An anthropometric approach to characterising neonatal morbidity and body composition, using air displacement plethysmography as a criterion method

Jacqueline Huvanandana*, Angela E. Carberry, Robin M. Turner, Emily J. Bek, Camille H. Raynes-Greenow, Alistair L. McEwan, Heather E. Jeffery

1 School of Electrical and Information Engineering, University of Sydney, Sydney, Australia, 2 School of Public Health and Community Medicine, University of New South Wales, Sydney, Australia, 3 Sydney Medical School, University of Sydney, Sydney, Australia, 4 Sydney School of Public Health, University of Sydney, Sydney, Australia

* j.huvanandana@gmail.com

Abstract

Background

With the greatest burden of infant undernutrition and morbidity in low and middle income countries (LMICs), there is a need for suitable approaches to monitor infants in a simple, low-cost and effective manner. Anthropometry continues to play a major role in characterising growth and nutritional status.

Methods

We developed a range of models to aid in identifying neonates at risk of malnutrition. We first adopted a logistic regression approach to screen for a composite neonatal morbidity, low and high body fat (BF%) infants. We then developed linear regression models for the estimation of neonatal fat mass as an assessment of body composition and nutritional status.

Results

We fitted logistic regression models combining up to four anthropometric variables to predict composite morbidity and low and high BF% neonates. The greatest area under receiver-operator characteristic curves (AUC with 95% confidence intervals (CI)) for identifying composite morbidity was 0.740 (0.63, 0.85), resulting from the combination of birthweight, length, chest and mid-thigh circumferences. The AUCs (95% CI) for identifying low and high BF% were 0.827 (0.78, 0.88) and 0.834 (0.79, 0.88), respectively.

For identifying composite morbidity, BF% as measured via air displacement plethysmography showed strong predictive ability (AUC 0.786 (0.70, 0.88)), while birthweight percentiles had a lower AUC (0.695 (0.57, 0.82)). Birthweight percentiles could also identify low and high BF% neonates with AUCs of 0.792 (0.74, 0.85) and 0.834 (0.79, 0.88). We applied...
a sex-specific approach to anthropometric estimation of neonatal fat mass, demonstrating the influence of the testing sample size on the final model performance.

Conclusions
These models display potential for further development and evaluation in LMICs to detect infants in need of further nutritional management, especially where traditional methods of risk management such as birthweight for gestational age percentiles may be variable or non-existent, or unable to detect appropriately grown, low fat newborns.

Introduction
Neonatal body composition assessment plays an important role in characterising the nutritional and dietary status of newborn infants. Those with limited body fat face risks of increased mortality and morbidity, with undernutrition linked to inhibited long-term growth and cognitive development [1, 2]. A 2010 report from the World Health Organization (WHO) attributed undernutrition as a contributing factor in one third of child deaths under five years of age [3]. The majority of these deaths occur within the first few days of life and in low and middle income countries (LMICs) [4].

Current validated methods for measuring body composition such as air displacement plethysmography (ADP), dual x-ray absorptiometry and hydrometric methods are often impractical in LMICs, given stipulations of portability, cost and operational expertise. Anthropometric measures such as mid-upper arm circumferences (MUAC), birthweight for gestational age percentiles (henceforth birthweight percentiles) and weight-for-length Z scores are commonly used in place of these more complex techniques to gauge undernutrition [5].

Simple cut-offs have been defined for MUAC to screen for moderate and severe acute malnutrition and although they have been evaluated in older infants (aged 6–60 months) with respect to risk of mortality [6], there is a lack of similar data on its reliability and association with these risks in younger infants (under 6 months). MUAC and abdominal circumference also reflect adiposity [7]. Head circumference reflects brain volume and thus intrauterine brain development [8, 9] while chest circumference has been shown to be a significant predictor of low birthweight [10, 11], commonly used to identify infants at risk from undernutrition. Though these circumferences have not been extensively evaluated in relation to malnutrition risk, their simplicity and scalability may render them suitable candidates for screening use in LMICs. In the newborn period, birthweight percentiles and less often, weight-for-length Z scores are traditionally used to identify malnutrition, though as with all anthropometry, they may be susceptible to measurement inaccuracies. Birthweight percentiles are limited by unknown or inaccurate gestational age in LMIC settings and cannot detect the appropriately grown (10-90th percentile) low fat newborn at risk of significant morbidity [12].

ADP has often been used as the reference method in infants, and has been previously validated for this population [13–15]. Carberry et al. have reported that body fat % (BF%) as measured by ADP offers a better composite measure of poor neonatal outcome than conventional birthweight measurements [12].

Anthropometric equations for the estimation of neonatal body fat have been developed against a range of reference methods. These include total body water as measured via total body electrical conductivity [16, 17], ADP [18, 19] and dual x-ray absorptiometry [20]. A recent validation of four anthropometric equations using skinfold thickness measurements
demonstrated poor explanation of variance (R-squared ranging from 0.55–0.63) between the
developed equations and against ADP [21]. High inter-individual variability in the first few
days of life may have contributed to the poor agreement observed and there is thus a need for
cautions in interpretation of the results from predictive equations.

Most models for the estimation of neonatal body fat account for sex of the infants using a
single variable in the linear regression model (often 1 = male, 0 = female) [16–19]. This may
not allow sufficient adjustments for sex-specific anthropometry [22] and may be biased by the
predominance of either sex in the dataset used for model development.

