QUANTILE CONTOURS AND ALLOMETRIC MODELLING WITH AN APPLICATION TO ANTHROPOMETRIC CHARTS IN PRETERM INFANTS

BY MARCO GERACI†‡, NANSI S. BOGHOSIAN†, ALESSIO FARCOMENI§ AND JEFFREY D. HORBAR¶

University of South Carolina†, Sapienza–University of Rome§, University of Vermont¶, and Vermont Oxford Network

Abstract We develop an approach to risk classification based on quantile contours and allometric modelling of multivariate anthropometric measurements. We propose the definition of allometric direction tangent to the directional quantile envelope, which divides ratios of measurements into half-spaces. This in turn provides an operational definition of directional quantile that can be used as cutoff for risk assessment. Throughout the paper, we show the application of the proposed approach using a large dataset from the Vermont Oxford Network containing observations of birthweight and head circumference for more than 150,000 preterm infants.

1. Introduction. The remarkable works on anthropometry by Adolphe Quetelet and Sir Francis Galton in the 19th century gave birth to a new field of scientific investigation within which the medical and statistical sciences developed a long-lasting and profitable collaboration. In turn, this has given rise to countless research studies in public health and to the development of important analytic methods. For example, the body mass index (BMI), also known as the Quetelet index, is universally applied by researchers and clinicians to classify individuals into categories such as ‘underweight’, ‘overweight’, and ‘obese’ as these may be at higher risks of poorer health outcomes.

It is no secret that Quetelet and Galton were particularly keen on the statistical aspects of anthropometry. The relative merits and demerits of

†Corresponding author: Marco Geraci, Department of Epidemiology and Biostatistics, Arnold School of Public Health, University of South Carolina, 915 Greene Street, Columbia SC 29209, USA. E-mail: geraci@mailbox.sc.edu

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different summary statistics (i.e., mean, mode, median, and percentiles) and the conformity of anthropometric measurements to the ‘laws of chance’ were already discussed back then (Boas, 1893). Galton himself provided a systematic definition of quantiles and popularized terms such as ‘median’, ‘quartile’ and ‘percentile’ (Galton, 1882, 1885). He understood the importance of looking at ordered data as a means to characterize the distribution of a random variable. Given his disposition to present data graphically, Galton also introduced the ogive, which today we call ‘quantile function’ (Gilchrist, 2008).

Anthropometric and growth charts are perhaps the best-known applications of quantile function modelling. International and national public health institutes like the World Health Organization (WHO) and the Centers for Disease Control and Prevention have published standard charts for important health-related measurements. These are usually taken on a large number of individuals who belong to either a standard or a referent population. The distribution of the outcome of interest is then estimated and plotted as a function of time (e.g., age). Conditional on each time point, an anthropometric chart gives estimated percentiles (e.g., 5th, 10th, 50th, etc.) against which a new measurement can be compared and ranked to identify unusual deviations from the ‘norm’ of the population at large. For example, WHO provides standards for individual anthropometric variables such as weight-for-age and height-for-age, or for pairs of measurements, one conditional on another, such as weight-for-length and weight-for-height (http://www.who.int/childgrowth/standards/en/). When collected over time, longitudinal measurements can be used to describe different stages of physical growth from the early stages of life to adulthood (growth charts). In the following we will use the terms ‘normal’, ‘subnormal’ (below normal), ‘supranormal’ (above normal), and ‘abnormal’ (not normal, either below or above) to classify observations based on arbitrary cutoffs but without giving them any clinical or diagnostic connotation.

In this paper, we are specifically interested in anthropometric charts for preterm infants (22 to 29 weeks’ gestation). Preterm babies, particularly those born at lower gestational ages, have high risks of mortality, morbidities, and neurodevelopmental impairment (Stoll et al., 2010; Horbar et al., 2012). For example, it is estimated that at 22 and 23 weeks’ gestation the mortality rate can be as high as 80% (Stoll et al., 2010). At these ages, there are significant rates of respiratory distress syndrome (94%), patent ductus arteriosus (46%), severe intraventricular hemorrhage (16%), necrotizing enterocolitis (11%), and late-onset sepsis (36%) (Stoll et al., 2010).

Preterm birth is not the only risk factor. Growth restriction, usually de-
fined as birthweight (BW) less than the 10th percentile for gestational age—or small for gestational age (SGA)—further raises already high risks among preterm infants (Bernstein et al., 2000) and, hence, is used as an indicator for secondary and tertiary prevention of mortality and adverse outcomes. The etiology of SGA is multifactorial with some causes linked to, for example, smoking, placental insufficiency, environmental factors, and maternal complications like preeclampsia. These factors not only impact BW but might also affect the size of the head (as measured by head circumference, HC, right after birth), with consequences that may vary according to the particular period of pregnancy in which the insult has occurred. It has been theorized that: if the insult occurs early during pregnancy or even before conception, growth restriction is symmetric (or proportional) and both BW and HC are affected; if the insult occurs later during pregnancy, growth restriction is asymmetric (or disproportional), with negative consequences mainly for BW, thus resulting in a larger HC-to-BW ratio (Vandenbosche and Kirchner, 1998; Saleem et al., 2011). Asymmetric growth is thought to be an adaptive mechanism that is put in place to protect the brain. In response to placental insufficiency, which is often caused by hypertension and leads to intrapartum growth restriction, the fetus adapts its circulation to preserve oxygen and nutrient supply to the brain (the ‘brain-sparing’ effect). Some studies investigated the determinants of fetal growth and body proportionality, as well the effect of the latter on neonatal outcomes. They found that (severe) pregnancy-related hypertension, which is the development of new hypertension after 20 weeks’ gestation, is strongly associated with a larger HC-to-BW ratio (Kramer et al., 1990a). The latter, in turn, was found to be a risk factor for stillbirth and fetal distress (Kramer et al., 1990b).

Most of the times, BW and HC are treated separately in statistical analyses. For example, they are analyzed as separate outcomes or as ‘independent’ predictors of postnatal child outcomes. However, there are good reasons why it could be informative to analyze these variables jointly. First of all, BW and HC are necessarily related. Larger weights correspond to larger head circumferences, although the younger the baby the larger the head size in relation to the size of body. In other words, the HC-to-BW ratio decreases with (gestational) age. Figure 1 shows the relationship between BW and HC in preterm infants from the Vermont Oxford Network (VON) dataset (Section 2) along with the HC-to-BW ratio as a function of gestational age (GA). Secondly, health outcomes may differ among infants whose BW and HC are ranked jointly normal or abnormal, as those with symmetric and asymmetric growth. Joint ranking obviously necessitates multivariate distributions.
Multivariate modelling has a long tradition in parametric statistics. Models for joint distributions are, more or less, direct extensions of well-known univariate distributions to higher dimensions. The multivariate normal distribution is, among others, often invoked for its mathematical and statistical properties. In the past few years, there has been a growing number of applications giving stronger attention to distributions that can flexibly account for heavier tails (Goodman and Kotz, 1973), skewness (Azzalini and Dalla Valle, 1996; Kozubowski and Podgorski, 2000; Kozubowski, Podgórski and Rychlik, 2013) and, more in general, to non-elliptical distributions.

