



Neonatal Percentile Curves: A Multivariate Normal Probability Density Approach

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Abstract

Background and Objectives: Percentile growth charts have been known as the standard to measure neonatal and child growth. However, there are several problems users face when using and analyzing percentile charts. Current univariate growth charts are generalized to global populations. To optimally identify high-risk neonates, we outline a multivariate approach. We first hypothesize that morphometrics will vary according to demographics such as location, gender, race, etc. Further, we propose creating percentile charts involving any number of growth parameters for identifying high-risk individuals for specific locations and populations based on the Multivariate Normal Probability Density.

Methods: We obtained data from neonates (38 to 42 weeks) involving four morphometrics (body length, chest circumference, cephalic perimeter and weight) from three locations: Phoenix and Yuma, AZ, and Jackson, WY. We investigated whether neonatal morphometrics differed significantly with respect to location, gender, and race; and that assumptions of the multivariate approach were met, justifying the procedure. We then applied the multivariate approach for different combinations of morphometrics for specific populations. Ten scenarios were designed to evaluate and compare percentile computations for different demographics and morphometrics. Results: Neonatal morphometrics varied significantly for different genders, races and locations. Morphometric data presented no serious deviation from normality and assumptions of the multivariate approach were supported. The analysis of different combinations of the four morphometrics for Yuma Hispanics demonstrated the importance of our procedure in identifying high-risk neonates over the current univariate charts. MANOVAs, ANOVAs, and Independent-samples t-Tests generally demonstrated that morphometric data varied for different populations based on demographics: Location effect was significant on Body Length and Weight; Gender effect was significant on Body Length and Weight; Race effect was significant on Body Length and Weight. Location did not significantly affect Cephalic Perimeter, while Gender and Race did. Two-variable percentile curves were constructed and percentiles (for more than two variables) were calculated for various scenarios and compared to conventional charts.

Conclusions: Demographic differences demonstrate that the multivariate percentile approach may better identify high-risk individuals because percentile calculations involve more morphometric information and the multivariate procedure accounts for inter-correlations. Specific locations throughout the world could potentially utilize our approach for global validation for more reliable identification of high-risk neonates. Furthermore, this user-friendly approach could be used in a multitude of scenarios involving morphometrics for any given population. It can also be used to study and understand current national trends and compare how neonatal growth has changed, showing greater need for a new and more accurate percentile-curve model.

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Abbreviations: BL – Body Length; BNPD – Bivariate Normal Probability Density; CC – Chest Circumference; CP – Cephalic Perimeter; CV – Coefficient of Variation; Ku – Kurtosis; M – Mean; MAB – Medical Advisory Board; MNPD – Multivariate Normal Probability Density; PH – Phoenix; Sk – Skewness; VAR – Variance; W – Weight; WY – Wyoming; YU – Yuma

Introduction

Several neonatal, infant, and child growth charts utilizing individual morphometrics have been proposed for assessment with the goal of detecting early nutritional defects or disease. Early recognition and identification of any anomalies will aid in early treatment in order to decrease morbidity, and to assist with normal growth and development.

Growth charts based on height, weight, and other morphometrics were developed and used to identify high-risk children since the early 1900s, and have evolved from simple data summaries into substantial statistical analyses.¹ Notable growth chart improvements were developed by the National Center for Health Statistics (NCHS) and Department of Health and Human Services (DHHS) in 1977 (known as the NHANES program), in 2000 by the Center for Disease Control (CDC), and again in 2006 by the World Health Organization (WHO).

Throughout the evolution of such charts, there have been specific factors that were utilized to determine nutritional status, which include length/height, weight, head circumference, chest circumference, and/or body mass index (BMI). Normally, several measures are taken from 0 to 24 months when growth is especially crucial to determine an infant's well-being. These values are then plotted onto growth charts that have been created based upon a population of interest. Different factors are generally used during distinctive times of development and growth. Neonates are typically measured using length, weight, head circumference, and chest circumference.

In spite of widespread international use of WHO growth charts, concern about the sample that provided these charts existed. Major concerns involved sample characteristics, lack of racial diversity, lack of formula fed infants, and difficulties with the transition from length to height at the two-year-old mark. Thus, to address these problems in 1994, the National Health and Nutrition Examination Survey (NHANES III) oversampled children younger than six years old to update and add to the 1970's data, which was then further revised by the CDC in 2000. CDC/NCHS growth charts were developed using this information and statistically converting it to standards specific to a certain reference population [1,2].

The NCHS later merged with the CDC, and their findings were derived from the Fels Longitudinal Growth Study. More precisely, the CDC created normalized growth charts for infants and children aged 0 to 59 months, using cross-sectional data of a population selected within the United States. Most children included were from a middle socioeconomic status, although the data were taken from a nationally representative survey. Thus, there have been difficulties when using these charts with diverse populations. These data were serially collected, normalized, and percentiles were created, in order to help identify individual developmental status trends, and recognize any children at risk or who deviate from the general population.

Abnormalities in growth were statistically determined to be any child in or below the 5th percentile, or at or above the 95th percentile (those beyond 2 and 3 standard deviations from the median). Most information is derived from observing how an infant is growing and to ensure their pattern of growth is occurring in a curvilinear fashion. If the infant continued to be below the fifth percentile or above the 95th percentile, or if growth was not following a normal pattern, further steps are taken to determine the reason. However, there were difficulties utilizing these growth charts with individuals and samples that deviated from the original population studied. Additionally, ethnicity, socioeconomic status, and breast-feeding all played a role in growth, and the growth charts lost validity and reliability.

Although the CDC had developed growth charts that continued to be widely used, the WHO developed growth charts in 2003 that were created to encompass a greater international population in order to be used globally, and were released in 2006 [3]. The data was extricated using a more generalized and valid population involving six countries (USA, Brazil, Ghana, India, Norway, and Oman), encompassing diverse ethnicities, socioeconomic statuses, and types of feeding. Those included were healthy singleton births, whose mothers were nonsmokers and received nutritional counseling before, during, and after pregnancy. They selected this sample to implicate healthy growth to thus create a universal standard for growth charts.

Interestingly, WHO measurements took breast-feeding into account, which was found to affect growth significantly. One study of 226 healthy breastfed infants evaluated and compared how CDC and WHO growth charts assessed breastfed infants [4]. Breastfed infants grew most rapidly within the first two months of life, with the greatest linear growth seen until the age of four months when plotted on WHO growth charts when compared to the CDC reference charts. Growth was less rapid from the third to twelfth month of age in relation to CDC growth charts. For this reason, WHO growth charts became more of a standard, and were more widely used [3]. Furthermore, growth velocity and birth

weight were comparable throughout the different countries of interest, and charts were created using z-scores, where the normal 98% of the population was found to be within 2 standard deviations of the mean.

With the evolution of two separate growth charts, there have been studies that have investigated the similarities and differences of the CDC/NCHS and WHO growth charts [5,6]. The population standard defined by WHO was found to be longer and thinner than that defined by the CDC/NCHS, which is most prevalently seen throughout mid- to late-infancy. It was additionally discovered that undernourished or underweight infants and children were less likely to be classified as such when using WHO growth charts when compared to the CDC/NCHS growth charts. This was an expected finding because the WHO used samples from different countries that typically had lower rates of obesity and lower BMIs. Also, throughout the first three months of age, WHO growth charts demonstrated a faster rate of weight gain, which led to the identification of slower growing infants, and found to be prevalent in bottle-fed infants [2].

One of the main differences found between the CDC/NCHS and WHO growth charts included those aged 24 to 59 months. Although this difference was thought to be due to differing sample selections [2], Flegal, Carroll, and Ogden [7] strived to determine if differences in methodology accounted for any variations seen in weight-for-height and BMI-for-age percentiles for this age group. The WHO selected criteria in order to define healthy growth in order to obtain smoothed percentiles. Therefore, some of the differences between the two datasets could be accounted for due to data trimming, which the CDC did not utilize. This study demonstrated that there was more than one factor involved in why the CDC/NCHS and WHO charts had different findings.

With the development of two separate growth charts, new recommendations were created to determine a standard of growth and which chart should be used [1,2]. They determined that the international growth standard was derived from WHO charts, whereas the CDC delineated a growth reference in the United States. WHO growth charts therefore were used to describe healthy growth under optimal environmental conditions. The CDC growth charts were used to describe how certain children grew during the period of 1963-1994, and were thus a growth reference. Furthermore, in 2010, the CDC released recommendations for healthcare professionals to follow in order to determine which growth charts should be used depending on age.

Recommendations suggested that WHO growth charts should be used from birth to 24 months of age, and CDC growth charts should be used from 24 to 59 months of age. This was based on the fact that the WHO study took breast-feeding into account, which thus reflected a better indication for the age group of birth to 24 months. Breast-fed infants

were also less likely to be defined as underweight when WHO growth standard was utilized versus the CDC growth charts.