The aim of this work was to develop anthropometric models for various applications within
the first few days post-delivery. We sought to develop logistic regression models for identifying
infants at risk of malnutrition, first using a composite measure of neonatal morbidity previ-
ously developed [12], while the second and third were to screen for low and high BF% neo-
nates measured via the reference method, ADP. We also developed a linear regression model
using a sex-specific approach to directly estimate neonatal fat mass (FM) using anthropometric
features and thus characterise nutritional status.

**Materials and methods**

**Data collection**

Eligible neonates were term (>37 weeks), singletons born at Royal Prince Alfred Hospital,
Sydney during September and October 2010. Those with major congenital abnormalities were
excluded from the study. Further details of recruitment and study data collection have been
previously reported [12]. Briefly, there were 782 eligible neonates born during the study
period, 581 of whom were enrolled in the study (75% recruitment rate). Of these, 524 neonates
had valid and complete measurements and were included for model development.

Body composition data including BF% and FM was collected via ADP (PEA POD;
COSMED, Concord, USA) and anthropometric measurements were collected within
48 hours of birth. ADP applies basic gas laws to determine the body volume from that of
the air displaced by the infant in an enclosed chamber, maintained at a constant tempera-
ture. Together with the weight measurement from the PEA POD scales, the density of
the subject can be determined and, assuming a two-compartment model and constant
density for each fat and fat-free mass, the weights of each component can be determined.
BF% measurements from ADP was used as the gold standard for subsequent model
development.

Anthropometric measurements (length and head, mid-upper arm, mid-thigh, abdominal
and chest circumferences) were standardised using skills-based educational methods and com-
petency confirmation [23]. Length was measured to approximately 0.1 cm heel to crown using
an Easy-Glide Bearing Infantometer (Perspective Enterprises, Portage, MI). Weight on day of
measurement (henceforth, weight) was measured to the nearest gram using the integrated
PEA POD scales. To simulate the accuracy of standard scales in LMICs, weight was subse-
quently rounded to the nearest 5 grams during pre-processing. Circumferences were measured
using a paper tape measure. Anthropometry and length were taken by a single researcher
except for a subset of approximately 40 infants where duplicate measurements were taken
[24].

**Ethics.** The study was approved by the Human Research Ethics Committees of Royal
Prince Alfred Hospital and the University of Sydney (HREC/09/RPAH645, SSA/09/RPAH646,
and University of Sydney Ref. No. 12732). Informed parental written consent was obtained,
and participation was voluntary.
Model development and statistical analyses

Data processing and feature selection was completed in Python (Python Software Foundation, version 2.7.11 [https://www.python.org/]), with further statistical analysis undertaken in R 3.3.1 [25].

Neonatal morbidity screening. Composite neonatal morbidity was defined on the basis of hypothermia, poor feeding and extended length of stay, as previously described [12]. This composite measure associated with undernutrition was developed using univariate logistic regression to identify the combination of variables that could identify small-for-gestational age neonates based on birthweight percentiles [12]. We completed an exhaustive search of all possible combinations of linear, inverse and square transformations of anthropometric features. Note that for all measures, gestational age was excluded from the feature set for model development as this may be unknown or unreliable in LMICs. We also examined the greatest AUC achieved by a model excluding length as a feature and compared model performance using the Delong method [26], should length boards and appropriate training not be available.

Logistic regression models were constructed using a maximum of four original features, balancing computational efficiency and model performance. Receiver-operator characteristic (ROC) curves were generated for each feature combination, providing an indication of sensitivity and specificity in identifying the class denoting composite morbidity. The final models were selected based on those which maximised the area under the ROC curves (AUC), a measure of predictive ability.

Screening of low and high BF% neonates. A similar approach was adopted for screening of low and high BF% neonates, which were defined respectively as 1 SD below and above the mean, stratified by sex. These cut-offs were consistent with previous work finding the low BF% infants exhibited greater risk of composite neonatal morbidity [12]. Logistic regression models were developed independently using an exhaustive search for combinations of transformed features that yielded the greatest AUC for identifying low and high BF% neonates.

Estimation of neonatal fat. For the estimation of neonatal fat mass (FM) using a linear regression model, relevant features and commonly-used combinations of anthropometric measures were included in the complete set of features. We sought to characterise the underlying drivers behind weight-for-length ratio (W/L) and its higher powers, W/L² (body mass index) and W/L³ (ponderal index) [27]. Inclusion of all three ratios would introduce multiple collinearity effects and thus, factor analysis was applied to determine the ratio for inclusion in the complete feature set. Weight rather than birthweight was used in these ratios given the weight loss observed in the first few postnatal days [28] and the varying ages at measurement.

To mitigate the influence of varying ranges, all continuous variables were standardised (mean = 0, SD = 1). Feature selection was then undertaken using recursive feature elimination, ranking features by their linear model coefficients, repeatedly removing them from the model and determining the optimal set of features. This was determined through minimisation of the root mean squared error score (RMSE) based on 10-fold cross-validation of the dataset. Once the set of features was determined, model fitting was completed on the sex-specific subgroups with the non-standardised features.