Here, rather than assuming a specific parametric distribution, we take a more agnostic approach and we propose to investigate these issues by using directional quantile envelopes (DQEs) for multivariate data (Kong and Mizera, 2012). The literature on quantile regression (QR) with multivariate data encompasses a number of different proposals (Chakraborty, 2003; Chaudhuri, 1996; Chavas, 2017; Hallin, Paindaveine and ˇSiman, 2010; Serfling, 2002) whose goal is to estimate the quantile of a \( k \)-variate response. The common denominator in these studies is the difficulty of defining a ‘multivariate quantile’ given that there is no natural ordering in a \( k \)-dimensional space. The methods employed here do not offer such a definition, but provide an operational framework for multivariate analysis nonetheless. A different problem concerns the simultaneous estimation of multiple quantiles of a univariate variable (Zou and Yuan, 2008) and is not relevant to our discussion. Similarly, we are not concerned with the identification of implausible observations that do not belong to the distribution under study (Filzmoser, Maronna and Werner, 2008). Although the problem of outlier detection is an important one and is related to ours, it entails separate developments from those discussed here.

The aim of our paper is to show how DQEs can be used to identify observations that deviate from the bulk of the multidimensional scatter of observations in anthropometric charts. These may represent infants at higher risk of adverse health outcomes. We further classify infants based on whether their measurements are proportional or disproportional, which leads to the use of ratios and, in general, allometric models. At that juncture of the paper, we establish, for the first time, a connection between DQEs and allometric modelling.

The rest of the paper is organized as follows. In Section 2, we give a general overview of VON and some details about the variables of interest. In Section 3, we briefly discuss quantiles for univariate data and their limitations when used as individual cutoffs in multivariate problems. In Section 4, we provide the formal definition of DQE and introduce the relationship
between directional quantiles and ratios. In Section 5, we establish the connection between DQEs and allometry in the bivariate case, while the general case is presented in Section 6. Rather than presenting the methods and the real data analysis separately, we ‘walk’ the reader through the exposition of the methods using the VON data so as to show that our modelling choices are deeply rooted in our application. Yet, extensions and generalizations to other settings are discussed throughout the paper including the Discussion (Section 7).
Figure 1. Left: head circumference (HC) vs birthweight (BW). The horizontal dashed line marks the estimated 10th percentile of HC at age 162 days (Bogossian et al., 2016); the vertical dashed line marks the estimated 10th percentile of BW at age 162 days (Bogossian et al., 2016). Right: HC-to-BW ratio vs gestational age. Superimposed solid lines represent smoothing splines predictions.
2. The Vermont Oxford Network. The Vermont Oxford Network (VON) is a nonprofit, voluntary collaboration of health care professionals ‘dedicated to improving the quality and safety of medical care for newborn infants and their families through a coordinated program of research, education, and quality improvement projects’ (https://public.vtoxford.org/about-us/). The Network was established in 1988 and comprises over 800 centers (hospitals) with a neonatal intensive care unit (NICU). The Very Low Birth Weight Database collects information from these centers which account for approximately 90% of all the births occurring at 22-29 weeks of gestation in the United States (US). A number of variables are collected from each center: maternal characteristics (e.g., ethnicity), infant characteristics (e.g., sex, gestational age, birthweight, head circumference, birth defects), and newborn health outcomes (mortality and major morbidities). Member hospitals collect the data using uniform definitions through medical record abstraction which are then submitted to VON electronically or through paper forms. Data pass automated checks and are returned for correction if needed.

Our study sample was restricted to inborn, singleton US infants born at 22 to 29 weeks of gestation between 2006 and 2014, with no congenital malformations. GA was determined using obstetrical measures based on prenatal ultrasound (accuracy ±7 days), last menstrual period (accuracy ±14 days), or a neonatologist’s estimate based on postnatal physical examinations (accuracy ±13 days for Dubowitz examination). BW was recorded from labor and delivery or, if unavailable, upon admission to the neonatal unit. HC was recorded on the day of birth or the day after. The data underwent some mild cleaning procedures as described elsewhere (Boghossian et al., 2016). In particular, we excluded infants with missing information on vital status (841), unknown gender (30), missing (71) or implausible (744) BW, missing (24,706) or implausible (860) HC, missing hospital length-of-stay (78), or who were hospitalized for longer than one year (565). Implausible values BW and HC were identified using thresholds based on nonparametric density estimation (Rich et al., 2014). Overall, about 15% infants were excluded, leaving 155,746 infants for our analysis.

Table 1 gives summary statistics of the sample by sex and four gestational age intervals: (21,23], (23,25], (25,27], and (27,29] weeks. These data were used in previous publications (Boghossian et al., 2016, 2018) to generate BW- and HC-for-gestational-age percentile charts for clinical use. As compared to other anthropometric charts (Olsen et al., 2010; Oken et al., 2003; Barbier et al., 2013), which had limited sample sizes or had no data on race, VON charts are based on the largest, nationwide, and racially diverse
dataset currently available.

| Gestational age | Females | | Males | |
|-----------------|---------|---------|--------|---------|
| (21,23]         | 5,496   | 550     | 20.5   | 6,036   | 580     | 21.0    |
| (23,25]         | 17,398  | 680     | 22.0   | 19,305  | 730     | 22.5    |
| (25,27]         | 22,448  | 890     | 24.0   | 24,996  | 950     | 24.5    |
| (27,29]         | 28,097  | 1,145   | 26.0   | 31,970  | 1,220   | 26.5    |
| All ages        | 73,439  | 880     | 24.0   | 82,307  | 945     | 24.5    |

3. Quantiles of univariate data. The quantile function (QF) of a random variable $Y$ with cumulative distribution function (CDF) $F_Y(y)$ is defined as

$$Q_Y(p) = \inf\{y \in \mathbb{R} : F_Y(y) \geq p\}, \quad 0 < p < 1.$$ 

Here we assume that $Y$ is absolutely continuous with probability density function $f_Y(y) > 0$ over the support of $Y$. Therefore the QF is simply the inverse of the CDF, $Q_Y(p) \equiv F_Y^{-1}(p)$.