WHO charts have been more effective at identifying slower-growing infants during the first three months, which is suggestive of formula-fed infants, or possible inadequate or difficulties with breast-feeding or lactation in babies who are breast-fed [2]. Although this is the recommended standard, there are still discrepancies that healthcare providers should be aware of when changing from one growth chart to another. The most important concern is that toddlers, who may be considered overweight by WHO standards at 24 months, may become normal weight when converted to the CDC growth chart. Also, when this transition is made, length of the infant/toddler is changed to height.

Mei and Grummer-Strawn [8] investigated the proportion of children less than two years of age who were deemed to be malnourished or failure-to-thrive (FTT) by CDC growth charts compared to WHO growth charts. This longitudinal study was conducted using 10,844 children that were 24 months or younger, and included 37,964 weight and length measurements. Data extracted were from only routine office visits in California, and the study excluded infants with intrauterine growth retardation (IUGR), serious congenital anomalies, and those of multiple births. These data were used to compare the proportion of children who crossed two of more major percentile lines on CDC growth charts versus those who did so on WHO growth charts. Major percentile lines were defined by the 5th, 10th, 25th, 50th, 75th, 90th, and 95th percentiles for weight-for-age (WA), length-for-age (LA), and weight-for-length (WL) as is typically used in the clinical setting.

The researchers concluded that switching from CDC growth charts to WHO growth charts revealed more infants crossing down two percentile lines in LA, and more infants crossing up or down two percentile lines for WA and WL for infants aged 6 to 12 months. These results suggested that clinicians using WHO growth charts were likely to have more infants from birth to six months that could be considered malnourished or possibly FTT, and may be less likely to diagnose infants from six to 12 months as FTT. Moreover, this study demonstrated that crossing percentile lines, regardless of which growth chart was used, was very common for infants aged 0 to six months old.

Although FTT has been defined in several ways, it is commonly diagnosed when an infant/child falls below the 5th percentile of the CDC growth chart, or if it crosses two or more major percentile lines over a short time [9,10]. Once FTT is suspected through this screening, there is typically a referral to for a full growth evaluation, at a costly and inefficient use of resources if deemed unnecessary. Therefore, it is critical for clinicians to understand the differences between CDC and WHO growth charts, and to be aware of

possible discrepancies that arise when using each or both of these growth charts.

Silveira et al. [11] compared NCHS, CDC, and WHO percentile growth charts in the assessment of nutritional statuses for hospitalized children from birth to five years old. The study assessed 337 children in Brazil, more than half of who were less than one year old, who were hospitalized. They concluded that there was a high correlation between the three growth charts. They also found that CDC and WHO growth charts are more likely to classify infants and children as underweight, malnourished, or FTT. Thus, overall, most studies have concluded that WHO charts are more likely to diagnose infants and children as underweight and malnourished than CDC and NCHS charts, thus leading to further evaluation, and possible misuse of data collected from the use of growth charts.

Although there have been effective recommendations created in order to understand and interpret neonate, infant, and child growth with the use of standardized growth charts, interpretation of NCHS versus WHO growth charts by clinicians may still be poorly understood. Ahmad, et al. [12] conducted a single, blind, randomized crossover trial involving 78 healthcare workers to assess how they interpreted growth chart information, and what guidelines they would suggest based on these findings. They were given scenarios with the same infant plotted on both NCHS WA percentile charts and on WHO growth charts, as well as other scenarios with one single final weight versus that same final weight with a leading linear growth trend, and asked to interpret the findings. The hope was that linear growth patterns would affect the clinicians' concerns and decisions regarding follow-up care.

They concluded that linear growth trends were inefficiently considered, especially in low WA infants, leading to unnecessary management decisions. Additionally, more infants aged less than six months were placed in low percentiles on WHO growth charts versus NCHS charts, leading to a greater amount of healthcare concern, management, and referral when using WHO charts with the same infants. These scenarios suggested clinicians would inappropriately manage several cases, and that they failed to take an infant's own growth pattern into account, which could result in excessive or unnecessary treatment and possible adverse effects. Finally, they recommended that WHO charts, and interpreting growth charts in general, should include training materials and guidelines. This study demonstrated the complexity of growth charts and that healthcare providers failed to understand the differences among NCHS and WHO growth charts, which could lead to the misdiagnosis of infants as being malnourished. Also, they failed to consider linear growth patterns on these curves as a whole, which could also lead to misdiagnosis on impaired growth.

More recently, Villar et al. [13] conducted a cross-sectional study including more than 20,000 deliveries from eight countries named the International Fetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st). The goal of the study was to develop multi-ethnic growth charts for newborn neonates born between 33 and 42 weeks from urban areas. Countries involved included USA, UK, Brazil, China, India, Italy, Kenya, and Oman.

Trained clinicians took measurements of healthy neonates within 12 hours of birth, and found that variables of interest were similar throughout the eight countries. Specifically, they found that at 40 weeks of gestation, the 50th percentile for boys' birth weight was 3.38kg (3rd to 97th percentile was 2.63-4.22kg), length was 49.92cm (46.75-53.13cm), and head circumference was 34.31cm (32.15-36.56cm). For females at 40 weeks gestation, birth weight was 3.26kg (2.55-4.08kg), length was 49.23cm (46.12-52.22cm), and head circumference was 33.76cm (31.72- 35.92cm).

Saugstad [14] discussed the relevance of this study and its implications for variables that can affect growth during the gestational and neonatal period. Specifically, he observed that several factors can affect birth weight, including maternal and paternal factors. Specifically, maternal weight gain during pregnancy was found to significantly impact the birth weight in females, while paternal birth weight was significantly associated with male birth weight [15].

INTERGROWTH-21st additionally compared their findings to the current reference standard of growth charts designed by WHO [1,13]. Findings suggested that the mean birth weight for neonates in Scandinavian countries were 0.3 kg greater than what was found by WHO in the same region. This could further implicate that the standard WHO growth charts utilized from 0 to 24 months may in fact underestimate birth weight, length, and head circumference.

Further studies are underway to try and discover diverse factors that may result in this increased birth weight, and include maternal BMI, diet, and nutrients. Additionally, WHO [16] recommends delayed cord clamping worldwide after delivery, as it has been found to increase birth weight significantly. A Cochrane systematic review of 3,911 neonates found that birth weight almost doubled after delayed cord clamping, as well as a higher hemoglobin concentration, and increased iron reserve up to six months post-birth [17]. Thus, substantial difference in birth weight could be accounted for in part, or entirely, based on the time of cord clamping, and could be an important variable of consideration when comparing birth weights found in different studies.

Determining neonate, infant, and child growth is of vital importance. It allows clinicians and healthcare workers to evaluate for any abnormalities, and to follow the trend of growth throughout development. There have been several

attempts to create growth charts that effectively capture growth, with the hopes that any abnormalities will be noted for further evaluation. Although the CDC and WHO have implemented growth charts that have been utilized worldwide, there are still setbacks to their effectiveness. Further, there have been concerns with the ability of clinicians to use these charts effectively, and apply the findings clinically.

Improvements are continuously implemented and the charts are currently ubiquitous and based on fairly sophisticated statistical techniques, such as curve-smoothing procedures involving regression [1]. Curves generated for the charts are based on extensive data sets of morphometric measurements of children and infants, and generalized to the U.S. population utilizing normalization techniques. Growth curves are periodically updated with considerable effort and complexity, with the hopes of developing an applicable chart that encompasses a representative population, while allowing healthcare workers to effectively use and interpret the findings clinically.

Several studies demonstrate that much confusion exists with the current charts available to determine growth status. There have been errors with utilizing growth charts when trying to evaluate FTT, obesity, and growth status. Current growth charts are not always representative of all populations, and have been shown to lead to clinical errors, misunderstanding, and inaccurate diagnoses. As discussed above, at 24 months a toddler is switched to another growth chart, which leads to some inaccuracies.

There are differing variables that are utilized to measure growth depending on the population of interest. For example, growth in utero is often measured by crown rump length (CRL), biparietal diameter (BPD), abdominal circumference (AC), and estimated fetal weight (EFW), whereas infant, toddler, and child growth are measured utilizing weight, length, and head circumference. There have been several confounding variables (such as breast feeding, geographic location, and ethnicity) that have been found to impact growth in diverse populations, suggesting that specific percentile measurements for differing populations are necessary for more precise identification of growth status and any possible morbidities.

To better identify high-risk neonates and children, we propose using a focused percentile approximation approach in place of the complex generalized growth curves described previously. The approximation is based on the multivariate normal probability distribution, and utilizes a simplified analysis strategy that is easily implemented to create either: 1) a two-variable percentile chart, or 2) a three-or-more variable percentile calculation. To our knowledge, our research is novel and original, and no prior research using our approach has been conducted.

The advantage of our approach is that the percentile approximations represent current trends, easily updated, location-specific, gender-specific, race-specific, age-specific, and based on any combination of demographics and morphometrics for which data are available. Any medical facility could create its own percentile charts at periodic age intervals relative to specific populations and risks endemic to its location. Morphometrics such as weight, body length, cephalic perimeter (head circumference), chest circumference, etc., and combinations of these measures may be analyzed, and growth charts constructed to display percentile values for the individual.