The performance of the sex-specific models was compared against combined sex models fitted to the determined feature set combined with a binary variable denoting sex (male = 1, female = 0). For the combined sex model, we also included sex-anthropometry interaction terms and examined the effect on the final model.
Model evaluation

Logistic regression models. We compared the developed logistic regression models against common anthropometric indices using the Delong method for comparison of correlated ROC curves [26]. Logistic regression models were further evaluated using leave-one-out cross-validation, with models rejected if the AUC from this was less than or equal to 0.5. This involved using all samples except one in fitting the logistic regression model and subsequently evaluating the predicted probability of the omitted sample. The process was repeated for all samples and the probabilities used to construct a ROC curve for evaluation of the leave-one-out cross validation AUC.

Linear regression models for neonatal fat mass estimation. To investigate the motivation for sex-specific model fitting, we compared anthropometric and other characteristic differences between male and female neonates. We applied a student’s t-test for continuous variables such as birthweight, length and head circumference and a chi-squared test for categorical variables. We then compared the performance of sex-specific models for a range of test sample sizes by first dividing the dataset into sex-stratified halves, a training and a testing set. The male and female portions of training set were used to fit sex-specific linear estimation models while an equal-sized subset containing an even distribution of sexes was used to fit the combined sex model. We continually and randomly restricted the testing set, determining RMSE of fat-free mass, FM and BF% estimations for each sample size over 100 iterations. The overall process was repeated for 10 divisions of training and testing sets and the mean RMSE calculated for a given sample size.

Results

The characteristics of the population are summarised in Table 1, with continuous variables expressed as mean and standard deviation (SD) and categorical variables as percentages (%).

Logistic regression models

We developed logistic regression models to screen for a composite measure of neonatal morbidity as well as low and high BF% neonates.

Neonatal morbidity screening. From the exhaustive search of all possible 4-feature models to screen for neonatal morbidity, the following features were frequently included in high scoring models: weight or birthweight, chest or abdominal circumference, mid-thigh circumference and length. The greatest AUC achieved was 0.740 (0.63, 0.85) by the combination of birthweight, length, chest and mid-thigh circumferences (Fig 1). The composite feature is defined in Eq 1, where circumference is denoted by \( circ \).

\[
CF_{morbidity} = \frac{\text{birthweight} \times \text{chest}_{circ}}{\text{length} \times \text{thigh}_{circ}}
\]

The greatest AUC for a model without length as a feature was 0.736 (0.62, 0.85) and combined the product of birthweight and abdominal circumferences, divided by that of head and mid-thigh circumferences. The AUC score difference between the reported model (Eq 1) and this length-free model was minimal and not significant.

We compared the ROC curves of the developed models with those of commonly used metrics. Table 2 reports the AUC, standard error and p-values from the Delong method for comparing correlated ROC curves [26]. The developed model (AUC 0.740 (0.63, 0.85)) displayed a high degree of overlap with the BF% ROC curve (AUC 0.786 (0.70, 0.88)) which exhibited the
next highest AUC. MUAC had a significantly poorer AUC of 0.655 (0.51, 0.80) \((p = 0.046)\) than that of BF%.

**Screening of low and high BF% neonates.** The logistic regression models for low and high BF% exhibited AUCs of 0.827 (0.78, 0.88) and 0.834 (0.79, 0.88) respectively (Fig 1). The features used to construct the corresponding composite features are summarised in Eqs 2 and 3.

\[
CF_{\text{low-fat}} = \frac{\text{weight}^2}{\text{length} \times \text{chest}_{\text{circ}}} \tag{2}
\]

\[
CF_{\text{high-fat}} = \frac{\text{head}_{\text{circ}} \times \text{length}^2}{\text{birthweight} \times \text{weight}} \tag{3}
\]

**Linear regression models**

**Feature selection.** Factor analysis was applied to the W/L ratio and its 2 higher powers to determine which of the ratios to be included in the set for subsequent feature selection and to avoid multiple collinearity effects. Results showed that 89.5% of the variance could be explained by a single underlying factor, driven mostly by W/L^2 (R-squared > 0.99). This ratio exhibited a R-squared of 0.874 with W/L and 0.809 with W/L^2. R-squared between W/L and W/L^2 was 0.472.

Recursive feature elimination identified the combination of weight, head circumference, mid-thigh circumference and W/L^2 as the optimal set of features for neonatal FM estimation.

**Table 1. Comparisons of anthropometry and body composition measures for male and female neonates.** An independent t-test (two-tailed) was applied to compare continuous variables and a chi-squared test for categorical variables (neonatal composite morbidity and proportions in each fat range). Statistical significance is denoted by \(*p<0.05\), \(**p<0.001\).