In the presence of covariates, the QF can be extended to conditional distributions. The linear specification of the QR model is (Koenker and Bassett, 1978)

$$Q_{Y|X}(p) = \mathbf{x}^\top \beta(p),$$

where $X$ is a $q$-dimensional vector and $\beta(p)$ is a vector of $q$ coefficients indexed by the quantile level $p$. A generalization of (2) defines

$$Q_{Y|X}(p) = h\{\mathbf{x}^\top \beta(p)\},$$

where the transformation $h$ can be modelled either parametrically or non-parametrically. Moreover, if $h$ is monotone, then $Q_{h^{-1}(Y)|X}(p) = \mathbf{x}^\top \beta(p)$, which we call transformation rule (Gilchrist, 2000) (also known as equivariance to monotone transformations). It is worth mentioning here that quantiles enjoy a number of other properties (Gilchrist, 2000), including the reflection rule $Q_{-Y|X}(p) = -Q_{Y|X}(1-p)$.

In clinical settings, it is customary to define a cutoff for subnormal measurements. Such a cutoff is often related to a specific quantile of the distribution. For example, infants are classified as SGA if their BW is below the
10th percentile of the BW distribution conditional on gestational age; otherwise, they are termed appropriate for gestational age (AGA). Assuming a model as in (3), the cutoff would be determined as

$$Q_{BW|GA}(0.1) = h_BW\{\beta_0(p) + \beta_1(p) \cdot GA\},$$

for some suitable transformation $h_BW$ (Geraci and Jones, 2015; Boghossian et al., 2016). Similarly, infants are said to have a subnormal head size if their HC is below the 10th percentile of the HC distribution conditional on GA, that is

$$Q_{HC|GA}(0.1) = h_{HC}\{\beta_0(p) + \beta_1(p) \cdot GA\},$$

assuming, as before, that model (3) holds for some transformation $h_{HC}$ (Geraci and Jones, 2015; Boghossian et al., 2016). Clearly, these cutoffs need be estimated, either externally using a representative sample from the standard or referent population of interest, or internally from within the same data. The cutoffs used in this paper were taken from published charts (Boghossian et al., 2016, 2018).

As mentioned in the introductory remarks, SGA infants and infants with subnormal HC are at increased risk of poor health outcomes. We can investigate exposure-outcome associations using appropriate regression models. In particular, if we have both BW and HC as exposures, we could define a categorical variable $u$ with categories ‘normal BW, normal HC’, ‘subnormal BW, normal HC’, and ‘subnormal BW, subnormal HC’ (we exclude the category ‘normal BW, subnormal HC’ as not clinically relevant to our specific analysis). Let $W$ be the outcome of interest (death) and $x$ a vector of covariates associated with $W$ (sex, gestational age, and their interaction). Using the VON data, we fitted the generalized linear model

$$E(W) = \phi^{-1}(u, x)$$

with log-link function $\phi$.

Table 2 shows the mortality risk of girls born at different gestational ages. The baseline is given by infants with normal (i.e., above the 10th percentile for gestational age and sex) BW and HC. At the lowest GA weeks, the baseline risk is 52%, that is, one out of two girls does not survive. The risk increases by 36% in SGAs. However, if both HC and BW are below their respective cutoffs, then the risk increases by 50%, meaning that 3 out of 4 of these small girls do not survive. At later gestational ages, the absolute risk of mortality is lower. However, the relative risk (RR) remains high and even increases within each group. Similar patterns were observed in boys, of which we omit the table to save space.
The risk categories in Table 2 are defined using separate rankings for BW and HC. This is the approach taken by some authors (Lin, Su and River, 1991; Guellec et al., 2015). However, this approach presents a difficulty. While the specific cutoff values (e.g., 10th percentile) may be relevant for BW and HC taken individually, nothing can be said about the joint ranking of the measurements. For example, the observation marked by a thick cross in the left plot of Figure 1 (a girl born at 162 days of gestation) presents normal (for gestational age) weight (489 g) and HC (30 cm) and thus falls in the baseline group for (23,25]-weekers in Table 2. Upon closer inspection, this infant has a rather extreme HC-to-BW ratio (right plot in Figure 1), a possible consequence of the ‘brain-sparing’ effect. Thus it is natural to wonder whether there are differences in terms of health outcomes between small infants (as defined by individual cutoffs for BW and HC) with unusual HC-to-BW ratio and those with normal HC-to-BW ratio. As we will show in Section 5, the study of the HC-to-BW ratio leads to allometric modelling and this, in turn, is intimately connected with directional quantile envelopes.

Table 2

The gestational-age-specific mortality risk and 95% confidence interval for girls born preterm (22 to 29 weeks) with normal birthweight (BW) and head circumference (HC) are shown in bold font. The other rows show the mortality relative risk (as compared to infants with normal BW and HC) and 95% confidence interval for infants with either one or both anthropometric measurements below the univariate 10th percentile. The sample size is denoted by N.

| BW      | HC      | N    | Risk | Lower | Upper |
|---------|---------|------|------|-------|-------|
| (21,23] weeks |
| Normal | Normal  | 4,655| **0.52** | **0.51** | **0.54** |
| < 10th | Normal  | 306  | 1.36  | 1.26  | 1.47  |
| < 10th < 10th | 213  | 1.50  | 1.39  | 1.61  |
| (23,25] weeks |
| Normal | Normal  | 14,979| **0.19** | **0.19** | **0.20** |
| < 10th | Normal  | 736  | 1.85  | 1.67  | 2.05  |
| < 10th < 10th | 1,033  | 2.69  | 2.51  | 2.88  |
| (25,27] weeks |
| Normal | Normal  | 19,571| **0.06** | **0.06** | **0.07** |
| < 10th | Normal  | 860  | 2.12  | 1.77  | 2.54  |
| < 10th < 10th | 1,368  | 4.19  | 3.77  | 4.65  |
| (27,29] weeks |
| Normal | Normal  | 24,318| **0.02** | **0.02** | **0.03** |
| < 10th | Normal  | 1,253| 1.70  | 1.28  | 2.25  |
| < 10th < 10th | 1,531  | 3.83  | 3.21  | 4.58  |
4. Quantiles of multivariate data. Let $\mathbf{Y} = (Y_1, \ldots, Y_K)^\top$ denote a multivariate random vector collecting measurements for $K$ continuous variables (e.g., BW and HC) and let $\mathbf{d} = (d_1, \ldots, d_K)^\top$ be a normalized (with unit norm) direction of dimension $K$. The $p$th directional quantile, in the direction $\mathbf{d}$, is the $p$th quantile of the corresponding projection of the distribution of $\mathbf{Y}$, that is $Q_{\mathbf{d}^\top \mathbf{Y}}(p)$. The supporting half-space determined by $\mathbf{d}$ is $H(\mathbf{d}, \xi) = \{ \mathbf{y} : \mathbf{d}^\top \mathbf{y} \geq \xi \}$. The $p$th directional quantile envelope (DQE) generated by $Q_{\mathbf{d}^\top \mathbf{Y}}(p)$ is given by the intersection (Kong and Mizera, 2012)

$$D(p) = \bigcap_{\mathbf{d}} H(\mathbf{d}, Q_{\mathbf{d}^\top \mathbf{Y}}(p)), \quad 0 < p \leq 0.5.$$  

