan 1 and 2 (c. +/– 75 g)
MRI	Adaptation of method for infants	Uthaya, 2004 [60]	>100 infants	Within-observer variation 2.83% for preterm infants	Repeatable measure of adiposity in infancy	Method well described, no validation measure used
	Evaluation of 3.0 T chemical shift MRI	Dyke, 2017 [65]	25 infants	Scan-rescan analysis showed 95% limits of agreement of 1.3% adiposity	Repeatable measure and rapid imaging (42 s)	No validation measure used, however MR considered "gold standard"
TOBEC	Validation study against chemical analysis	Fiorotto, 1987 [48]	12 infant miniature pigs	High FFM correlation (r = 0.998) and TBW (r = 0.998)	TOBEC can be used to predict TBW and FFM piglets	
	Validation study vs isotope dilution	Cochran, 1986 [47]	16 infants	Good TBW correlation r = 0.95	Some innacuracies but general concordance with isotope dilution	Significant underestimation of FFM
	Validation study vs isotope dilution	Hashimoto, 2002 [49]	40 infants	%Fat and FM showed poor correlation with TOBEC estimates (r = 0.22–0.57)	TOBEC provides unreliable estimation of FM	Disagreement for FM estimation between different isotope dilution methods
TBK	Validation study against chemical analysis (piglets only)	Spady, 1986 [68]	50 infants 11 piglets	High correlation between K$^+$ and weight (r = 0.92)	Demonstrated TBK possible and potentially accurate in <1.5 kg despite theoretical increased error	Total body potassium mean absolute difference between TBK counter and chemical analysis 7%.

List of abbreviations: BMI– Body mass index, ADP- Air displacement plethysmography, FM- Fat mass, DXA- Dual-energy X-ray absorptiometry, SFT- Skin fold thickness, TBF- Total body fat, SD- Standard deviation, BIA- Bioelectrical impedance analysis, FFM- Fat-free mass, TBW- Total body water, MRI- Magnetic resonance imaging, TOBEC- Total body electrical conductivity, TBK- Total body potassium.

ADP has been validated in multiple studies of term infants, but there are fewer data available for preterm infants [38]. This at least partially reflects the practicalities of doing it, particularly in the sick preterm infant, as subjects cannot be on respiratory support or other treatment or monitoring which prevents them being sealed in the chamber of the device from the outside. Roggero et al. assessed the inter device reliability of ADP in 70 preterm and 9 term infants demonstrating high concordance [39]. However the study only benchmarked ADP against the reference measure of deuterium dilution in 12 infants with gestational ages of 35 weeks or more at time of measurement [39]. A further study evaluated the use of ADP in 14 infants born between 32 and 35 weeks gestation [40]. The authors contrasted the ADP PEAPOD device against reference values obtained from isotope dilution and found no statistical difference between the FFM or body fat percentage references of the two measures. The lowest weight of an infant measured was 1710 g and no infants less than 33 weeks postmenstrual age (PMA) had measurements taken [40]. ADP is an emerging and potentially accurate technology. The manufacturers state that the PEAPOD is validated on preterm and term infants from 1 to 8 kg [41]. It is limited to infants from approximately 32 weeks PMA to around 6 months of life due to the size of the PEAPOD. It is only around 24 months of age that infants can be placed in the BODPOD plethysmography system, designed for larger infants, children and adults. With the absence of robust data in infants who are more than moderately premature with weights <2 kg and the practicalities of moving preterm infants from their incubators into a separate chamber for measurement this methodology currently has clear limitations [40].

Hydrodensitometry, or underwater weighing, works on similar principles to ADP. It is however impractical in the preterm infant due to the need to submerge the infant and will not be discussed in detail here.