| Characteristics                  | Male         | Female       | p       |
|-----------------------------------|--------------|--------------|---------|
| n                                 | 272          | 252          |         |
| Birthweight (g)                   | 3533 ± 475   | 3366 ± 411   | <0.001*** |
| Weight (g)                        | 3359 ± 448   | 3193 ± 398   | <0.001*** |
| Length (cm)                       | 50.4 ± 1.9   | 49.2 ± 1.7   | <0.001*** |
| Gestational age (weeks)           | 39.6 ± 1.1   | 39.5 ± 1.2   | 0.120   |
| Age at measurement (days)         | 1.17 ± 0.6   | 1.19 ± 0.6   | 0.695   |
| Mid-upper arm circumference (cm)  | 11.0 ± 1.0   | 10.9 ± 0.9   | 0.0897  |
| Head circumference (cm)           | 35.0 ± 1.1   | 34.1 ± 1.1   | <0.001*** |
| Mid-thigh circumference (cm)       | 15.1 ± 1.3   | 15.0 ± 1.2   | 0.568   |
| Abdominal circumference (cm)      | 30.6 ± 2.2   | 30.5 ± 2.0   | 0.511   |
| Chest circumference (cm)          | 32.7 ± 1.8   | 32.4 ± 1.6   | 0.023*  |
| Neonatal composite morbidity* (%) | 3.7          | 3.2          | 0.176   |
| Proportion low fat (%)            | 12.5         | 14.7         | 0.100   |
| Proportion moderate fat (%)       | 71.7         | 71           | 0.199   |
| Proportion high fat (%)           | 15.8         | 14.3         | 0.143   |
| Body fat %                        | 8.89 ± 4.0   | 10.09 ± 3.9  | <0.001*** |
| Fat mass (g)                      | 310 ± 167    | 332 ± 155    | 0.119   |

*Composite neonatal morbidity defined as a composite of hypothermia, poor feeding and extended length of stay. Previously described in [12]

https://doi.org/10.1371/journal.pone.0195193.t001
Linear estimation of neonatal fat mass. The sex-specific and combined sex linear regression model coefficients are detailed in Table 3. Weight and $W/L^2$ were significant predictors of male and female neonatal FM, whereas head circumference was significant ($p = 0.018$) in the male population only. All three models exhibited similar R-squared statistics of approximately 0.786, 0.726, and 0.655 for male, female, and combined sex models, respectively. The ROC curves for each of the developed (CF) models and other comparative models for the identification of composite neonatal morbidity [12], low BF% and high BF%, respectively. Comparative models include those fitted using body fat percentage (BF%), weight for length (W/L), mid-upper arm circumference (MUAC) and birthweight percentile (BW_pctl). Corresponding boxplots in (b), (d) and (f) show the predicted probabilities from the corresponding CF logistic regression models for each of the two classes: negative (N) and positive (M: composite neonatal morbidity, L: low BF% and H: high BF%).

https://doi.org/10.1371/journal.pone.0195193.g001
For the combined sex model, all variables including sex were significant predictors of neonatal fat mass. There were no significant interactions between sex and anthropometric features (p > 0.3).

**Model evaluation.** To characterise model performance, we evaluated RMSE and R-squared statistics for both sex-specific and combined sex models for a range of test sample sizes.

Table 2. Comparison of receiver-operator characteristic curves for the prediction of composite neonatal morbidity, low and high fat BF% using the Delong method [26]. For each pair of logistic regression models, the standard error and p-value from the Delong method for ROC curve comparison are reported [26]. Comparisons include BF% from ADP, weight-for-length-for-gestational age (W/L/GA), weight-for-length-squared (W/L^2), mid-upper arm circumference (MUAC), birthweight percentiles (BW_pctl) and developed composite feature (CF). Statistical significance is denoted by *p<0.05, **p<0.01***p<0.001.

| Model                      | AUC (95% CI)     | W/L^2   | MUAC    | BW_pctl | CF       |
|----------------------------|------------------|---------|---------|---------|----------|
| **Composite neonatal morbidity** |                  |         |         |         |          |
| BF%                        | 0.786 (0.70, 0.88) | 0.555, 0.24 | 0.066, 0.046* | 0.062, 0.141 | 0.061, 0.453 |
| W/L^2                      | 0.726 (0.61, 0.84) |         | 0.061, 0.239 |          | 0.04, 0.729 |
| MUAC                       | 0.655 (0.51, 0.80) |         | 0.047, 0.510 |          | 0.07, 0.227 |
| BW_pctl                    | 0.695 (0.57, 0.82) |         | 0.067, 0.548 | 0.071, 0.227 | 0.051, 0.376 |
| CF                         | 0.740 (0.63, 0.85) |         |         |         |           |
| **Low BF%**                |                  |         |         |         |          |
| W/L/GA                     | 0.817 (0.77, 0.87) | 0.012, 0.174 | 0.028, 0.006** | 0.011, 0.031* | 0.014, 0.455 |
| W/L^2                      | 0.800 (0.75, 0.85) |         | 0.029, 0.035* |          | 0.019, 0.141 |
| MUAC                       | 0.740 (0.68, 0.80) |         | 0.021, 0.712 |          | 0.028, 0.002* |
| BW_pctl                    | 0.792 (0.74, 0.85) |         | 0.030, 0.076 | 0.028, 0.002* | 0.018, 0.056 |
| CF                         | 0.827 (0.78, 0.88) |         |         |         |           |
| **High BF%**               |                  |         |         |         |          |
| W/L/GA                     | 0.836 (0.79, 0.88) | 0.011, 0.06 | 0.026, *** | 0.010, 0.832 | 0.047, 0.961 |
| W/L^2                      | 0.816 (0.77, 0.87) |         | 0.028, 0.001** | 0.177, 0.309 | 0.049, 0.715 |
| MUAC                       | 0.726 (0.67, 0.78) |         | 0.026, *** |          | 0.047, 0.02* |
| BW_pctl                    | 0.834 (0.79, 0.88) |         | 0.007, 0.202 | 0.028, 0.002* | 0.044, 0.998 |
| CF                         | 0.834 (0.79, 0.88) |         |         |         |           |