In a bivariate space ($K = 2$), the geometric intuition behind (4) is as follows. Consider a scatter of points as that on the left plot in Figure 1; fix $p$ equal to 0.1; and define a direction on the circle at an angle $\theta$. For example, the west-east direction is for $\theta = 0$ while the south-north direction is for $\theta = \pi/2$. Next, we cumulate data points while moving along the chosen direction and we stop when the cumulative proportion is 10%. We demarcate a line which divides the plane into two half-planes, a ‘lower’ half-plane with 10% of the points, and an ‘upper’ half-plane with the remaining 90%. If we repeat this process for all the possible directions on the circle, then the intersection of all the demarcation lines defines an oval-shaped contour within which the data points belong to the upper half-planes in all directions. These data points represent the set $D(0.1)$. Similarly, the points outside the perimeter, which we denote by $\overline{D(0.1)}$, belong to the lower half-planes in some directions.

From the above exemplification it becomes clear that the proportion of points that are in $D(p)$ will be less than $(1 - p)$ since these points satisfy $\mathbf{d}^\top \mathbf{y} \geq Q_{\mathbf{d}^\top \mathbf{Y}}(p)$ for all $\mathbf{d} \in \mathbb{R}^K$. It also becomes clear that the quantile $p$ in a given direction is equivalent to the quantile $1 - p$ in the opposite direction, e.g., the 10th directional percentile in the south-north direction is equivalent to the 90th directional percentile in the north-south direction (hence, $0 < p \leq 0.5$).

Directional quantiles can be easily extended to conditional distributions. If we assume a linear model as in (2), we obtain

$$Q_{\mathbf{d}^\top \mathbf{Y} | \mathbf{X}}(p) = \mathbf{x}^\top \beta(p).$$

Then the DQE (4) can be applied to the conditional quantiles in (5).

Model (5) presupposes the additivity of the coordinates of $\mathbf{Y}$ since $\mathbf{d}^\top \mathbf{Y} = d_1 Y_1 + d_2 Y_2$. If, instead, a multiplicative relationship is to be studied, then
the logarithmic transformation of the measurements is more appropriate (Kong and Mizera, 2012), i.e.

\[ Q_{d^\top Z|X}(p) = x^\top \beta(p), \]  

where \( Z = (\log Y_1, \log Y_2)^\top \). The \( p \)th directional quantiles of the coordinates on the log-scale therefore corresponds to the \( p \)th quantile of the log-ratio of the scaled coordinates, that is

\[ d_1 \log Y_1 + d_2 \log Y_2 = \log \left( \frac{Y_2^{d_2}}{Y_1^{d_1}} \right). \]

In public health and clinical settings, examples of widely-used ratios of anthropometric variables are the BMI index (mass/height\(^2\)) and the corpulence or Rohrer index (mass/height\(^3\)). Indeed, there exists a plethora of indices where body measurements are combined as ratios, often upon power transformations.
Figure 2. Left: directional quantile envelopes (DQEs) of birthweight (BW) and head circumference (HC) at levels $p = 0.1$ and $p = 0.005$ for girls born at [23, 25] weeks of gestation. The dashed line marks the 90th percentile of the HC-BW ratio in the allometric direction. Right: gestational-age-specific DQEs of BW and HC for all girls at level $p = 0.1$. 
Given that traditionally the scaling variable in allometric studies is mass, we let \( Y_1 = BW \). An illustration of the DQE of \( Z = (\log BW, \log HC)^\top \) at level \( p = 0.1 \) for girls born at \((23, 25]\) weeks is given in the left plot of Figure 2. The outer points (i.e., \( D(0.1) \)) represent BW and HC measurements that are jointly abnormal as compared to those that fall in \( D(0.1) \). Note the difference between \( D(0.1) \) and \( D(0.005) \) in terms of shape, which gives insight into the advantages of a nonparametric approach. If we stay in the more central regions of the data points, the almost elliptical shape of the 90th DQE suggests a well-behaved, symmetric distribution. Indeed, the 90th DQE of the bivariate normal distribution fitted on the data (not shown) would not be far from the nonparametric DQE. As we move towards a more extremal region, we notice that the 99.5th DQE is skewed towards larger values of HC.

We can take advantage of model (6) to estimate conditional DQEs. The right plot of Figure 2 shows the estimated \( D(0.1) \) of log-BW and log-HC conditional on gestational age for all girls using directional quantiles

\[
Q_d^{\top} z; x(p, 0.1) = \beta_0(p) + \beta_1(p)x_1 + \beta_2(p)x_2 + \beta_3(p)x_3,
\]

where the reference is \((21, 23]\) weeks and \( x_j, j = 1, 2, 3 \), are dummy variables for the other gestational age intervals.

Classifying infants based on the DQE for BW and HC, in addition to the standard univariate cutoffs for these measurements, has an immediate consequence on the estimation of the mortality risk, as shown in Table 3. The latter provides gestational-age-adjusted estimates of risk for all girls and all boys. First of all, we note that the baseline risk is similar in both DQE groups. However, the RR for infants inside the DQE that have individual subnormal BW and HC, is substantially lower than the RR for infants in similar groups but outside the DQE. In other words, the second level of grouping based on the DQE represents a refinement of risk classification.

Depending on the specific application, we still may want to focus on a particular group of measurements that are jointly abnormal, since the ‘abnormal’ labelling of these measurements applies to disparate groups (SGA infants with subnormal HC, infants that have supranormal BW and HC, and those with asymmetric BW and HC). Suppose that we are interested in the brain-sparing effect. The dashed line in Figure 2 marks the 90th percentile of the HC-to-BW ratio in a particular direction (note that this is tangent to the DQE). Points to its left have a relatively large value of HC as compared to that of BW. Among these, marked by a thick cross, we find the girl born at 162 days of gestation that was featured in Figure 1. Indeed, this observation seems to be rather extreme even at \( p = 0.005 \). In the next section,
we formalize the relationship between directional quantiles and ratios via an allometric equation.