2.1.5. Bioelectrical impedance analysis

Bioelectrical impedance analysis (BIA) is widely used for body composition assessment in older children and adults and is now accessible to large numbers of members of the public in commercially available devices. It is a non-invasive and portable measure using electrode placement. The basis of the analysis is to pass a weak alternating frequency electrical current through the subject. Impedance to the flow of current is then measured, and this will be directly related to the length of the conductor and inversely related to cross-sectional area of the conductor [42,43]. Body water constitutes the main conductive volume in humans and so BIA measurements will reflect total body water (TBW). As almost the entire TBW is located in FFM, BIA can in turn be used to estimate FFM [42] by using a prediction equation which converts the impedance value into an estimate of FFM, normally utilising a combination of height and weight [43].

Dung et al. measured 116 preterm infants with a mean gestational age at birth of 30.1 weeks with BIA and compared the estimation of FFM with that from DXA. The mean age of measurement in the study was 38.6 weeks and the authors found that weight alone was a better predictor of FFM than BIA [43]. BIA has also been validated against isotope dilution in 28 infants with a median gestational age of 30.5 weeks (range 24—38 weeks) receiving intensive care and showed a high correlation for TBW with isotope dilution [44]. In this study deuterium dilution was used as the gold standard and various BIA models, frequencies and electrode positions were reviewed to assess their accuracy [44].

Bioelectrical impedance spectroscopy (BIS) differs slightly from BIA as impedance data is collected over a range of current frequencies, rather than a single frequency as in standard BIA. BIS has been compared to isotope dilution in 91 preterm infants (with a mean gestational age of 32 weeks and at 3 weeks of life) and found a small but non-significant over estimation of TBW and extracellular water when compared to deuterium dilution [42]. A preponderance of BIS to overestimate TBW at lower weights and underestimate at higher weights amount was also found [42]. A further study compared the utility of BIA in predicting FFM in term neonates compared to simple anthropometric measures, using ADP as a reference measure in the infants [45]. The study found that BIA did not add to the prediction of FFM at birth but at 1—2 weeks of age its predictive value became significant [45]. This contrasted with an earlier study of 77 infants that suggested BIA only became a more useful predictor of FFM than routine anthropometry until 3—4.5 months of age [46].

BIA and BIS therefore represent technology that is becoming more widely available with increased portability. It is an indirect technique that is reliant on several assumed or reference variables that all have associated error, and this can affect the final individual results. The study of BIA uses the assumption that fat is non-conductive, given the increased vascularity and higher water content of fat in early life, this may not be accurate [46]. Movement artefact is also difficult to eliminate in infants, which in turn affects accuracy. BIA results are also influenced by size, gender and disease states and studies have used a variety of frequencies, models and electrode placements which decreases generalisability. The appeal of BIA is the cost and portability of the technology. Despite this more validation studies need to be done to ascertain appropriate reference values for body composition and ensure this is a reliable method before a clinical application in preterm infants can be realised.

2.1.6. Total-body electrical conductivity

Total-body electrical conductivity (TOBEC) is based on the principle that an oscillating magnetic field can determine conductivity by detecting changes in the impedance of the coil. The conductive differences between fat and lean tissue allow body composition values to be inferred from the obtained values [47].

Validation studies of TOBEC have been carried out on infant miniature piglets comparing their TOBEC signal to chemical analysis of FFM and total body water [48]. The authors concluded that TOBEC (with signal adjusted for length and individual variability accounted for in weight/length^2) was an accurate predictor of FFM and TBW [48]. Cochran et al. compared TOBEC with isotope dilution in 16 infants ranging from 2 days to 9 months and found that TOBEC underestimated FFM [47]. TOBEC was further compared with isotope dilution in 40 healthy term newborns and the authors concluded that neither FM nor percentage body fat demonstrated good correlation with the isotope benchmark [49].

There is very limited use of TOBEC for measuring body composition in preterm infants. This is due to the requirement of infants to be placed on a "carriage" for measurement as well as limited and mixed data regarding its accuracy in this group.