Methods

Institutional Review Board approval was granted from the University of Arizona to conduct this study. Four health organizations were contacted in Arizona and Wyoming, and three agreed to participate in the research (St. John's Medical Center, Jackson, WY; Maricopa County Public Health Office of Epidemiology, Phoenix, AZ; and Sunset Community Health Center, Yuma, AZ). Data were collected over the course of approximately one year, and included body length (BL), chest circumference (CC), cephalic perimeter (CP), weight (W), race, gender, and location. Our target populations consisted of full-term neonates born between 38 and 42 weeks after conception, and additional demographic data that included race of mother (Hispanic or Non-Hispanic) and gender of the neonate.

Our multivariate normal probability distribution (MNPDP) approach was based on two fundamental assumptions:

1. Morphometric data are normally distributed, and may be incorporated jointly into a MNPDP;
2. Morphometric data vary for different populations based on location, race, gender, etc., so that different MNPDPs should be applied to different populations.

To confirm the fundamental premises of our research, preliminary descriptive analyses involved:

- Normality tests (skewness and kurtosis analyses) of all morphometric data for the various populations that were included in our research;
- MANOVAs, ANOVAs and independent samples t-tests to demonstrate that significantly different populations based on location, race and gender occurred;
- Descriptive summaries of all data pertaining to the various populations.

Having confirmed our fundamental assumptions, we then directed the analysis to the calculations of MNPDP percentiles based on two-, three-, and four-variable percentile combinations for specific locations and races. We chose the

MNPD multivariate approach because morphometric data are generally normally-distributed, and when analyzed jointly, the variables are generally correlated. The multivariate approaches allow us to account for this correlation because it is an intrinsic component of the joint probability density, while the univariate approach (one morphometric at a time) does not account for inter-correlations of the morphometrics.

We provide percentile calculations for up to four morphometrics that are measured on a neonate, principally for validation of our multivariate approach, and for comparison of percentiles for different combinations of morphometrics. We generally emphasize analyzing only two morphometrics jointly using the bivariate normal probability density (BNPD), a two- variable version of the MNPD. The BNPD provides a more powerful analysis than analyzing one variable at a time (the correlation between the two variables is accounted for), and it allows construction of percentile charts (contour charts) for convenient determination of high-risk neonates. When analyzing more than two morphometrics, construction of contour charts is not possible due to the additional dimensions, but the MNPD can be used to calculate percentiles when a high-risk infant is involved. This would provide for greater certainty about the status of a high-risk neonate.

In the case of two measured morphometric, the BNPD is given by:

$$f(x, y) = \frac{e^{-\frac{(\frac{x-\mu_1}{\sigma_1})^2 + (\frac{y-\mu_2}{\sigma_2})^2 - \frac{2\rho(x-\mu_1)(y-\mu_2)}{\sigma_1\sigma_2}}{2(1-\rho^2)}}}{2\pi\sigma_1\sigma_2\sqrt{(1-\rho^2)}}$$

where, for example: $x = BL$; $y = W$; $\mu_1 = \text{Mean BL}$, $\mu_2 = \text{Mean W}$, $\sigma_1 = \text{Standard Deviation BL}$, $\sigma_2 = \text{Standard Deviation W}$, and $\rho = \text{Correlation of BL and W}$. A profile of the BNPD, the cumulative BNPD distribution, and a percentile chart are given below in Figures 1, 2, and 3.

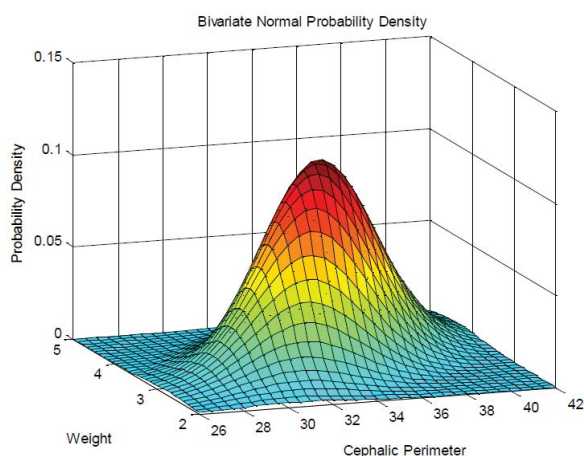


Figure 1: The bivariate normal probability density for a simulated data set.

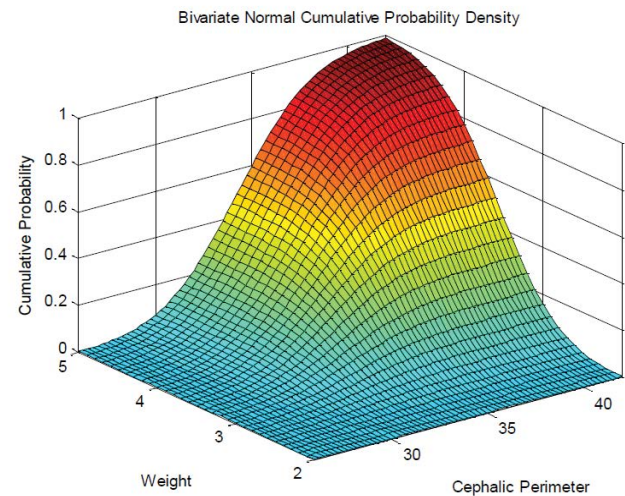


Figure 2: The cumulative bivariate normal probability density for simulated data.

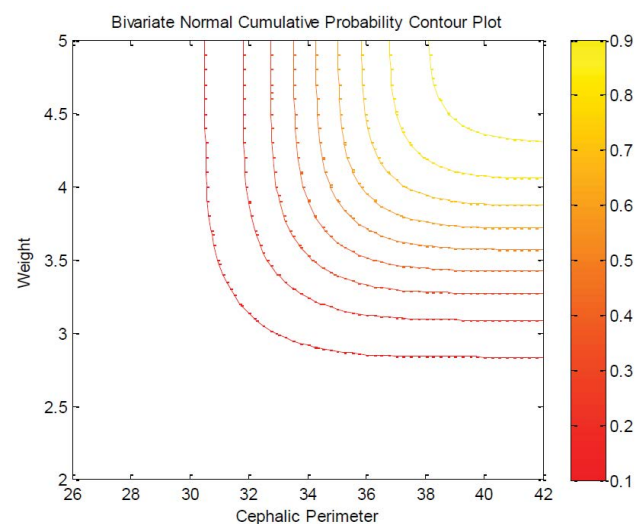


Figure 3: The contour chart of the cumulative bivariate normal probability density.

When more than two morphometrics are used for percentile calculations, we use the generalized matrix form of the MNPD, consisting of d variables, which is given by:

$$f(x, \mu, \Sigma) = \frac{1}{\sqrt{|\Sigma|(2\pi)^d}} e^{-\frac{1}{2}(x-\mu)\Sigma^{-1}(x-\mu)'}.$$

where $\Sigma = \text{covariance matrix}$, $x = \text{vector corresponding to the variables}$ and $\mu = \text{vector of the means of the variables}$.

Several additional analyses were incorporated into our research to demonstrate the superiority of our approach over traditional approaches, including:

- Percentile calculations based on the actual data were calculated for all one-variable, two-variable, three-

variable, and four-variable morphometric combinations to insure the integrity of our higher-dimensional approach;

- For various significantly different populations, percentile calculations were compared for various combinations of morphometrics based on sets of scenarios created by adding and subtracting approximately 1.5 standard deviations to the mean of each morphometric;
- Conventional percentile calculations (from hospital charts), were compared to percentile calculations using our approach;
- When more than two morphometric variables were measured, but two-variable percentile contour charts are desired for easy percentile calculations, we describe a procedure for choosing two variables based on a Coefficient of Variation (CV) analysis, where CV equals the standard deviation divided by the mean for any population.

Results

After obtaining the Institutional Review Board approval from the University of Arizona to conduct our research, we solicited participation from four organizations, and three agreed to participate in the research (St. John's Medical Center, Jackson, WY; Maricopa County Public Health Office of Epidemiology, Phoenix, AZ; and Sunset Community

Health Center, Yuma, AZ). Data were collected over the course of approximately one year, and included body length (BL), chest circumference (CC), cephalic perimeter (CP), weight (W), race, gender, and location.

Neonatal morphometric measurements that were provided differed for the various locations. Maricopa County Public Health Office (PH) provided BL and W, Sunset Community Health Center (YU) provided BL, CC, CP, and W; and St. John's Medical Center (WY) provided BL, CC, and W. A descriptive summary of the data including number of infants (N), mean (M), and standard deviation (SD) are given in Table 1 below. Information displayed in this table will be cited throughout the document.