Table 3

The gestational-age-adjusted mortality risk and 95% confidence interval for infants born preterm (22 to 29 weeks) with normal birthweight (BW) and head circumference (HC) are shown in bold font. The other rows show the mortality relative risk (as compared to infants with normal BW and HC) and 95% confidence interval for infants with either one or both anthropometric measurements below the univariate 10th percentile. Estimates are given separately for infants whose BW and HC measurements belong to $D(0.1)$ (jointly normal) or to $D(0.1)$ (jointly abnormal). The sample size is denoted by $N$.

| BW    | HC     | N    | Risk | Lower | Upper | N    | Risk | Lower | Upper |
|-------|--------|------|------|-------|-------|------|------|-------|-------|
| Females | Jointly normal | Jointly abnormal |
| Normal | Normal | 41,067 | 0.12 | 0.11 | 0.12 | 22,456 | 0.11 | 0.10 | 0.11 |
| < 10th Normal | 442 | 0.96 | 0.74 | 1.26 | 2713 | 2.07 | 1.91 | 2.25 |
| < 10th | < 10th | 195 | 1.11 | 0.77 | 1.61 | 3950 | 2.81 | 2.64 | 2.98 |
| Males | Jointly normal | Jointly abnormal |
| Normal | Normal | 46,627 | 0.14 | 0.14 | 0.14 | 24,443 | 0.12 | 0.12 | 0.13 |
| < 10th Normal | 413 | 1.32 | 1.08 | 1.62 | 3193 | 2.02 | 1.89 | 2.17 |
| < 10th | < 10th | 199 | 1.46 | 1.11 | 1.92 | 4353 | 2.68 | 2.54 | 2.83 |

5. Bivariate percentiles and allometric analysis. In this section, we address in more detail the allometric relationship between BW and HC, a matter that we only briefly touched upon in the previous sections. We consider an allometric model of the type

$$Y_2 = aY_1^b,$$

$a, b > 0$. Equation (8) implies that the allometric ratio $Y_2/Y_1^b$ is constant and equal to $a$. In our specific application, the scaling exponent $b$ captures the differential growth ratio between the head and the body as a whole. For $b = 1$, the variables $Y_1$ and $Y_2$ are said to be isometric.

We fitted model (8) for BW and HC on the log-scale using standardized major axis (MA) regression as implemented in the R package smatr (Warton et al., 2012). The reason for this choice lies in the likely presence of measurement error in both variables (Warton et al., 2006). Table 4 shows estimates of the coefficients and standard errors for all infants as well as by sex and by gestational age. Overall, the estimated coefficient $\hat{b} \approx 0.32$ hints at the cubic relationship between length and volume, although the test of the null hypothesis $H_0 : b = 1/3$ gave a $p$-value less than 0.001. The estimated scaling exponent was almost identical for boys and girls ($p = 0.841$), but changed
significantly \((p < 0.001)\) across gestational ages. The rightmost column of Table 4 shows the 90th percentile of the estimated allometric ratio \(\text{HC}/\text{BW}^b\), whose relevance in our discussion is made clear further below.

### Table 4
Estimates (standard errors) of the coefficients of the allometric model for \(\text{BW}\) and \(\text{HC}\), along with the \(p\)-values of the test on equality of the slopes. The 90th percentile of the allometric ratio is reported in the last column.

| Parameter | \(\log_{10} a\) | \(b\) | \(Q_R(0.9)\) |
|-----------|-----------------|------|---------------|
| All       | 0.4488 (0.0011) | 0.3166 (0.0004) | 2.9647 (0.0006) |
| Sex (\(p\)-value 0.841) | | | |
| Females   | 0.4488 (0.0017) | 0.3166 (0.0006) | 2.9641 (0.0008) |
| Males     | 0.4497 (0.0016) | 0.3164 (0.0005) | 2.9704 (0.0009) |
| Gestational age (\(p\)-value < 0.001) | | | |
| \(21,23\] | 0.1816 (0.0087) | 0.4125 (0.0032) | 1.6123 (0.0018) |
| \(23,25\] | 0.4212 (0.0034) | 0.3260 (0.0012) | 2.7798 (0.0013) |
| \(25,27\] | 0.5102 (0.0027) | 0.2963 (0.0009) | 3.4026 (0.0011) |
| \(27,29\] | 0.5413 (0.0024) | 0.2865 (0.0008) | 3.6553 (0.0010) |

Model (8), if correctly specified, provides a benchmark against which we can classify abnormal \(\text{HC}\)-to-\(\text{BW}\) ratios. We have also seen that bivariate percentiles are instrumental to the modelling of ratios. The following proposition establishes the connection between (4) and (8).

**Proposition 1.** Let \(Y_1\) and \(Y_2\) be two continuous and strictly positive random variables, and assume that the allometric model \(Y_2 = aY_1^b, a,b > 0\), holds true. Also, define \(Z = (\log Y_1, \log Y_2)^\top\) and assume that the \(p\)th directional quantile envelope \(D(p)\) generated by \(Q_{a\top Z}(p)\) is smooth. Then the lines

\[
\log Y_2 = \log \{Q_R(p)\} + b \cdot \log Y_1
\]

(9)

\[
\log Y_2 = \log \{Q_R(1-p)\} + b \cdot \log Y_1
\]

where \(R = \frac{Y_2}{Y_1^b}\), are tangent to \(D(p)\).

**Proof.** We only need to prove that the line tangent to \(D(p)\) is of the form (9). By definition of \(D(p)\), the former is given by

\[
Z_2 = \frac{1}{d_2} Q_{a\top Z}(p) - \frac{d_1}{d_2} Z_1
\]
for any given direction $d$.

On the log-scale, the allometric equation given in Proposition 1 relating $Y_1$ to $Y_2$ can be re-written as

$$b \log(Y_1) - \log(Y_2) = -\log a,$$

which has the same form of (7) with $d_1 = b$ and $d_2 = -1$. Therefore, for $d = (b, -1)^\top$, which we call allometric direction, the line tangent to $D(p)$ is $\log Y_2 = -Q_d \top Z(p) + b \log Y_1$. Now, by (7) we have that $d \top Z = -\log (Y_2/Y_1^b) = -\log R$. Since the logarithm is a monotone transformation, we use the transformation rule introduced in Section 3 and obtain $Q_d \top Z(p) = Q_{-\log R}(p) = -\log \{Q_R(p)\}$. Then the tangent line equation becomes $\log Y_2 = \log \{Q_R(p)\} + b \log Y_1$, which corresponds to the first equation given in (9). To obtain the second equation in (9), it is sufficient to notice that $Q_{-\log R}(p) = -Q_{\log R}(1-p) = -\log \{Q_R(1-p)\}$, where the first equality follows from the reflection rule and the second equality follows from the transformation rule.

For a rigorous proof of the geometric properties of $D(p)$, the reader is referred to Kong and Mizera (2012).

Two corollaries to Proposition 1 follow.

**Corollary 1.** The tangent lines are unique.

**Corollary 2.** The tangent half-spaces are the sets of points $Y = (Y_1, Y_2)^\top$ such that $R < Q_R(p)$ and $R > Q_R(1-p)$.