2.2. Direct methods of body composition analysis

2.2.1. Isotope/total body water dilution

Isotope dilution is an accurate tool for measuring FFM with well-established, internationally recognised protocols and high reliability.

The normal body water pool naturally contains a small amount of deuterium (^{2}H) [50]. A known quantity of deuterium oxide (or other stable isotope) is administered to the subject and subsequent levels measured [50]. As deuterium distributes across body tissues at the same rate as water, once it has equilibrated in the body, measuring levels in blood or urine enable estimation of total body water (TBW) [51]. Assuming that body fat is anhydrous and using a constant value for the hydration status of FFM it is possible to use

values of TBW to estimate body composition. The international atomic energy agency (IAEA) have published guidance on the use of the deuterium dilution technique [50]. The IAEA propose a "back extrapolation" technique in infants due to their high body water turnover.

Piglets have been considered appropriate comparators to preterm infants due to their similar lean tissue hydration of around 80% and low body fat stores [52]. Initial studies on piglets to refined the technique and demonstrated it be accurate in estimating body composition [53]. Trowbridge et al. showed that TBW estimates using the very small sample volumes required in preterm infants were possible, although equilibration took longer in infants than previously found in adults [54]. A strong correlation between urine and serum isotope levels were seen [54]. Tang et al. looked at 13 preterm infants born at less than 32 weeks PMA and took baseline blood and urine samples prior to the administration of oral $H_2^{18}O$, with subsequent urine and blood samples collected in order to establish equilibration and elimination kinetic [55]. Isotope dilution has also been used in a body composition study of infants 25–30 weeks gestation in a study to determine values for preterm infants both appropriate for gestational age and small for gestational age, and values were compared to reference values from cadaver studies [9].

Factors precluding its widespread use include the high associated workload as a method and the necessity for access to mass spectrometry for sample analysis. Importantly though, isotope dilution does have the ability to be used in unwell, ventilated and extremely preterm infants. This, coupled with its demonstrated accuracy and repeatability makes it a useful reference measure.

2.2.2. Dual-energy X-ray absorptiometry

Dual-Energy X-ray Absorptiometry (DXA) uses a self-contained x-ray tube that is fixed below the patient and an x-ray detector above passing a tightly collimated, narrow x-ray beam through the patient [56]. Two x-ray beams, with distinct energy peaks are passed though the subject with one energy peak absorbed largely by bone and the other by soft tissue, and a comparison is made of the absorption at each energy peak. Different models of densitometers, scan modes and software have been used and influence the accuracy and prediction of body composition [57].

This modality has been validated on piglets, showing a significant overestimation of total body fat compared to chemical analysis, although this effect was diminished on larger piglets [52,58]. Subsequent reference corrections and software adjustments have been attempted to compensate for this overestimation [57]. Another study compared body composition analysis of DXA scans with reference historical cadaveric chemical analysis. This showed similar obtained body composition values with the exception of overestimating fat in the DXA group [56]. The study of tissue phantoms suggested the greatest accuracy in assessing FM was at a tissue thickness of 10–20 cm. Thicknesses outside this range incurred increased attenuation error caused by fractional crossover of the beams. It is important to note that the majority of an infant <1.6 kg is likely to be <10 cm thickness, hence the lower accuracy in smaller subjects [52].

Various cross-validation studies have taken place on term infants or preterm infants at term age, showing a good correlation for FFM and bone mineral content but poor FM estimation compared to historical reference values determined by chemical analysis [52,57]. Godang et al. performed reliability measurements on repeated DXA scans on 50 term neonates and found a high inter-reliability between scans but only used validation against caliper and circumference measurements [59].

The assessment of bone mineral content by DXA is well established and validated, and forms part of a multi-component body composition model. The accurate assessment of bone mineral content is useful if body composition models consider TBW, lean mass, BMC and FM. If such a model is used DXA has utility in contributing to this.