Table 3. Linear regression model coefficients for estimation of neonatal fat mass in grams.

| Variable | Intercept | Weight (g) | circ_mean (cm) | circ_high (cm) | W/L^2 (g/cm^2) | Sex |
|----------|-----------|------------|---------------|---------------|----------------|-----|
| **Male** |           |            |               |               |                |     |
| Coefficient | -309.54  | 0.226      | -19.93        | 15.74         | 243.53         | -   |
| SE       | 261.74    | 0.035      | 8.35          | 8.42          | 105.11         | -   |
| p        | 0.238     | <0.001***  | 0.018*        | 0.063         | 0.021*         | -   |
| **Female** |          |            |               |               |                |     |
| Coefficient | -677.90  | 0.190      | -8.280        | 11.47         | 390.141        | -   |
| SE       | 270.16    | 0.038      | 8.705         | 7.95          | 105.060        | -   |
| p        | 0.013*    | <0.001***  | 0.342         | 0.150         | <0.001***      | -   |
| **Combined sex** |         |            |               |               |                |     |
| Coefficient | -445.45  | 0.212      | -14.857       | 13.191        | 312.795        | -47.21 |
| SE       | 186.35    | 0.0255     | 6.008         | 5.780         | 74.00          | 10.14 |
| p        | 0.017**   | <0.001***  | 0.014*        | 0.023*        | <0.001***      | <0.001*** |

R-squared statistics for the male, female and combined sex regression models were 0.589, 0.591 and 0.590, respectively. Units for each variable are shown in parentheses, with coefficients, standard error (SE) and p value from linear regression model fitting shown for the sex-specific and combined sex models. The variable denoting sex comprises 1 = male and 0 = female. Statistical significance is denoted by *

*<p<0.05, **p<0.01***p<0.001.

https://doi.org/10.1371/journal.pone.0195193.t003
sizes, displayed in Fig 2. The R-squared statistics for combined sex and sex-specific models were similar, as also reflected by model fit to the complete dataset in Table 3 (R-squared combined: 0.590, male: 0.589, female: 0.591), though sex-specific models tended to exhibit a lesser RMSE in the estimation of FM, FFM and BF%.

**Discussion**

**Summary of findings**

In this study, we developed and evaluated a range of models for characterising neonatal nutritional status. Using a composite neonatal morbidity, we developed a model to detect undernourished newborns which exhibited an AUC of 0.740 (0.63, 0.85). We also examined the greatest AUC achieved by a model excluding length as a feature and found that a combination of birthweight, abdominal, head and mid-thigh circumferences yielded a AUC of 0.736 (0.62, 0.85).
Models for identifying low and high BF% neonates exhibited AUCs of 0.827 (0.78, 0.88), and 0.834 (0.79, 0.88), respectively. This suggests potential for application in LMICs, offering a low-cost and scalable approach for screening at birth, though this may depend on measurement accuracy and reproducibility, availability of appropriate equipment, training and evaluation of competency [24]. These factors considered, the models could nevertheless motivate the routine collection of anthropometric measurements, especially considering the socio-economic transition that many LMICs are undergoing, with both under and overnutrition present at birth.

Neonatal morbidity screening

The combination of birthweight, length, chest and mid-thigh circumferences exhibited the greatest AUC of 0.740 (0.63, 0.85) to identify neonatal morbidity. AUC from leave-one-out cross-validation was 0.698. It was interesting to note the presence of the birthweight-to-length ratio, possibly corrected for chest and mid-thigh circumferences as a potential marker for composite neonatal morbidity. Neither of these circumferences have been routinely used as a marker of adiposity, though chest circumference has been identified as a strong predictor of low birthweight [10] and there have been similar correlations reported between mid-thigh circumference, antenatal nutrition [29] and birthweight [30].

The model excluding length as a feature exhibited a AUC of 0.736 (0.62, 0.85) and did not exhibit a significantly poorer performance than that where length was included. Given the more expensive and bulkier nature of length boards compared with paper tape measures for circumference measurements, this length-free composite measure may be preferred for use in LMICs.

MUAC is a simple and fast measurement widely-used to detect undernutrition in LMICs. Though MUAC in infants under 6 months may have predictive value for infant death [31], the difference between the ROC curves for MUAC and BF% would suggest that prediction of morbidity as defined by our composite measure in this population may be improved by accurate measurement of BF% if available, or by using our anthropometric model, subject to further evaluation and validation in an independent dataset. Our model exhibited an AUC of 0.740 (0.63, 0.85) which was the next highest to BF%, among other comparisons including W/L (0.726 (0.61, 0.84)), birthweight percentiles (0.695 (0.57, 0.82)) and MUAC (0.655 (0.51, 0.80)) (Fig 1, Table 2).

Screening of low and high BF% neonates

Both models yielding the greatest AUC for screening low and high BF% contained a ratio between weight and length in some form, with the low BF% neonates consisting of weight, length and chest circumference and the high BF% containing birthweight, weight, length and head circumference.