The first corollary follows from the smoothness of $D(p)$. The second corollary is a consequence of the definition of $D(p)$. More importantly, this corollary provides the operational definition of subnormal ($R < Q_R(p)$) and supranormal ($R > Q_R(1-p)$) ratios corresponding to the allometric direction. The dashed line in the left plot of Figure 2 is indeed an illustration of the allometric direction. One may wonder if there is anything special about this direction. The answer lies in the properties of the estimator of $b$. In particular, if $b$ is estimated using MA regression, the directional quantile in the allometric direction is in the same direction as the principal axis of the bivariate normal ellipse fitted to the log-transformed data. It is well-known that this is the direction of the first eigenvector of the variance-covariance matrix of $Z$. Of course, there is nothing necessarily prescriptive about the normal distribution, so one can explore an alternative estimator for $b$ under a different distribution, if that distribution has a theoretical or empirical
relevance, or use a nonparametric estimator. For example, it is common to estimate the slope of MA regression under the assumption of homoscedasticity for the log-additive counterpart of model (8). If necessary, this assumption may be relaxed to improve on accuracy and efficiency of the estimates by introducing a variance function of the type \( \text{var}(Y_2) = \tau^2 Y_1^c \), where \( \tau > 0 \) and \( c > 0 \). Alternatively, using a distribution-free approach, one could estimate \( b \) by means of median regression on the log-scale (Geraci, Alston and Birch, 2013), with advantages in terms of robustness to outliers and error distribution, as well as in terms of lossless transformation between scales due to the equivariance property. Moreover, such estimator has a close relationship with the Laplace distribution. However, the median estimator would not be robust to measurement error in the covariates and hence would require the application of methods that are computationally more complex than MA regression (Wei and Carroll, 2009; Mao, Wei and Liu, 2017).

In general, there is a stronger motivation for using the allometric direction and this is related to body proportionality in human growth assessment. If we consider studies on infants, the definition of ‘proportionality’ varies from study to study, where body weight is sometimes related to HC, or abdomen circumference, or more commonly to length. Except for some studies (e.g., as those based on the Rohrer index, Olsen et al., 2009), several other implicitly assume isometric scaling by defining ratios of the type \( R_0 = Y_2/Y_1 \) (Kramer et al., 1990a; Lin, Su and River, 1991; Williams and O’Brien, 1998; Dashe et al., 2000). However, if the true scaling exponent \( b \) is different from one, then the ratio

\[
R_0 = aY_1^{b-1}
\]

depends on \( Y_1 \). This requires that a definition of abnormal ratio should be based on the conditional quantile \( Q_{R_0|Y_1}(p) \), not on the marginal \( Q_{R_0}(p) \). The consequence of using the latter would be a misclassification of infants in categories of possibly different risks.

In Table 5, we report the results of an analysis similar to that conducted for Table 3. This time we classified infants based on whether their allometric ratio \( HC/BW^b \) was above the 90th percentile, where \( b \) was the gestational-age-specific estimated coefficient given in Table 4. While the baseline risk (normal BW and HC) is comparable in these two groups, the mortality risk among SGA infants with subnormal HC and supranormal ratio is about three times the baseline risk, but about twice the baseline risk in those with a normal ratio. Moreover, disproportionately small infants have a higher absolute risk \((3.17 \times 0.14 = 0.44)\) than proportionately small infants \((2.16 \times 0.14 = 0.30)\). Note that Tables 3 and 5 both stratify relative risks by a third variable (the DQE and the allometric ratio, respectively) to differentiate
Table 5
The gestational-age-adjusted mortality risk and 95% confidence interval for infants born preterm (22 to 29 weeks) with normal birthweight (BW) and head circumference (HC) are shown in bold font. The other rows show the mortality relative risk (as compared to infants with normal BW and HC) and 95% confidence interval for infants with either one or both anthropometric measurements below the univariate 10th percentile. Estimates are given by sex, separately for infants whose HC-to-BW ratio is below the 90th percentile (normal) or above it (supranormal). The sample size is denoted by N.

| BW | HC | N   | Risk | Lower | Upper | N   | Risk | Lower | Upper |
|----|----|-----|------|-------|-------|-----|------|-------|-------|
| Females | Normal | Normal | 59,033 | 0.11  | 0.11  | 0.11 | 4,490 | 0.13  | 0.12  | 0.14  |
| | < 10th Normal | 1,425 | 1.70  | 1.52  | 1.90  | 1,730 | 1.62  | 1.44  | 1.82  |
| | < 10th < 10th | 3,284 | 2.30  | 2.16  | 2.45  | 861 | 3.14  | 2.82  | 3.50  |
| Males | Normal | Normal | 65,984 | 0.14  | 0.13  | 0.14 | 5,086 | 0.14  | 0.13  | 0.15  |
| | < 10th Normal | 1,425 | 1.77  | 1.61  | 1.95  | 2,181 | 1.81  | 1.64  | 2.00  |
| | < 10th < 10th | 3,384 | 2.16  | 2.04  | 2.28  | 1,168 | 3.17  | 2.88  | 3.48  |

between groups. However, while the former type of stratification does not discriminate between directions, the latter operates in a specific direction. Despite the fact that the calculation of the DQE is not necessary to obtain Table 5, yet Proposition 1 asserts that the allometric direction as in (9) is tangent to the DQE. This in turn guarantees that all the points such that \( R > Q_R(0.9) \) represent a subset of \( D(0.1) \).

We then investigated maternal hypertension, which has been previously found to be a determinant of the HC-to-BW ratio in its severe, pregnancy-induced form (Kramer et al., 1990a). While information on hypertension is available in the VON data, unfortunately this variable has two limitations: it includes both chronic and pregnancy-induced hypertension (PIH), and is missing for about 21% (though mostly in early years of data collection). Yet, some interesting observations can be made.
Figure 3. Directional quantile envelopes (DQEs) of birthweight (BW) and head circumference (HC) at levels $p = 0.1$ and $p = 0.005$ for infants born to normotensive (solid lines) and hypertensive mothers at different gestational ages.
Hypertension is known to increase the likelihood of growth restriction. This is apparent from Figure 3 which shows estimated DQEs conditional on hypertension status. Its relationship with mortality risk is, however, controversial. Some studies suggested that PIH increases the risk of fetal, perinatal, and early neonatal mortality (Jain, 1997), while other studies found the opposite (Chen et al., 2006). In our data, the prevalence of hypertension (chronic and gestational) is overall about 28%, while infant mortality rates are approximately 0.15% and 0.11% in, respectively, normotensive and hypertensive mothers, suggestive of a ‘protective’ effect of hypertension. However, the rate of hypertension is 25% among mothers of babies with normal HC-to-BW ratio, but 54% in mothers of disproportionately small babies. In other words, there is a strong, positive association between hypertension and supranormal ratios ($\chi^2$ test’s $p$-value $< 0.001$). As shown in Table 6, the mortality risk in infants with normal BW and HC is lower if born to hypertensive mothers as compared to normotensive mothers, regardless of their HC-to-BW ratio. However, disproportionately small infants born to hypertensive mothers have an absolute risk of $6.21 \times 0.07 = 0.43$ which, compared to an absolute risk of $2.40 \times 0.17 = 0.41$ in their peers born to normotensive mothers, gives a rather different picture of the association between mortality and hypertension. It has been speculated that, in preterm infants born to hypertensive mothers, maternal hypertension is less damaging for fetal development than other causes of growth restriction (McBride et al., 2017). Our results do not exclude this hypothesis, but they also point to an interaction between hypertension (presumably its severe forms) and asymmetric growth restriction.
Table 6