Assumption 1: Morphometric Data are Normally Distributed

Data were first assed for normality, an underlying premise of the analysis. The normality assessment was based on skewness (Sk) and kurtosis measurements (Ku). Because normality tests are very sensitive to sample size, and the original data from PH (N = 18,522) greatly exceeded that from YU (N = 299) or WY (N = 376), we randomly chose 338 participants from the PH data. (The value 338 represents the average of the YU and WY sample sizes.) Although there are several criteria for assessing normality, our assessment was based on that proposed by West et. al. (1995), which

Table 1: Descriptive statistics summary of the morphometric measurements.

| | | | BL | CC | CP | W |
|---------------|-----------------------|---------------------|-------------------------|-------------------------|-------------------------|------------------------|
| PH N = 18,522 | Hispanic N = 9,879 | Female N = 4,824 | M = 49.95 SD = 2.458 | | | M = 3.32 SD = 0.424 |
| | | Male N = 5,055 | M = 50.71 SD = 2.483 | | | M = 3.44 SD = 0.451 |
| | Other N = 8,643 | Female N = 4,295 | M = 50.55 SD = 2.565 | | | M = 3.32 SD = 0.452 |
| | | Male N = 4,348 | M = 51.29 SD = 2.572 | | | M = 3.42 SD = 0.454 |
| YU N = 299 | Hispanic N = 271 | Female N = 140 | M = 49.80 SD = 2.629 | M = 32.91 SD = 2.067 | M = 33.79 SD = 1.573 | M = 3.28 SD = 0.515 |
| | | Male N = 131 | M = 51.01 SD = 2.461 | M = 33.40 SD = 1.832 | M = 34.41 SD = 1.635 | M = 3.44 SD = 0.446 |
| | Other N = 28 | Female N = 18 | M = 50.07 SD = 2.659 | M = 33.78 SD = 2.144 | M = 34.39 SD = 1.290 | M = 3.53 SD = 0.460 |
| | | Male N = 10 | M = 51.20 SD = 2.431 | M = 33.70 SD = 1.252 | M = 34.23 SD = 1.731 | M = 3.39 SD = 0.509 |
| WY N = 376 | Hispanic N = 73 | Female N = 44 | M = 49.19 SD = 1.992 | M = 33.20 SD = 1.370 | | M = 3.17 SD = 0.413 |
| | | Male N = 29 | M = 50.13 SD = 2.376 | M = 34.17 SD = 1.416 | | M = 3.25 SD = 0.403 |
| | Other N = 303 | Female N = 160 | M = 49.59 SD = 2.177 | M = 33.99 SD = 1.554 | | M = 3.24 SD = 0.408 |
| | | Male N = 143 | M = 50.50 SD = 2.049 | M = 34.57 SD = 1.546 | | M = 3.35 SD = 0.415 |

indicated a substantial departure from normality when the absolute skewness value >2 and absolute kurtosis value >4 . Additionally criteria will be addressed in the Discussion Section of this manuscript; thus, additional information is presented in Table 2.

Several summaries are presented in Tables 2, 3, and 4 below. Based on the above criteria, there is no reason to suspect that the morphometric data presented any serious deviation from normality. This is a necessary requirement for the

assumption that the morphometric data may be incorporated jointly into a MNPD. However, it is not sufficient [19].

Characteristics of multivariate normality also require that any linear combination of the variables are normally distributed, and all pairwise subsets are (bivariately) normally distributed. This is not a trivial analysis; however, it is simplified by examination of bivariate scatterplots for approximately elliptical shapes, which is shown in Figure 4 below.

Table 2: Skewness and kurtosis analyses by location.

| | | N | Sk | SE _{Sk} | Z | Ku | SE _{KU} | Z |
|---------------|----|-------|--------|------------------|--------|--------|------------------|--------|
| Combined Data | BL | 1,013 | -0.093 | 0.077 | -1.208 | 0.178 | 0.154 | 1.156 |
| | CC | 299 | -0.260 | 0.141 | -1.844 | 1.366 | 0.281 | 4.861 |
| | CP | 675 | -0.094 | 0.094 | -1.000 | 0.574 | 0.188 | 3.053 |
| | W | 1,013 | 0.096 | 0.077 | 1.247 | 0.931 | 0.154 | 6.045 |
| Phoenix | BL | 338 | -0.163 | 0.133 | -1.226 | 0.138 | 0.265 | 0.521 |
| | W | 338 | -0.017 | 0.133 | -0.128 | -0.103 | 0.265 | -0.389 |
| Yuma | BL | 299 | -0.140 | 0.141 | -0.993 | 0.410 | 0.281 | 1.459 |
| | CC | 299 | -0.260 | 0.141 | -1.844 | 1.366 | 0.281 | 4.861 |
| | CP | 299 | -0.068 | 0.141 | -0.482 | 0.629 | 0.281 | 2.238 |
| | W | 299 | 0.217 | 0.141 | 1.539 | 1.690 | 0.281 | 6.014 |
| Wyoming | BL | 376 | -0.138 | 0.126 | -1.095 | -0.237 | 0.251 | -0.944 |
| | CP | 376 | -0.115 | 0.126 | -0.913 | 0.548 | 0.251 | 2.183 |
| | W | 376 | 0.049 | 0.126 | 0.389 | 0.529 | 0.251 | 2.108 |

Table 3: Skewness and kurtosis analyses by race.

| | | N | Sk | SE _{Sk} | Z | Ku | SE _{KU} | Z |
|--------------|----|-----|--------|------------------|--------|-------|------------------|-------|
| Hispanic | BL | 509 | -0.032 | 0.108 | -0.296 | 0.191 | 0.216 | 0.884 |
| | CC | 271 | -0.352 | 0.148 | -2.378 | 1.206 | 0.295 | 4.088 |
| | CP | 344 | -0.073 | 0.131 | -0.557 | 0.552 | 0.262 | 2.107 |
| | W | 509 | 0.195 | 0.108 | 1.806 | 1.459 | 0.216 | 6.755 |
| Non-Hispanic | BL | 504 | -0.154 | 0.109 | -1.413 | 0.183 | 0.217 | 0.843 |
| | CC | 28 | 1.010 | 0.441 | 2.290 | 2.740 | 0.858 | 3.193 |
| | CP | 331 | -0.104 | 0.134 | -0.776 | 0.652 | 0.267 | 2.442 |
| | W | 504 | -0.016 | 0.109 | -0.147 | 0.285 | 0.217 | 1.313 |

Table 4: Skewness and kurtosis analyses by location and race.

| | | | Sk | SE _{Sk} | Z | Ku | SE _{KU} | Z |
|--------------------|---------------------|----|--------|------------------|--------|--------|------------------|--------|
| Phoenix N = 338 | Hispanic N = 615 | BL | 0.061 | 0.189 | 0.323 | 0.172 | 0.376 | 0.457 |
| | | W | 0.263 | 0.189 | 1.392 | -0.010 | 0.376 | -0.027 |
| | Other N = 173 | BL | -0.402 | 0.185 | -2.173 | 0.571 | 0.367 | 1.556 |
| | | W | -0.265 | 0.185 | -1.432 | -0.015 | 0.367 | -0.041 |
| | | BL | -0.145 | 0.148 | -0.980 | 0.419 | 0.295 | 1.420 |
| | | CC | -0.352 | 0.148 | -2.378 | 1.206 | 0.295 | 4.088 |
| | Hispanic N = 271 | CP | -0.054 | 0.148 | -0.365 | 0.625 | 0.295 | 2.119 |
| | | W | 0.191 | 0.148 | 1.291 | 1.860 | 0.295 | 6.305 |
| | | BL | -0.087 | 0.441 | -0.197 | 0.604 | 0.858 | 0.704 |
| | | CC | 1.007 | 0.441 | 2.283 | 2.740 | 0.858 | 3.193 |
| Yuma N = 299 | Other N = 28 | CP | -0.133 | 0.441 | -0.302 | 0.812 | 0.858 | 0.946 |
| | | W | 0.607 | 0.441 | 1.376 | -0.209 | 0.858 | -0.244 |
| | | BL | 0.151 | 0.281 | 0.537 | -0.340 | 0.555 | -0.613 |
| | Hispanic N = 73 | CP | -0.382 | 0.281 | -1.359 | -0.094 | 0.555 | -0.169 |
| | | W | 0.178 | 0.281 | 0.633 | -0.033 | 0.555 | -0.059 |
| | | BL | -0.208 | 0.140 | -1.486 | -0.142 | 0.279 | -0.509 |
| Wyoming N = 376 | Other N = 303 | CP | -0.100 | 0.140 | -0.714 | 0.652 | 0.279 | 2.337 |
| | | W | 0.017 | 0.140 | 0.121 | 0.708 | 0.279 | 2.538 |