Although DXA represents a highly repeatable and relatively quick way of obtaining data, it comes with associated drawbacks. The accuracy of DXA appears to diminish with increasing prematurity and the associated reality of preterm infants being nursed in incubators further reduces its practical use and accuracy. In addition, there is an associated, but small, radiation dose associated with DXA scanning which equates to c.0.03 mSv [57]. Although this is a small amount, parents are often understandably reluctant to expose their child to any extra radiation than is necessary.

2.2.3. Magnetic resonance imaging

Magnetic resonance imaging (MRI) represents a non-invasive, direct and radiation free imaging modality that has been used across age ranges to assess body composition [60]. The accuracy and high repeatability make it a gold standard for body composition assessment and it can give measures on whole body, as well as regional, distribution of adipose tissue, lean tissue and skeletal muscle quantification and the measurement of visceral adiposity [61]. This enhanced ability to report different measures of body composition is not matched in other described methods of body composition analysis for preterm infants.

MRI estimates volume of adipose tissue and this has previously been validated on adult human cadavers [62]. MRI studies require the subject to be positioned adequately and to be still to reduce movement artefact [61]. This can often be achieved in clinically stable infants via the "feed and wrap" technique [63]. Harrington et al. developed a whole-body MRI protocol that allowed measurement of adiposity in newborn term infants with an inter-user variability of <7% [64]. Uthaya et al. described results from MRI undertaken on over 100 infants, demonstrating the reliability of the technique and describing adipose tissue distribution between intra-abdominal and subcutaneous compartments [60]. The authors noted that adipose tissue MRI had previously been validated in animals, human adults and human cadavers, but did not perform this study as a validation study [60].

Newer imaging modalities have been used within MRI (such as Tesla chemical shift MRI) that allow for a more rapid image acquisition with accurate body composition assessment on term infants and preterm infants at term corrected age [65]. The assessment of adiposity has been reported as being performed either by computer algorithm or adipose tissue areas highlighted by researchers and the volume subsequently calculated. MRI has also been used as an analytical tool in nutritional interventional studies due to the high level of accuracy as well as a low inter observer variability in interpretation [21]. Body composition measured with MRI can also be coupled with concomitant brain volume analysis, and this has been used previously as a complementary measure as a proxy of brain growth and as a tool for nutritional assessment in both research settings and clinical practise [21,66].

MRI estimates adipose tissue volume in an infant and this is converted to and subsequently reported as adipose tissue mass using a conversion factor (0.9 g/cm^3) for the density of adipose tissue. This then requires a conversion to FM based on an estimation of the fat content of adipose tissue (previously calculated at 0.66 g/cm^3) introducing another potential layer for error [67].

The accuracy and spread of useful measures that MRI can offer make it an ideal tool for assessing body composition in preterm infants. The major drawbacks of the time required to be positioned and still in an MRI scanner make this impractical for a significant proportion of infants. The majority of neonatal units do not have an MRI scanner within the unit and the logistics, risk to the patient and

staff workload become more difficult if the infant is unwell or receiving mechanical ventilation.

2.2.4. Total body potassium

Total Body Potassium (TBK) measurement is based on the measurement of the small proportion of the naturally occurring radioactive isotope ^{40}K present in the body[68]. This requires a whole body counter to be placed underneath the infant who is then surrounded by at least 10 cm of lead shielding in order to isolate the infant from interference from background radiation [68]. Measurement of TBK aims to provide an accurate assessment of "functional mass", as the amount of total body potassium is proportional to cell mass and is independent of changes in hydration status. Validation studies on stillborn piglets have been undertaken and compared with chemical analysis from piglets as small as 600g [68]. The same authors performed TBK counts on 50 infants weighing between 1100 and 3600g and found an increasing standard error in lighter infants which has been borne out in other literature [68,69].