The gestational-age-adjusted mortality risk and 95% confidence interval for infants born preterm (22 to 29 weeks) with normal birthweight (BW) and head circumference (HC) are shown in bold font. The other rows show the mortality relative risk (as compared to infants with normal BW and HC) and 95% confidence interval for infants with either one or both anthropometric measurements below the univariate 10th percentile. Estimates are given by HC-to-BW ratio groups, separately for infants born to normotensive and hypertensive mothers. The sample size is denoted by N.

| BW     | HC                | N     | Risk | Lower | Upper | N     | Risk | Lower | Upper |
|--------|-------------------|-------|------|-------|-------|-------|------|-------|-------|
|        | Normal HC-to-BW ratio |       |      |       |       |       |      |       |       |
| Normal | Normal            | 76,700| 0.13 | 0.13  | 0.13  | 22,136| 0.07 | 0.07  | 0.08  |
| < 10th | Normal            | 666   | 2.65 | 2.39  | 2.94  | 1,631 | 2.05 | 1.81  | 2.32  |
| < 10th | < 10th            | 1,972 | 2.43 | 2.28  | 2.60  | 3,479 | 3.30 | 3.06  | 3.56  |
|        | Supranormal HC-to-BW ratio |       |      |       |       |       |      |       |       |
| Normal | Normal            | 3,993 | 0.17 | 0.16  | 0.19  | 3,353 | 0.07 | 0.06  | 0.08  |
| < 10th | Normal            | 951   | 1.80 | 1.61  | 2.03  | 2,080 | 2.75 | 2.36  | 3.22  |
| < 10th | < 10th            | 579   | 2.40 | 2.14  | 2.70  | 1,041 | 6.21 | 5.37  | 7.19  |
6. Multivariate percentiles and allometric analysis. Our discussion so far has focussed on two variables only, mainly for practical reasons but also because the VON data do not provide anthropometric variables besides BW and HC. However, it is natural to consider a generalization for $K > 2$. One of the first problems we would encounter is, obviously, visualizing a multivariate DQE in more than, say, three or four dimensions. However, computationally (4) can be applied for any $K \geq 2$. In contrast, equation (8) does not seem to have an immediate multivariate counterpart and different approaches can be considered. A popular approach to multivariate allometry is based on principal component analysis (Jolicoeur, 1963; Corruccini, 1983) (PCA) due to its geometric properties. Further below we provide a generalization of Proposition 1 using PCA but we do not elaborate on it.

Let us consider a $k$-dimensional vector $Y$, $K \geq 2$, and the element-wise log-transformed vector $Z = (\log Y_1, \log Y_2, \ldots, \log Y_K)$. Also, let $\Sigma$ be the positive-definite variance-covariance matrix of $Z$. The goal of PCA applied to $Z$ is to obtain the decomposition $\Sigma = \Delta \Lambda \Delta^\top$. (As noted elsewhere (Jolicoeur, 1963), the log-transformation removes measurement scale differences and therefore makes the use of the correlation matrix unnecessary. However, some authors (Somers, 1986) advocate the use of the correlation matrix to separate size and shape variation.) The columns of $\Delta$, say $\delta_k$, $k = 1, \ldots, K$, are the unit-norm eigenvectors of the decomposition, while the diagonal matrix $\Lambda$ has diagonal elements $\lambda_k$, $k = 1, \ldots, K$, and are given by the corresponding eigenvalues. The PCA scores are then obtained as $\tilde{Z} = Z \Delta$.

The first component $\delta_1$ (major axis) is the direction with maximal variance and its equation can expressed as (Jolicoeur, 1963)

$$\frac{1}{\cos \theta_1} (Z_1 - E(Z_1)) = \ldots = \frac{1}{\cos \theta_i} (Z_i - E(Z_i)) = \frac{1}{\cos \theta_j} (Z_j - E(Z_j)) = \ldots = \frac{1}{\cos \theta_K} (Z_K - E(Z_K)),$$

where $\theta_i$ is the angle made by the first principal component with the coordinate axis of $Z_i$. Thus

$$\left(\frac{Y_1}{g_1}\right)^{1/\cos \theta_1} = \ldots = \left(\frac{Y_i}{g_i}\right)^{1/\cos \theta_i} = \left(\frac{Y_j}{g_j}\right)^{1/\cos \theta_j} = \ldots = \left(\frac{Y_K}{g_K}\right)^{1/\cos \theta_K},$$

where $g_i$ is the geometric mean of $Y_i$. It follows that

$$Y_i = a_{ij} Y_j^{b_{ij}}, \quad i \neq j, \quad j = 1, \ldots, K,$$
where \( a_{ij} = g_i / g_j^{b_{ij}} \) and \( b_{ij} = \cos \theta_i / \cos \theta_j \). That is, the ratio of any pair of PCA loadings, say \( i \) and \( j \), from the first component \( \delta_1 \) approximates the slope of the bivariate MA regression for the variables \( Z_i \) and \( Z_j \) (Corruccini, 1983). Using these results, we offer the following proposition.

**Proposition 2.** Let \( \mathbf{Y} = (Y_1, \ldots, Y_K)^\top \) be a multivariate random vector collecting \( K \) continuous and strictly positive random variables, and assume that the PCA allometric model (11) holds true for any pair of variables \( i, j \), with \( i \neq j \). Also, define \( \mathbf{Z} = (\log Y_1, \ldots, \log Y_K)^\top \) and assume that the \( p \)th directional quantile envelope \( D(p) \) generated by \( Q_d^\top \mathbf{Z}(p) \) is smooth. Then the hyperplanes

\[
\log Y_i = \frac{1}{K-1} \log \{Q_{R_i}(p)\} + \sum_{j \neq i} \frac{b_{ij}}{K-1} \log Y_j
\]

\[
\log Y_i = \frac{1}{K-1} \log \{Q_{R_i}(1-p)\} + \sum_{j \neq i} \frac{b_{ij}}{K-1} \log Y_j,
\]

where \( R_i = \frac{Y_i^{K-1}}{g_{-i}} \) and \( g_{-i} = \prod_{j \neq i} Y_j^{b_{ij}} \), are tangent to \( D(p) \).