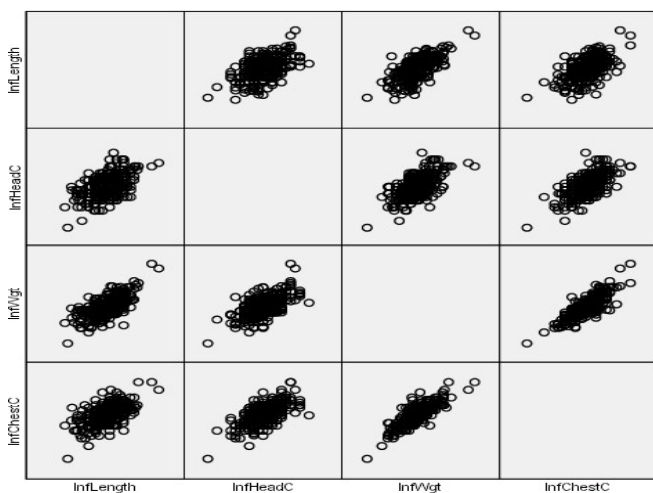


Figure 4: Bivariate scatterplots for the combined data

Assumption 2: Morphometrics Vary for Different Populations

The second fundamental assumption of our research stipulates that morphometric data vary for different populations based on location, race, gender, etc., so that different MNPDs should be applied to the different populations. In the Introduction Section, we cited several

studies that supported our assumption; however, to support this claim with our data, we performed several parametric tests. Similar to normality tests, sample sizes that are substantially different can significantly influence results. We therefore used the reduced, randomly-selected data from the PH population (N = 338 instead of 18,522) in the analyses. All tests were run at an experiment-wise level of significance, α , equal to 0.05

The first analysis involved a multivariate ANOVA (MANOVA) designed to test the significance of three independent variables (Gender, Location, and Race) on a best linear combination of two dependent variables (BL and W). We used a best linear combination of BL and W because they were measured at all locations, and the combination of the two variables provided a more holistic multidimensional analysis of the phenomenon under investigation [20]. The results of the analysis indicated a significant effect of Location (Wilks' Lambda = 0.970, df = 4, 2000, p = 0.000) and Gender (Wilks' Lambda = 0.003, df = 4, 292, p = 0.001) on the combined dependent variable. All two-way and three-way interactions were not significant. Follow-up ANOVAs and Independent-Samples t-tests assessed significance of the main effects of the dependent variables, Gender, Location, and Race, on each of the dependent variables, BL and W, examined one at a time. Significant results included:

- Location demonstrated a significant effect on BL [$F(2, 1001) = 10.576, p = 0.000$]. A Bonferroni Post-Hoc analysis indicated that infants from WY were significantly shorter ($M = 49.4\text{cm}$) than those from PH ($p = 0.000$) or YU ($p = 0.036$), while there was no significant difference ($p = 0.100$) in BL between infants from PH ($M = 50.8\text{cm}$) and YU ($M = 50.4\text{cm}$).
- Gender demonstrated a significant effect on BL [$F(1, 1001) = 20.431, p = 0.000$].
- Male infants ($M = 50.9\text{cm}$) were significantly longer than female infants ($M = 49.9\text{cm}$).
- Race demonstrated a significant effect on BL [$F(1, 1001) = 4.609, p = 0.032$].
- Hispanic infants ($M = 50.3\text{cm}$) were significantly shorter than non-Hispanic infants ($M = 50.4\text{cm}$).
- Location demonstrated a significant effect on W [$F(2, 1001) = 14.064, p = 0.000$]. A Bonferroni Post-Hoc analysis indicated that infants from WY were significantly lighter ($M = 3.27\text{kg}$) than those from PH ($p = 0.000$) or YU ($p = 0.036$), while there was no significant difference ($p = 0.100$) in W between infants from PH ($M = 3.44\text{kg}$) and YU ($M = 3.37\text{kg}$).
- Gender demonstrated a significant effect on W [$F(1, 1001) = 4.206, p = 0.041$]. Male infants ($M = 3.42\text{kg}$) were significantly heavier than female infants ($M = 3.30\text{kg}$).
- Race demonstrated a significant effect on W [$F(1, 1001) = 4.841, p = 0.028$].

Hispanic infants ($M = 3.35\text{kg}$) were significantly lighter than non-Hispanic infants ($M = 3.36\text{kg}$).

The second analysis investigated CP, which was measured in WY and YU, but not in PH. A three-way ANOVA assessed significance of the main effects of the dependent variables, Gender, Location, and Race, on CP. A summary of the results follows:

- Location did not significantly affect CP [$F(1, 667) = 1.333, p = 0.247$]. CP in YU had a mean, $M = 34.13\text{cm}$, while that in YU was $M = 34.11\text{cm}$.
- Gender demonstrated a significant effect on CP [$F(1, 667) = 6.939, p = 0.009$]. Male infants ($M = 34.45\text{cm}$) had a significantly longer CP than female infants ($M = 33.83\text{cm}$).
- Race demonstrated a significant effect on CP [$F(1, 667) = 4.463, p = 0.035$].

Hispanic infants ($M = 33.98\text{cm}$) had a significantly shorter CP than non-Hispanic infants ($M = 34.27\text{cm}$).

The final analysis investigated CC, which was only measured in Yuma. Independent samples t-tests indicated that there were no significant differences [$t(297) = 1.808, p = 0.072$] on CC between male infants ($M = 33.4\text{cm}$) and female infants ($M = 33.0\text{cm}$); nor were there any significant differences [$t(297) = 1.554, p = 0.121$] on CC between Hispanic infants ($M = 33.1\text{cm}$) and non-Hispanic infants ($M = 33.8\text{cm}$).

The above analyses demonstrated that morphometric data do vary for different populations based on location, race, and gender, so that different MNPDs should be applied to the different populations. The descriptive statistics used in the above analyses for the reduced data are summarized in Table 5:

Table 5: Descriptive Statistics for the Reduced Data Set

| | Gender | | Location | | | Race | |
|---------|------------|------------|------------|------------|------------|------------|------------|
| | Female | Male | PH | YU | WY | Hispanic | Other |
| BL (cm) | M = 49.88 | M = 50.85 | M = 50.79 | M = 50.39 | M = 50.79 | M = 49.92 | M = 50.42 |
| | SD = 2.473 | SD = 2.301 | SD = 2.502 | SD = 2.610 | SD = 2.502 | SD = 2.155 | SD = 2.389 |
| | N = 525 | N = 488 | N = 338 | N = 299 | N = 376 | N = 509 | N = 504 |
| CC (cm) | M = 33.01 | M = 33.42 | | M = 33.20 | | M = 33.15 | M = 33.75 |
| | SD = 2.087 | SD = 1.796 | | SD = 1.963 | | SD = 1.968 | SD = 1.848 |
| | N = 158 | N = 141 | | N = 299 | | N = 271 | N = 28 |
| CP (cm) | M = 33.84 | M = 34.45 | | M = 34.11 | M = 34.13 | M = 33.98 | M = 34.27 |
| | SD = 1.547 | SD = 1.576 | | SD = 1.612 | SD = 1.574 | SD = 1.606 | SD = 1.561 |
| | N = 362 | N = 313 | | N = 299 | N = 376 | N = 344 | N = 331 |
| W (kg) | M = 3.30 | M = 3.42 | M = 3.44 | M = 3.37 | M = 3.27 | M = 3.35 | M = 3.36 |
| | SD = 0.445 | SD = 0.423 | SD = 0.401 | SD = 0.488 | SD = 0.414 | SD = 0.450 | SD = 0.427 |
| | N = 525 | N = 488 | N = 338 | N = 299 | N = 376 | N = 509 | N = 504 |

Percentile Calculations:

Having substantiated our assumptions, we first assessed the integrity of the MNPD procedure. Using Matlab (R2014b), percentiles based on the actual data for all one-variable, two-variable, three-variable, and four-variable morphometric combinations were calculated without any issues, and random examination of the percentiles revealed no discrepancies. All available complete data for each location were used in the percentile validation. Descriptive statistics used in the calculations, specifically the means (M), variances (VAR), and covariances, are given in Tables 6 and 7 below. Matlab commands for running the percentile calculations are listed in the Appendix, as well as information about obtaining a Matlab compiler program provided by the authors at no cost that provides percentile calculations and charts.

Ten scenarios were designed to: 1) evaluate and compare percentile computations for the different locations with respect to BL and W; and 2) evaluate and compare percentile computations within the YU area for different combinations of BL, CC, CP, W, and currently- used hospital charts. Scenarios were based on different combinations of morphometrics by adding and subtracting approximately 1.5 standard deviations to the mean of each morphometric, and dividing the resulting range into ten segments. The scenarios were then arranged in order so that the lowest percentile to the largest percentile would result from the various combinations of the morphometrics. The ten scenarios are listed in Table

8, and the resulting percentile calculations for the Hispanic and Non-Hispanic (or Other) races in the WY, PH and YU locations are given in Table 9.