The developed model for screening low BF% neonates exhibited a AUC of 0.827 (0.78, 0.88), greater than that of the W/L for gestational age model, though the difference was not statistically-significant. In contrast, the W/L for gestational age exhibited the greatest AUC of 0.836 (0.79, 0.88) for identifying high BF% neonates, consistent with previous reports of increasing BF% with increasing gestational age [32], due to rapid fat gain late in gestation [33]. This is followed by both the composite feature and the birthweight percentile models with AUCs of 0.834 (0.79, 0.88), suggesting that for this cohort, accounting for multiple anthropometric measures performs no better than considering the birthweight percentile alone, despite the latter being considered a limited predictor of morbidity and mortality. Such percentiles are nevertheless problematic as gestational age is frequently unreliable in LMICs.
Linear estimation of neonatal fat

Anthropometric models for the estimation of neonatal fat mass developed by Catalano et al. [16], Schmelze et al. [20] and Deierlein et al. [18] exhibit an R-squared of 0.84, 0.94 and 0.81, respectively. A direct comparison between our models and those developed previously is difficult given the lack of corresponding skinfold thickness measurements, differences in the criterion method for FM estimation and demographic variations. Our developed models exhibited an R-squared of 0.59 for both male and female populations, accounting for a lower variance in FM than previous reported models. This highlights the important contribution and correlation of skinfold measurements to FM estimation, though without considerable practice, these measures may have poor reproducibility amongst multiple users [34].

Comparisons of sex-specific anthropometry revealed that males tended to be longer and heavier than females, with larger head and chest circumferences on day of measurement (Table 1). The male neonates in our cohort also had lower BF%, which also remains consistent with previous studies [32]. In the anthropometric models previously developed for estimation of body composition [16–20], sex is often not included or adjusted for using a binary variable in the linear regression model. This adjustment for sex differences in anthropometry and body composition may well be inadequate, especially for robust model development. Though variability in body composition measures were similar across both sex-specific and combined sex models, we observed a greater estimation error for the combined sex models (Fig 2) and a different combination of variables that were significantly predictive of fat mass between male and female-specific models (Table 3).

The population-specific nature of body composition also extends beyond sex; there are also differences between infants of different ethnicities [35, 36], that may be genetic, biological, environmental or composites of these. Body composition is also influenced by perinatal characteristics, infant feeding methods [37] and days after birth, with infants undergoing an initial weight loss particularly during the first four postnatal days [28]. In this period, energy intake is limited until breastfeeding is established by day 5 when fat stores are no longer needed as alternative energy stores and energy is expended to the requirements of extrauterine life including thermoregulation, fluid balance and respiration [38, 39]. These factors contribute to high variability observed in the neonatal period and thus need to be considered in robust model development and application.

The changes in RMSE and R-squared with testing set size in Fig 2 demonstrate the influences of both training and testing sets on the performance and robustness of the final model. These results support sex-specific model fitting, highlighting the potentially inflated error from combining both male and female subjects in the same model with a single variable adjusting for sex. It also aids in establishing a context for model evaluation, with different target variables (fat-free mass, FM and BF%) tending towards different degrees of correlation with anthropometric variables. An understanding of model fit and robustness extends beyond R-squared which characterise the relationship between two variables, rather than agreement or differences between them. Despite similar R-squared statistics across both combined sex and specific model estimations of neonatal body composition, the RMSE tended to be lower for sex-specific models.

Strengths and limitations

The strengths of this study include the large sample size of neonates and the use of ADP as the criterion method which has been specifically validated in this population [13–15]. The model development for detecting neonatal morbidity was limited by the low representation (3.4%) of neonatal morbidity [12]. Although we approached this by using leave-one-out cross-validation...
for model evaluation, there is a need for further evaluation on a population with higher neonatal morbidity. The optimal measurement of morbidity may change in a different population, as the composite score used for this analysis was based on a logistic regression analysis of potentially significant factors in the given population [12]. This dataset would ideally be sourced from LMICs where demographic characteristics align with the intended area of application for the model.

Due to the accurate measurement of weight using the integrated PEA POD scale, further validation of accurately measuring weight for the models may be required. Anthropometry including length and circumference measurements were also not obtained in duplicate except for a small subset of approximately 40 infants [24].

Body composition estimation in the neonatal population is especially difficult given the varying criterion methods, the growing evidence to suggest poor agreement between gold standards in this population [40] and the variation in body composition during the first few days of life. The model development and potentially, predictive ability, may be improved by adjusting for additional features such as skinfold measurements, which were not collected in this dataset. Evaluation in an independent population to gauge estimation error and robustness of predictive ability for neonatal morbidity, low and high BF% infants is also needed.

Conclusions
The greatest burden of neonatal and infant undernutrition and morbidity lies in LMICs, where there is an urgent need for suitable, simple approaches to monitor and manage infants. Using combinations of anthropometric features, we fitted models for application in these settings that could detect composite morbidity with an AUC of 0.740 (0.63, 0.85) in neonates in the first few days of life. Composite features involving simple, accurate, easily-measured anthropometric features could also identify low BF% infants with an AUC of 0.827 (0.78, 0.88). These models have demonstrated potential for further development and evaluation in LMICs for identifying infants in need of further nutritional management.

Supporting information
S1 Dataset. Neonatal anthropometric data.
(CSV)

Acknowledgments
The PEA POD donors included TENIX (Sydney, Australia) and an anonymous donor to the University of Sydney. The authors thank Royal Prince Alfred Hospital medical and nursing staff and Lucia Wang, Cheryl Au, Elizabeth Hayles and Erin Donnelley for assisting with data collection. We thank the parents for their assistance in this research.