TBK measurements are limited in their utility for performing body composition analysis in preterm infants due to the long period required to obtain a count and the decreasing accuracy at lower infant weights. This method is also unsuitable for any infant that is unwell due to the need for the infant to be sealed inside the counter chamber. The associated cost and scarcity of the instruments required also diminishes the utility of TBK measurement.

3. Discussion

This paper has reviewed current methods of evaluating body composition with specific reference to recent data published in preterm infants. Despite a wealth of data on improving nutritional outcomes in preterm infants, methods for body composition analysis during care are not routinely implemented.

The majority of the methods described all rely on underlying assumptions. These include assumptions around the density of fat, the anhydrous nature of fat and the hydration percentage of FFM. Fat deposits in the neonate have a significantly higher water percentage than in later life [46]. FFM is also assumed to have a constant hydration (around = 0.732), however FFM hydration is not constant and decreases after birth, as well as in normal infancy [5]. An increased number of assumptions necessarily increases the scope for inaccuracy. This is even true of the measures that are considered as "reference measures" such as deuterium dilution or MRI. This source of error increases further in more indirect methods such as BIA, and has rendered it of uncertain usefulness in its current state for assessing body composition in preterm infants. The evidence table (Table 2) demonstrates the limits of evidence for the modalities discussed.

A significant number of the papers discussed above attempt to validate measures of body composition assessment. Many of these, however actually represent cross-validation studies, comparing two different, but both potentially inaccurate methods. Doubly-indirect methods, where one method based on assumptions is used to assess another method, are used due to practicality and cost but come with an increased risk of error. This problem radiates from their being no readily achievable "gold standard" method of body composition analysis. Subsequently, many validation studies must be interpreted as studies that do not have a reference that has watertight accuracy.

Both deuterium dilution and MRI methods for estimating body composition are among the most accurate techniques. However, both methods come with practical obstacles. MRI involves transfer of the infant into an MRI scanner and their remaining still, and deuterium dilution is a labour-intensive exercise requiring access to a mass spectrometer. Deuterium dilution does, however, represent a technique that can be used in preterm infants regardless of size, mode of respiratory support or clinical condition.

A simple FM vs FFM mass model has been employed in most of the papers discussed. However, a multi component model that combines existing technologies such as DXA, MRI and isotope dilution could give a more detailed picture of the body composition of the infant. This is complicated by the associated practicalities in using multiple assessment techniques to gain a single snapshot of body composition, which would further preclude its use in routine care.

For the assessment of body composition in preterm infants there are currently no modalities that represent accurate, quick and achievable measures. Many of the methods discussed are impractical in extremely preterm infants, have decreasing accuracy in small subjects or are impractical to perform on critically unwell infants.

All analysed methodology comes with significant drawbacks and none are currently widely performed in the routine care of infants. Measures that can be performed at the bedside and validated against MRI or isotope dilution represent a goal for future research. Further data is also required on the "ideal" body composition of preterm infants, how this changes over time and what the targets should be for when at term corrected age. There is both a lack of, and need for, a practical, cheap, reliable and repeatable bedside method. This would be of value to understand how the pattern of body composition in preterm infants changes over time, as well as being able to both guide and monitor the impact of clinical nutrition management.

Although no "perfect" method of measuring preterm infant body composition is yet defined, meaningful data can still be gathered from comparing cohorts of infants over time to review change in body composition and its response to nutritional intervention [70,71]. This has previously been performed on preterm infants undergoing serial ADP assessment from term and with measurements taken later in life using methods well validated in older infants and children [4,71].

Despite the toolset for measuring body composition in preterm infants being limited, we should not rely on weight alone as our only marker for growth, and there is a need to further develop methods for body composition assessment in this vulnerable population. MRI and isotope dilution remain the most useful tools for body composition analysis but given their associated costs and workload remain predominantly research tools. Methods based on anthropometry such as BMI, MUAC and MTC offer potential for bedside use but require careful validation against these more complex and technically challenging methods.

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Conflict of interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2018.12.033.

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