Figure 5 provides a summary plot of the percentiles presented in Table 9. Although Figure 5 will be analyzed in-depth in the Discussion Section, noteworthy observations include:

1. All populations have approximately equal percentile calculations for Scenario 1;
2. Scenario 4 indicates that the WY Hispanic population falls in the 23.4th percentile, while the PH Other population falls in the 12.7th percentile;
3. Scenario 6 indicates that the WY Hispanic population falls in the 57.8th percentile, while the PH Other population falls in the 35.4th percentile.

Table 10 and Figure 6 provide a summary of scenario percentile computations for the Hispanic race within the YU area for different combinations of BL, CC, CP, W, and currently- used hospital charts. Any combination of two or more morphometrics used the MNPD in its computation, combinations containing one variable used the univariate normal probability distribution approximation (Excel), and combinations of one variable based on hospital charts were estimated from the respective chart. There was no hospital chart available for CC. Trends demonstrated below will be addressed more thoroughly in the Discussion Section.

Table 6: Descriptive statistics for the percentile computations.

| | | BL | CC | CP | W |
|----|-------------------|--------------------------|--------------------------|--------------------------|-------------------------|
| PH | Hispanic N = 9879 | M = 50.34 VAR = 6.244 | | | M = 3.38 VAR = 0.195 |
| | Other N = 8640 | M = 50.92 VAR = 6.735 | | | M = 3.37 VAR = 0.208 |
| YU | Hispanic N = 271 | M = 50.38 VAR = 6.823 | M = 33.15 VAR = 3.860 | M = 34.09 VAR = 2.647 | M = 3.36 VAR = 0.238 |
| | Other N = 28 | M = 50.47 VAR = 6.481 | M = 33.75 VAR = 3.295 | M = 34.33 VAR = 1.979 | M = 3.48 VAR = 0.216 |
| WY | Hispanic N = 72 | M = 49.63 VAR = 4.418 | | M = 33.61 VAR = 2.094 | M = 3.21 VAR = 0.154 |
| | Other N = 303 | M = 50.02 VAR = 4.658 | | M = 34.26 VAR = 2.471 | M = 3.29 VAR = 0.171 |

Table 7: Covariances of morphometrics used in percentile computations.

| | | BL - CC | BL - CP | BL - W | CC - CP | CC - W | CP - W |
|----|----------|---------|---------|--------|---------|--------|--------|
| YU | Hispanic | 2.9297 | 2.066 | 0.8809 | 2.0528 | 0.8058 | 0.4849 |
| | Other | 3.3199 | 2.2234 | 0.8368 | 1.4509 | 0.666 | 0.4698 |
| PH | Hispanic | | | 0.6166 | | | |
| | Other | | | 0.7206 | | | |
| WY | Hispanic | | 1.2086 | 0.5284 | | | 0.2737 |
| | Other | | 0.972 | 0.5498 | | | 0.3358 |

Table 8: Ten scenarios for percentile comparisons.

| Scenario | BL | CC | CP | W |
|----------|-------|-------|-------|------|
| 1 | 46.00 | 31.50 | 32.00 | 2.60 |
| 2 | 46.89 | 32.06 | 32.44 | 2.78 |
| 3 | 47.78 | 32.61 | 32.89 | 2.96 |
| 4 | 48.67 | 33.17 | 33.33 | 3.13 |
| 5 | 49.56 | 33.72 | 33.78 | 3.31 |
| 6 | 50.44 | 34.28 | 34.22 | 3.49 |
| 7 | 51.33 | 34.83 | 34.67 | 3.67 |
| 8 | 52.22 | 35.39 | 35.11 | 3.84 |
| 9 | 53.11 | 35.94 | 35.56 | 4.02 |
| 10 | 54.00 | 36.50 | 36.00 | 4.20 |

Table 9: Scenarios with Percentile Calculations Expressed as Percentages

| Scenario | Wyoming | | Phoenix | | Yuma | |
|----------|----------|--------|----------|--------|----------|--------|
| | Hispanic | Other | Hispanic | Other | Hispanic | Other |
| 1 | 1.68% | 1.14% | 1.03% | 1.03% | 2.04% | 1.23% |
| 2 | 4.89% | 3.42% | 2.88% | 2.74% | 4.72% | 3.15% |
| 3 | 11.72% | 8.53% | 6.89% | 6.29% | 9.68% | 7.07% |
| 4 | 23.42% | 17.87% | 14.20% | 12.66% | 17.63% | 13.92% |
| 5 | 39.63% | 31.86% | 25.41% | 22.45% | 28.78% | 24.26% |
| 6 | 57.78% | 49.00% | 39.95% | 35.39% | 42.42% | 37.71% |
| 7 | 74.31% | 66.24% | 55.93% | 50.16% | 56.97% | 52.80% |
| 8 | 86.56% | 80.53% | 70.86% | 64.76% | 70.58% | 67.44% |
| 9 | 94.01% | 90.32% | 82.78% | 77.32% | 81.72% | 79.74% |
| 10 | 97.73% | 95.87% | 90.94% | 86.78% | 89.74% | 88.70% |

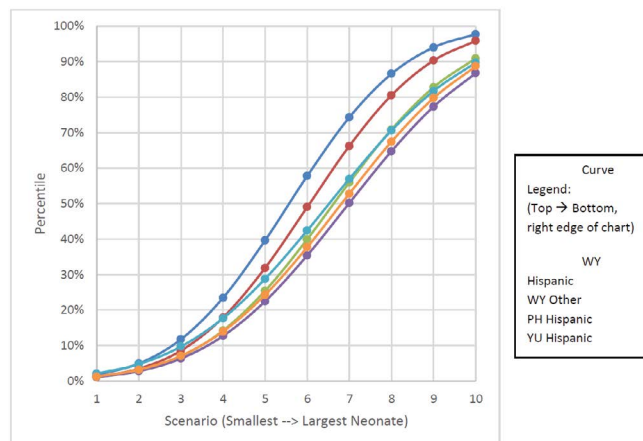


Figure 5: Neonate percentile growth curves based on length and weight for ten scenarios

Table 11 presents coefficients of variation (CV) for the four morphometrics where CV equals the standard deviation divided by the mean. Pairwise correlations for all morphometrics are listed in Table 12. The CV was used

to select the most important morphometrics to include in the percentile calculations in the event that only two morphometrics (of three or four measured morphometrics) are used to create bivariate percentile charts. Variables with higher (but not excessively higher) CVs allow for better, more powerful, estimates of percentiles. As noted in Table 11, W has the largest CV, followed by CC; however, W and CC are highly correlated ($r = 0.837$). Therefore BL, with the next highest CV, is more appropriate to use with W in constructing two-variable percentile charts. Also, BL and W are commonly measured in all locations. A two-variable percentile (contour) chart, calculated from actual data and based on BL and W for YU Hispanics, is shown in Figure 7.

Discussion

Results of studies described in the introduction, along with results from our research, provide substantial evidence that current growth morphometric measurements are both controversial and inadequate in determining high risk neonates (and other age groups) using conventional percentiles charts developed by WHO, CDC, etc. These current percentile charts are univariate (they describe one morphometric) and are generalized to global populations.

Without any doubt, populations based on different demographics demonstrate significantly different neonatal growth parameters. Although research cited in the introduction identifies the issue, any realistic solutions are not explicitly stated other than the suggestion of the need for percentile charts specific to different populations.

Table 10: Percentile calculation comparisons for three scenarios for YU hispanics based on different combinations of morphometrics.

| Scenario | 1 | 5 | 10 |
|------------|--------|--------|--------|
| BL, CC, CP | 0.0094 | 0.1764 | 0.7772 |
| BL, CC, CP | 0.0116 | 0.1862 | 0.7798 |
| BL, CC, W | 0.0151 | 0.2295 | 0.8334 |
| BL, CP, W | 0.0113 | 0.2039 | 0.8183 |
| CC, CP, W | 0.0223 | 0.2491 | 0.8116 |
| BL, CC | 0.0199 | 0.2468 | 0.8370 |
| BL, CP | 0.0178 | 0.2357 | 0.8282 |
| BL, W | 0.0205 | 0.2883 | 0.8976 |
| CC, CP | 0.0388 | 0.2829 | 0.8163 |
| CC, W | 0.0412 | 0.3452 | 0.8770 |
| CP, W | 0.0277 | 0.2976 | 0.8611 |
| BL | 0.0468 | 0.3761 | 0.9171 |
| CC | 0.2005 | 0.6146 | 0.9559 |
| CP | 0.0995 | 0.4239 | 0.8798 |
| W | 0.0597 | 0.4601 | 0.9574 |
| Chart BL | 0.1200 | 0.5800 | 0.9900 |
| Chart CP | 0.1200 | 0.5000 | 0.9500 |
| Chart W | 0.0900 | 0.6000 | 0.9900 |