**Proof.** In its implicit form, the hyperplane tangent to \( D(p) \) is by definition given by

\[
\sum_{j=1}^{K} d_j Z_j = Q_d^\top \mathbf{Z}(p),
\]

for any given direction \( \mathbf{d} = (d_1, \ldots, d_K)^\top \). We also note that

\[
\mathbf{d}^\top \mathbf{Z} = \sum_{k=1}^{K} d_k \log Y_k = \log \left( \frac{Y_i^{d_i}}{\prod_{j \neq i} Y_j^{-d_j}} \right).
\]

On the log-scale, the \( K-1 \) allometric equations given in Proposition 2 relating a given \( Y_i \) to the other variables \( Y_j, j \neq i \), can be re-written as

\[
b_{i1} \log(Y_1) - \log(Y_i) = -\log a_{i1}
\]

\[
\vdots
\]

\[
b_{i(i-1)} \log(Y_{i-1}) - \log(Y_i) = -\log a_{i(i-1)}
\]

\[
b_{i(i+1)} \log(Y_{i+1}) - \log(Y_i) = -\log a_{i(i+1)}
\]

\[
\vdots
\]

\[
b_{iK} \log(Y_K) - \log(Y_i) = -\log a_{iK}.
\]
If we take the sum of the terms on the left- and right-hand sides, respectively, we obtain

\[(14) \quad \log \left( \frac{Y_i^{-(K-1)}}{\prod_{j \neq i} Y_j^{-b_{ij}}} \right) = - \sum_{j \neq i} \log a_{ij}, \]

which has the same form of (13) with \(d_j = b_{ij}\), for all \(j \neq i\), and \(d_i = -(K - 1)\). Therefore, the hyperplane tangent to \(D(p)\) in the allometric direction, defined as \(d = (b_{i1}, \ldots, b_{i(i-1)}, -K + 1, b_{i(i+1)}, \ldots, b_K)^\top\), is

\[\log Y_i = -\frac{1}{K-1} Q_{d^\top z}(p) + \sum_{j \neq i} b_{ij} \log Y_j.\]

By (13) we have that

\[d^\top Z = -\log \left( \frac{Y_i^{K-1}}{\prod_{j \neq i} Y_j^{-b_{ij}}} \right) = -\log R_i.\]

Similarly to before, we find \(Q_{d^\top Z}(p) = Q - \log R_i(p) = - \log \{Q R_i(p)\}\). Then the tangent hyperplane becomes

\[\log Y_i = \frac{1}{K-1} \log \{Q R_i(p)\} + \sum_{j \neq i} b_{ij} \log Y_j,\]

which corresponds to the first equation given in (12). The second equation in (12) is found with similar arguments as those used in Proposition 1.

Model (11) is rather flexible as it allows for \(K(K-1)/2\) distinct slopes \(b_{ij}\) to be estimated. If there is evidence or theoretical justification of equality of slopes, some restrictions can be imposed, for example, by assuming homogeneity of the \(b_{ij}\)'s for some \(j\)'s or using an even more parsimonious model of the kind \(Y_i = a_i \left( \prod_{m_i} Y_{m_i} \right)^{b_i}, i = 1, \ldots, K\), where \(m_i\) indexes a subset of \(K - 1\) variables \(Y_j\), \(j \neq i\).

7. Discussion. In this study, we applied directional quantiles (Kong and Mizera, 2012) to model the joint distribution of birthweight and head circumference in a large cohort of preterm infants to identify unusual measurements. These may represent infants at higher risk of adverse health outcomes. Also, we formally established a connection between DQEs (Kong and Mizera, 2012) and allometric modelling which, to the best of our knowledge, does not seem to have been reported before. There are, however, precedents of applications of quantile contours to multivariate anthropometric and growth charts. Some authors (McKeague et al., 2011) proposed quantile contours based on Tukey’s notion of halfspace depth, while others (Wei, 2008) considered directional reference intervals built around a central point of the distribution (location parameter). These studies offer approaches to nonparametric estimation of quantiles with multivariate data when parametric (normality) assumptions are inappropriate. They do not, however,
elaborate on the role of measurements ratios as we did in the present paper. Moreover, the particular definition of quantile contours based on DQEs is amenable to an elegant and immediate connection with allometric models in two or higher dimensions. We do not know whether a similar relationship exists with other definitions of quantiles contours (Wei, 2008; McKeague et al., 2011) but, surely, such a relationship does not seem to be immediate. On the other hand, we have not explored alternative functional forms, such as Geraci-Jones (Geraci and Jones, 2015) and Aranda-Ordaz (Dehbi, Cortina-Borja and Geraci, 2016) transformations which were found to be optimal for BW and HC univariate charts (Boghossian et al., 2016, 2018). A different functional form of the quantile function may, in turn, be related to different allometric models. This topic deserves further investigation.

Our analysis suggests that small preterm infants with large HC-to-BW ratio are at increased mortality risk as compared to AGA as well as proportionately growth-restricted preterm infants. There is evidence in the literature that asymmetric growth restriction increases the likelihood of adverse outcomes. One study concluded that “the prognosis of SGA infants with asymmetric growth [defined by the ratio of HC to abdominal circumference] is poorer than that of symmetrically grown infants and much worse than that of AGA infants” (Dashe et al., 2000). We also found that the mortality risk is associated with an interaction between asymmetric growth restriction and hypertension. Our study offers not only an approach to risk classification, but also large-sample estimated cutoffs that can be immediately used by practitioners together with previously published anthropometric charts for BW and HC using the same data (Boghossian et al., 2016, 2018). Suppose for instance that an infant is born at 23 weeks and that her BW is 390 g and HC is 19.5 cm. These measurements already put her in a high-risk category since both measurements are below their respective 10th percentile (univariate) thresholds for gestational age and sex (Boghossian et al., 2016, 2018). Using gestational-age specific estimates from Table 4, the allometric HC-to-BW ratio is easily found as \(19.5/390^{0.4125} = 1.6643\) which is greater than the cutoff \(\hat{Q}_R(0.9) = 1.6123\).

There are some limitations in our data. Firstly, gestational age is subject to measurement error and the accuracy depends on the method of estimation as well as when the measurement is made. We believe that our proposed approach can be extended to account for this error when estimating directional quantiles and allometric directions. Another possible limitation in our analysis is the omission of covariates that might explain different allometric relationships. In a separate analysis (results not shown), we investigated the allometric model (8) conditional on ethnicity but no meaningful differences
were found. Unfortunately, other potentially relevant covariates such as maternal age or parental weight and height, which are known to be associated with birthweight (Griffiths et al., 2007; Geraci, 2016), are not available in the VON data.

There are, however, a number of in-hospital morbidity outcomes which we will explore in a separate study. Furthermore, it may be relevant to extend the analysis to infants with subnormal HC-to-BW ratios. Suboptimal head size at birth is known to be a risk factor for poor neurodevelopmental outcomes if it persists after birth (Hack et al., 1991; Kuban et al., 2009). This type of investigation would require follow-up information which is not available to us at this time.

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