Author Contributions
Conceptualization: Camille H. Raynes-Greenow, Heather E. Jeffery.
Data curation: Angela E. Carberry, Heather E. Jeffery.
Formal analysis: Jacqueline Huvanandana, Robin M. Turner, Emily J. Bek, Alistair L. McEwan.
Investigation: Jacqueline Huvanandana.
Methodology: Jacqueline Huvanandana, Robin M. Turner.
**Project administration:** Angela E. Carberry.

**Supervision:** Robin M. Turner, Camille H. Raynes-Greenow, Alistair L. McEwan, Heather E. Jeffery.

**Writing – original draft:** Jacqueline Huvanandana.

**Writing – review & editing:** Jacqueline Huvanandana, Angela E. Carberry, Robin M. Turner, Emily J. Bek, Camille H. Raynes-Greenow, Alistair L. McEwan, Heather E. Jeffery.

**References**

1. Levitsky DA, Strupp BJ. Malnutrition and the brain: changing concepts, changing concerns. The Journal of Nutrition. 1995; 125(8):2212S.

2. Prado EL, Dewey KG. Nutrition and brain development in early life. Nutrition Reviews. 2014; 72(4):267–84. https://doi.org/10.1111/nure.12102 PMID: 24684384

3. UNICEF. Facts for life: UNICEF; 2010.

4. WHO. World Health Statistics 2010: World Health Organization; 2010.

5. WHO. WHO child growth standards and the identification of severe acute malnutrition in infants and children: a Joint Statement by the World Health Organization and the United Nations Children’s Fund. Geneva: World Health Organization. 2009.

6. Pelletier DL, Frongillo EA. Changes in child survival are strongly associated with changes in malnutrition in developing countries. The Journal of Nutrition. 2003; 133(1):107–19. PMID: 12514277

7. Yajnik C, Fall C, Coyaji K, Hirve S, Rao S, Barker D, et al. Neonatal anthropometry: the thin–fat Indian baby. The Pune maternal nutrition study. International Journal of Obesity. 2003; 27(2):173–80. https://doi.org/10.1038/sj.ijo.802219 PMID: 12586996

8. Cooke R, Lucas A, Yudkin P, Pyse-Davies J. Head circumference as an index of brain weight in the fetus and newborn. Early human development. 1977; 1(2):145–9. PMID: 617306

9. O’Connell EJ, Feldt RH, Stickler GB. Head circumference, mental retardation, and growth failure. Pediatrics. 1965; 36(1):62–6.

10. Thi HN, Khanh DKT, Thu HLT, Thomas EG, Lee KJ, Russell FM. Foot length, chest circumference, and mid upper arm circumference are good predictors of low birth weight and prematurity in ethnic minority newborns in Vietnam: A hospital-based observational study. PloS one. 2015; 10(11):e0142420. https://doi.org/10.1371/journal.pone.0142420 PMID: 26555356

11. Goto E. Meta-analysis: identification of low birthweight by other anthropometric measurements at birth in developing countries. Journal of epidemiology. 2011; 21(5):354–62. https://doi.org/10.2188/jea.JE20100182 PMID: 21768738

12. Carberry AE, Raynes-Greenow CH, Turner RM, Askie LM, Jeffery HE. Is body fat percentage a better measure of undernutrition in newborns than birth weight percentiles? Pediatric Research. 2013; 74(6):730–6. https://doi.org/10.1038/pr.2013.156 PMID: 24002331

13. Ellis KJ, editor Evaluation of body composition in neonates and infants. Seminars in Fetal and Neonatal Medicine; 2007: Elsevier.

14. Ellis KJ, Yao M, Shyapalo RJ, Urlando A, Wong WW, Heird WC. Body-composition assessment in infancy: air-displacement plethysmography compared with a reference 4-compartment model. The American Journal of Clinical Nutrition. 2007; 85(1):90–5. PMID: 17209182

15. Ma G, Yao M, Liu Y, Lin A, Zou H, Urlando A, et al. Validation of a new pediatric air-displacement plethysmograph for assessing body composition in infants. The American Journal of Clinical Nutrition. 2004; 79(4):653–60. PMID: 15051161

16. Catalano PM, Thomas AJ, Avallone DA, Amini SB. Anthropometric estimation of neonatal body composition. American Journal of Obstetrics and Gynecology. 1995; 173(4):817–8. PMID: 7485315

17. Lingwood BE, van Leeuwen A-MS, Carberry AE, Fitzgerald EC, Callaway LK, Colditz PB, et al. Prediction of fat-free mass and percentage of body fat in neonates using bioelectrical impedance analysis and anthropometric measures: validation against the PEA POD. British Journal of Nutrition. 2012; 107(10):1545–52. https://doi.org/10.1017/S0007114511004624 PMID: 21917194

18. Deierlein AL, Thornton J, Hull H, Paley C, Gallagher D. An anthropometric model to estimate neonatal fat mass using air displacement plethysmography. Nutrition & Metabolism. 2012; 9(1):1.
19. Aris I, Soh S, Tint M, Liang S, Chinnadurai A, Saw S, et al. Body fat in Singaporean infants: development of body fat prediction equations in Asian newborns. European Journal of Clinical Nutrition. 2013; 67(9):922–7. https://doi.org/10.1038/ejcn.2013.69 PMID: 23549200