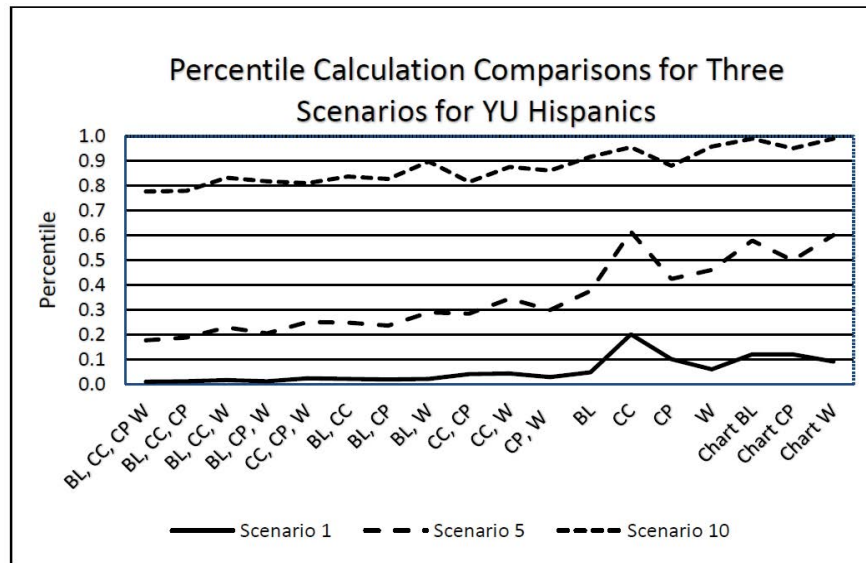


Figure 6: Percentile calculation comparisons for three scenarios for YU hispanics.

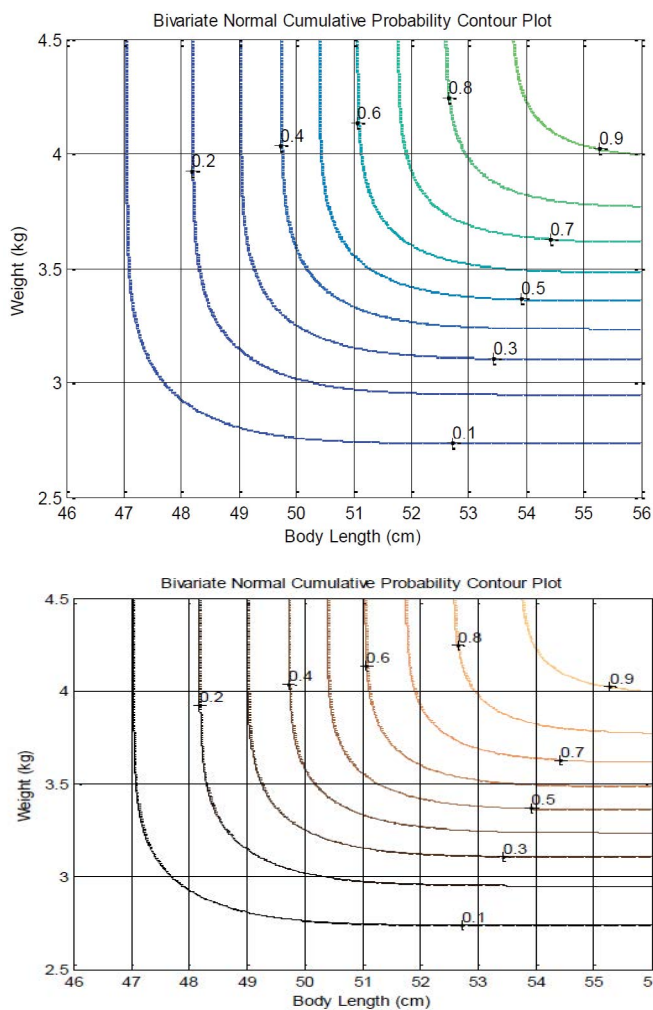


Figure 7: The contour chart of BL and W for YU hispanics based on the cumulative BNPD.

Table 11: Coefficients of variation for the YU hispanic morphometrics.

| | BL | CC | CP | W |
|----|---------|---------|---------|--------|
| M | 50.5942 | 33.2027 | 34.1224 | 3.3739 |
| SD | 2.556 | 1.9592 | 1.5884 | 0.4488 |
| CV | 0.0505 | 0.059 | 0.0465 | 0.133 |

Table 12: Correlations of all pairs of yuma hispanic morphometrics.

| BL - | BL - | BL - W | CC - | CC - W | CP - W |
|-------|-------|--------|-------|--------|--------|
| 0.582 | 0.403 | 0.581 | 0.637 | 0.838 | 0.562 |

In our manuscript, we outline a simplistic approach for creating percentile charts and percentile calculations for use in identifying high-risk individuals at specific locations for specific populations. Percentile charts are based on the Multivariate Normal Probability Density (MNPD), and defined by any number or combinations of morphometrics, although we emphasize two morphometrics which can optimally identify high-risk individuals via a convenient chart.

These charts need not be generalized to larger populations but are specific to the populations from which the data were collected.

Our approach was based on the assumption that growth measurements are normally distributed and may be incorporated jointly into a MNPD when taken together. Our assessment for validating the assumption was based on that proposed by West et al. [18], which indicated a substantial departure from normality when the absolute skewness value >2 and absolute kurtosis value >4 . We preferred this assessment because of its simplicity and the fact that tests for normality of data generally are very sensitive to sample

size and often overly conservative. We also assessed our data using other procedures:

1. A Z-test for normality of data, proposed by West et al, where $Z = Sk/SE_{Sk}$ or $Z = Ku/SE_{Ku}$, with the criteria: Ku
 1. For small samples ($n < 50$), if absolute z-scores for either skewness or kurtosis are >1.96 , the sample may be non-normal;
 2. For medium-sized samples ($50 < n < 300$), if absolute z-scores for either skewness or kurtosis are >3.29 , the sample may be non-normal;
 3. For sample sizes greater than 300, depend on the histograms and the absolute values of skewness and kurtosis without considering z-values. Either an absolute skew value >2 or an absolute kurtosis >7 may be used as reference values for determining non-normality.

Using this approach, seven minor potential, borderline discrepancies out of a possible 78 comparisons were observed (see Tables 2 through 4, which investigate skewness and kurtosis for Location, Race, and Location-by-Race, respectively).

2. Assessment of histograms, using stem-and-leaf plots, boxplots, and Normal Q-Q plots, did not display any major deviations from normality.
3. Assessment of bivariate normality using bivariate scatterplots of the morphometrics, supported multivariate normality by demonstrating approximately elliptical shapes.

Examination of all the criteria suggested above provides strong evidence in the assertion that morphometric data generally follow a normal probability distribution when analyzed univariately, and when analyzed jointly follow a multivariate normal probability distribution.

This in turn supports the approach we propose. We wish to emphasize several points:

1. The approach is intentionally designed for percentile chart creation at specific locations and for specific populations based on race, gender, etc. It is easy to create these percentile curves; hence, they can target specific populations without need for generalization to all populations.
2. The approach could be extended to encompass any age group, perhaps defined at three-month intervals.
3. A Medical Advisory Board (MAB) would be responsible for defining risk categories and protocols for the categories.

4. We do not suggest that conventional percentile charts are useless. For a generalized assessment of the status of newborns with respect to their development, they provide a quick reference. Our procedure, however, provides an enhanced, more comprehensive assessment in the event that more detail is required in the management of high-risk neonates.

Having established the fact that our MNPD assumptions were not violated, we next investigated the integrity and validity of our approach. Calculations of cumulative multivariate normal probabilities are numerically intensive, and any high multicollinearity between morphometrics could potentially force an ill-conditioned or near-singular matrix to not converge to an answer. We therefore applied the cumulative MNPD analysis to all combinations of two or more morphometric measures for PH, YU, WY, and the 10 scenarios, and calculated percentiles for 23,418 scenarios. No problems were noted in the calculations, even after several sorting arrangements for easier observation, and no value deviated from reasonable expectation.

If in some instance the technique were to fail, we suggest checking bivariate correlations.

High correlations indicate that variables are highly related and account for much of the same variability. In the generalized MNPD formula, as the correlation between any two variables approach one, the covariance matrix Σ approaches singularity, and its determinant approaches zero. Division by zero occurs, and the technique fails. Hence, in the presence of high correlation, we recommend removal of one of the correlated variables using the Coefficient of Variation technique discussed below. Finally, providing that bivariate correlations are not excessively high, we feel that inclusion of up to four morphometrics for higher dimensional percentile calculations would be beneficial in identification of high-risk neonates when there is any doubt about the condition of the neonate.

Ten scenarios (Table 8, Results Section) were designed to: 1) evaluate and compare percentile computations for the different locations with respect to BL and W (Table 9 and Figure 4, Results Section); and 2) evaluate and compare percentile computations for YU Hispanics for different combinations of BL, CC, CP, W, and currently-used hospital charts (Table 10, Results Section). Scenarios were based on different combinations of morphometrics by adding and subtracting approximately 1.5 standard deviations to the mean of each morphometric, and dividing the resulting range into ten segments. The scenarios were then arranged in order so that the lowest percentile to the largest percentile would result from the various combinations of the morphometrics. Noteworthy observations include the following:

4. All populations have approximately equal percentile calculations for Scenario 1;

5. As morphometric size measurements increase, percentile calculations for the various populations differ substantially:
 - a. Scenario 4 indicates that the WY Hispanic population falls in the 23.4th percentile, while the PH Other population falls in the 12.7th percentile, a difference of 10.7 percentile points;
 - b. Scenario 7 indicates that the WY Hispanic population falls in the 74.3th percentile, while the PH Other population falls in the 50.2th percentile, a difference of 24.1 percentile points (the largest percentile point difference);
6. Percentile point differences begin to narrow as Scenario 10 is approached, but still remain fairly large (WY Hispanic population falls in the 97.7th percentile, while the PH Other population falls in the 86.8th percentile, a difference of 10.9 percentile points).

The above percentile point differences suggest that a significant underestimation or overestimation of the status of a neonate could result if a single set of population parameters were generally applied to all populations, as is the current case with generalized hospital charts that measure morphometrics one at a time. For example, if WY parametric measures were applied to PH Other neonates according to criteria in Scenario 4, the PH Other neonate would be assigned to the 23.4th percentile, when in actuality, its percentile is 12.7th. Medical follow-up protocols for the different percentiles would certainly follow different standards of care.

In Table 10 and Figure 6, we compare percentile computations for YU Hispanics for different combinations of BL, CC, CP, W, and currently-used hospital charts. The pattern that emerges is that conventional hospital charts based on BL, CP, or W tend to significantly overestimate neonatal percentiles for all scenarios. The combination consisting of all four morphometrics produces the lowest percentiles for all scenarios. This is expected because when four morphometrics are all taken into account simultaneously, and their correlations are accounted for, a very precise percentile measurement results. If protocols globally accepted this approach (using all four measures), it would be the most accurate; however, if percentile charts based on two measures were more convenient, the four-measure approach could be excessive. As noted below in the table and figure, a two-measure percentile calculation falls somewhat in the middle of extremes, and the BL-W combination could be preferred because it is commonly measured. We will also argue for the BL-W combination based on the Coefficient of Variation (CV) analysis that follows.

CV is defined as the standard deviation divided by the mean, and is summarized in Table 11. CV essentially represents a scaled standard deviation, or the amount of variability in a measure relative to its mean (Howell, 2010). Variables with higher (but not excessively higher) CVs

allow for better, more powerful, analyses and, in our case, estimates of percentiles. We propose the use of CV to select the most important morphometrics to include in the percentile calculations in the event that only two morphometrics (of three or four measured morphometrics) are used to create bivariate percentile charts. Variables with higher CVs allow for better, more powerful, estimates of percentiles. As noted in Tables 11, W has the largest CV, followed by CC; however, W and CC are highly correlated ($r = 0.837$, Table 12). Therefore BL, with the next highest CV, is more appropriate to use with W in constructing two-variable percentile charts. Also, BL and W are commonly measured in all locations.

A contour chart of BL and W for YU Hispanics based on the Cumulative BNPD is shown in Figure 7. The contour chart was easily constructed using Matlab (see Appendix for the command code). Using this chart, input of a BL = 51cm and W = 3.5kg would result in a percentile calculation for a YU Hispanic neonate = 48th.

To summarize our approach, a Medical Advisory Board (MAB) in PH could select a target population, select two (or more) variables of interest, collect recent data (for example, over six months), and produce a percentile chart for its specific population. The target population could be, for example, gender-specific, race-specific, etc., and defined over ages for neonates, at three-month intervals, etc. (a separate chart would be created at each age interval). The MAB would also be responsible for defining percentiles corresponding to high-risk, medium-risk, low-risk, and normal individuals, and protocols for addressing each risk category.

We feel that higher dimensional percentiles may better identify high-risk individuals because the percentile calculation would involve more morphometric information and be more precise. For example, a neonate who has a small body length may not necessarily be considered high-risk, while a neonate who has a small body length and low weight might raise more concern. However, a neonate with a small body length, small cephalic perimeter, small chest circumference, and low weight would certainly be of concern, especially if he/she fell into the 10th or lower percentile.

We will make available upon request a Matlab Compiler program free of charge. The program will compute percentiles based on any number of morphometrics, and/or create a percentile chart similar to the one in Figure 7 when two morphometrics are specified.

What's Known on this Subject:

Current neonatal growth charts are univariate and globally applied to all populations. Current research has demonstrated problems with this approach and discrepancies between the CDC and WHO charts. Also, the charts are misinterpreted and incorrectly applied by health care providers.

What this Study Adds:

We propose a multivariate approach that simultaneously incorporates any number of morphometrics into the calculation of a percentile. The approach can be designed for any specific population based on any combinations of demographics such as race, gender, location, etc.

Contributors' Statement Page

Michelle Montopoli, MDC, and Dr. George Montopoli conceptualized and designed the study, procured the IRB approval through the University of Arizona College of Medicine, obtained data collection from one of the sites, performed the analyses, drafted the initial manuscript, and approved the final manuscript as submitted.

Dr. Will Smith and Delia Montopoli, CNM, OB/GYN NP, assisted with study design variables, assisted with the literature review, coordinated and helped with the procurement of data collection at two of the three sites, critically reviewed the manuscript, and approved the final manuscript as submitted.

Appendix:

1. EXCEL 2013 intrinsic functions for generating parameters (the data encompass the entire population, and not a sample):

Mean: =AVERAGE(DataRange)

Standard Deviation: =STDEV.P(DataRange)

Variance: =VAR.P(DataRange)

Correlation: =CORREL((DataRange1, DataRange2)

Covariance: =COVARIANCE.P(DataRange1, DataRange2).

2. Using MATLAB R2014b, we defined the row-vector of means μ by [34.28328 3.56779] and the covariance matrix Σ by $\begin{bmatrix} 8.639222 & 0.831953 \\ 0.831953 & 0.326451 \end{bmatrix}$, and produced the following BNPD (Figure 1). We plotted CP and W over intervals approximately equal to $\mu \pm 3\sigma$ to capture the entire probability density. The MATLAB code for generating the BNPD:

```
mu = [34.28328 3.56779];
```

```
Sigma = [8.639222 0.831953; 0.831953 0.326451];
```

```
x1 = 26:.25:42; x2 = 2:.1:5;
```

```
[X1,X2] = meshgrid(x1,x2);
```

```
F = mvnpdf([X1(:) X2(:)],mu,Sigma);
```

```
F = reshape(F,length(x2),length(x1));
```

```
surf(x1,x2,F);
```

```
caxis([min(F(:))-5*range(F(:)),max(F(:))]);
```

```
axis([26 42 2 5 0 .15])
```

```
xlabel('Cephalic Perimeter');
```

```
ylabel('Weight');
```

```
zlabel('Probability Density');
```

```
title('Bivariate Normal Probability Density')
```

3. We next generated the Cumulative BNPD (Figure 2), which we used to define the Contour Chart (Figure 3) for the 10th, 20th, ... , 90th percentile curves. The MATLAB code for generating the Cumulative BNPD:

```
F = mvncdf([X1(:) X2(:)],mu,Sigma);
```

```
F = reshape(F,length(x2),length(x1));
```

```
surf(x1,x2,F);
```

```
caxis([min(F(:))-5*range(F(:)),max(F(:))]);
```

```
axis([26 42 2 5 0 1])
```

```
xlabel('Cephalic Perimeter');
```

```
ylabel('Weight'); zlabel('Cumulative Probability');
```

```
title('Bivariate Normal Cumulative Probability Density')
```

4. The MATLAB code for generating the Contour Plot of the Cumulative BNPD:

```
contour(x1,x2,F,[.1:.9]);
```

```
xlabel('Cephalic Perimeter'); ylabel('Weight');
```

```
title('Bivariate Normal Cumulative Probability Contour Plot');
```

```
colormap autumn;
```

```
colorbar('location','eastoutside');
```

Higher dimensional percentile computations were calculated using MATLAB; however, contour charts cannot be not meaningfully constructed for >2 dimensions. For example, we decided to include body length (BL) in our percentile computation along with CP and W. Values corresponding to BL were then included in the row vector of means and the covariance matrix Σ .

For example, suppose Mean(BL) = 43.2 cm, Variance(BL) = 4.0, Covariance(CP,BL) = 0.532, and Covariance(W,BL) = 0.412, then the row-vector of means μ = [34.28328 3.56779 43.2] and the covariance matrix Σ =

```
8.63922  0.831953  0.532
0.831953  0.326451  0.412
0.532    0.412    4.0 ,
```

To find the percentile for an infant with CP = 30, W = 3.2, and BL = 41, the MATLAB command is mvncdf([30 3.2 41], mu, Sigma). The following percentile value is obtained: 0.0208 = 20.28th percentile.

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Michelle and George Montopoli had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. No authors have conflicts of interest, financial interests, activities, relationships, and/or affiliations related to the study, nor did they receive financial remuneration of any sort.

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