20. Schmelzle HR, Fusch C. Body fat in neonates and young infants: validation of skinfold thickness versus dual-energy X-ray absorptiometry. The American Journal of Clinical Nutrition. 2002; 76(5):1096–100. PMID: 12399284

21. Cauble JS, Dewi M, Hull HR. Validity of anthropometric equations to estimate infant fat mass at birth and in early infancy. BMC Pediatrics. 2017; 17(1):88. https://doi.org/10.1186/s12887-017-0844-6 PMID: 28347278

22. Rodriguez G, Samper MP, Ventura P, Moreno LA, Olivares JL, Pérez-González JM. Gender differences in newborn subcutaneous fat distribution. European Journal of Pediatrics. 2004; 163(8):457–61. https://doi.org/10.1007/s00431-004-1468-z PMID: 15168110

23. Jeffery H, Henderson-Smart D, Hill D. Competency-based learning in neonatology. Medical Education. 1996; 30(6):440–4. PMID: 9217907

24. Wood AJ, Raynes-Greenow CH, Carberry AE, Jeffery HE. Neonatal length inaccuracies in clinical practice and related percentile discrepancies detected by a simple length-board. Journal of Paediatrics and Child Health. 2013; 49(3):199–203. https://doi.org/10.1111/jpc.12119 PMID: 23432733

25. R Core Team. A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing; 2013.

26. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics. 1988:837–45. PMID: 3203132

27. Koo WW, Walters JC, Hockman EM. Body composition in neonates: relationship between measured and derived anthropometry with dual-energy X-ray absorptiometry measurements. Pediatric research. 2004; 56(5):694–700. https://doi.org/10.1203/01.PDR.0000142587.59238.BD PMID: 15371563

28. Roggero P, Gianni ML, Orsi A, Piemontese P, Amato O, Moioli C, et al. Neonatal period: body composition changes in breast-fed full-term newborns. Neonatology. 2010; 97(2):139–43. https://doi.org/10.1159/000297967 PMID: 19776647

29. Donnelly JM, Walsh JM, Byrne J, Molloy E, McAuliffe F. Impact of maternal diet on neonatal anthropometry: a randomized controlled trial. Pediatric Obesity. 2015; 10(1):52–6. https://doi.org/10.1111/2047-6310.2013.00216.x PMID: 24443392

30. Lawoyin T. Validation and use of a simple device to identify low birth weight babies at birth. African Journal of Medicine and Medical Sciences. 1997; 27(3–4):143–5.

31. Mwangome MK, Fegan G, Fulford T, Prentice AM, Berkley JA. Mid-upper arm circumference at age of routine infant vaccination to identify infants at elevated risk of death: a retrospective cohort study in the Gambia. Bulletin of the World Health Organization. 2012; 90(12):887–94. https://doi.org/10.2471/BLT.12.109009 PMID: 23284194

32. Hawkes CP, Hourihane JOB, Kenny LC, Irvine AD, Kiely M, Murray DM. Gender-and gestational age-specific body fat percentage at birth. Pediatrics. 2011; 128(3):e645–e51. https://doi.org/10.1542/peds.2010-3856 PMID: 21824882

33. Flynn M, Goldberg G, Prentice A, Cole T. Aetiology of obesity III: critical periods for the development of obesity. Obesity: The report of the British Nutrition Foundation Task Force. 1999:45–60.

34. West J, Manchester B, Wright J, Lawlor DA, Waiblinger D. Reliability of routine clinical measurements of neonatal circumferences and research measurements of neonatal skinfold thicknesses: findings from the Born in Bradford study. Paediatric and perinatal epidemiology. 2011; 25(2):164–71. https://doi.org/10.1111/j.1365-3016.2010.01181.x PMID: 21281329

35. Singh KA, Huston-Presley LP. Birth weight and body composition of neonates born to Caucasian compared with African-American mothers. Obstetrics and Gynecology. 2010; 115(5):998. PMID: 20410774

36. Paley C, Hull H, Ji Y, Toro-Ramos T, Thornton J, Bauer J, et al. Body fat differences by self-reported race/ethnicity in healthy term newborns. Pediatric obesity. 2015.

37. Sauder KA, Kaar JL, Starling AP, Ringham BM, Glueck DH, Dabelea D. Predictors of Infant Body Composition at 5 Months of Age: The Healthy Start Study. The Journal of Pediatrics. 2017; 183:94–9. e1. PMID: 28161200

38. Regnault N, Botton J, Blanc L, Hankard R, Forhan A, Goua V, et al. Determinants of neonatal weight loss in term-infants: specific association with pre-pregnancy maternal body mass index and infant feeding mode. Archives of Disease in Childhood—Fetal and Neonatal Edition. 2011;(96):F217–F22.

39. Fonseca M, Severo M, Santos A. A new approach to estimating weight change and its reference intervals during the first 96 hours of life. Acta Paediatrica. 2015; 104(10):1028–34. https://doi.org/10.1111/apa.12894 PMID: 25488548
40. Wrottesley S, Pisa P, Micklefield L, Pettifor J, Norris S. A comparison of body composition estimates using dual-energy X-ray absorptiometry and air-displacement plethysmography in South African neonates. European Journal of Clinical Nutrition. 2016; 70(11):1254–8. https://doi.org/10.1038/ejcn.2016.91 PMID: 27245207