The problem with using the birthweight:placental weight ratio as a measure of placental efficiency

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Abstract

Introduction: The ratio of birthweight to placental weight (BW:PW) is often used as a measure of placental efficiency in humans and animals. However, ratios have properties that are known to lead to spurious results. An alternative approach is the use of residuals from regression, which reflect whether birthweight is higher or lower than expected for a given placental weight, given the population pattern. We hypothesized that biologically meaningful measures of placental efficiency would differ between placentas with and without pathology, and between adverse and normal perinatal and postnatal outcomes.

Methods: We examined associations between measures of placental efficiency (BW:PW ratio or residuals) and placental pathology, Apgar scores and infant death using National Collaborative Perinatal Project data (4645 preterm births and 28497 term births).

Results: BW:PW ratios and residuals were significantly lower in placentas showing pathologies including signs of large infarcts or hemorrhage, although many of these differences were small. Low BW:PW ratios and residuals were also associated with low Apgar scores and increased risk of postnatal death. Whereas residuals were lower in term placentas that appeared immature by microscopic examination, the opposite was true for BW:PW ratios.

Conclusion: The BW:PW ratio produced an artefact whereby histologically less mature placentas at term appeared to be more "efficient" than mature placentas, illustrating a known problem with the use of ratios. For other traits, residuals generally showed differences between placentas with and without pathology that were as great as those seen with BW:PW ratios, and often showed stronger associations with adverse outcomes.

Keywords: placenta; birthweight; efficiency; pathology; outcome

1. Introduction

Placental dysfunction is a major cause of fetal growth restriction and stillbirth [1], and places the newborn at increased risk of postnatal complications and health problems throughout life [2]. Assessments of placental function and the effects of gestational insults frequently use the ratio of birthweight to placental weight (BW:PW) as a proxy measure of placental efficiency [3]. BW:PW ratio has been suggested to reflect placental exchange surface area, rates of nutrient transport and blood flow [2], potentially reflecting adjustments in placental development and/or function in order to meet fetal demand [3]. While a high number of grams of fetus per gram of placenta may be considered efficient in some sense, the phrase "efficiency" implies aspects of placental function, e.g., rates of nutrient transport per gram of placenta. While the BW:PW ratio often shows the expected relationship with measures of nutrient transport, surface area and vasculature [3–5], this is not always the case in humans [6] and other species [3].

Gross measures such as birthweight and placental weight provide an approximate assessment of placental development and function, but it is not clear that a simple ratio is the best way to combine these two variables, as there are inherent properties of ratios that can lead to spurious results. In particular, if a regression of Y on X is not linear and/or if it does not pass through the origin, the ratio of Y:X will change along the regression line [7–10]. A plot of birthweight against placental weight, with shading indicating the BW:PW ratio, is shown in Fig. 1 (data described below). Babies on the regression line (i.e., babies with the expected weight for their placental size) have lower ratios as placental weight increases. Furthermore, a small baby with a small placenta below the regression line may have a higher BW:PW ratio than a big baby with a big placenta that is above the regression line, i.e., some babies that are smaller than expected for their placenta size have higher placental "efficiency" than other babies that are

bigger than expected for their placenta size. This is unlikely to be the case and, rather, may be an artefact of the use of BW:PW as a proxy of efficiency. In some cases, smaller fetuses with small placentas will indeed demonstrate increased rates of nutrient transfer measured per gram of placenta [3–6]. However, the BW:PW ratio does not provide evidence of this. The change in BW:PW ratio with placental size occurs because the intercept (i.e., the predicted birthweight when placental weight is zero) is not zero. It therefore reflects a known artefact of ratios [7–9], and not interesting biology. A biological interpretation of the non-zero intercept (i.e., why the predicted birthweight is positive when placental weight is zero) would be difficult and controversial at best. Such plots cannot be interpreted in terms of developmental trajectories, i.e., a plot of term or near-term births does not reflect the relationship between fetal and placental weight throughout gestation.

The issue of the linearity of the relationship between birthweight and placental weight has been considered by Salafia et al. [11], who suggested that the ratio should be calculated as $BW^{0.75}$:PW on theoretical grounds. This approach could potentially address the issue of nonlinearity of the relationship between birthweight and placental weight, but would not address the problem of a non-zero intercept. Furthermore, this approach assumes a scaling exponent to be a specific value based on theory, which was valid for the dataset analysed, but which might not hold true in other datasets (e.g., using a broader/ narrower range of gestational ages).

An alternative approach to combining birthweight and placental weight to assess placental function is the use of residuals from a linear regression [7–9]. A residual is the difference between the actual value of the dependent variable (in this case, birthweight), and its predicted value based on the regression line. Residuals thus indicate whether birthweight is higher or lower than expected for a given placental weight, given the population pattern. The

goal of this study is to compare the use of the BW:PW ratio, the $BW^{0.75}$:PW ratio, and residuals as measures of "placental efficiency". We hypothesize that biologically meaningful measures of placental efficiency will differ between placentas with and without pathology, and between adverse and normal perinatal and postnatal outcomes, and test predictions from this hypothesis using data from the National Collaborative Perinatal Project. Given the previous work on the allometric scaling of placental weight with birthweight [11], we also examine whether the scaling exponent is sensitive to the range of gestational ages included.

2. Methods

The National Collaborative Perinatal Project (NCPP) has been described elsewhere, and its data are publicly available (https://catalog.archives.gov/id/606622). We used only singleton, live births where offspring sex was assigned male or female; stillbirths were excluded, but cases with neonatal deaths were included. Where a woman had more than one pregnancy included in the study, we included only her first study pregnancy, resulting in 43673 eligible births. We performed analyses separately for preterm (24 - 36 weeks, inclusive, based on the limit of viability [12]; N = 5967) and term (37 – 43 weeks, inclusive; N = 34907) births given that the BW:PW ratio would be expected to change with gestational age; in this dataset gestational age was calculated based on the last menstrual period to the nearest week. Cases were not excluded on the basis of maternal health conditions or congenital abnormalities.

Some clear errors in the data were observed (e.g., a placenta weight of 28 g at term), and so to objectively exclude biologically implausible values, we excluded the top and bottom 0.5% of raw birthweights and placental weights (determined separately for preterm and term) [11]. Placental weights were obtained from fresh placentas trimmed of cord and membranes. At term,

the 10^{th} and 90^{th} percentiles for placental weight were 330 g and 560 g, while those for birthweight were 2637 g and 3827 g. Corrected values of birthweight and placental weight were calculated using the residuals from a general linear model with effects of maternal race, offspring sex and gestational age. This resulted in 4645 preterm and 28497 term pregnancies with corrected values of both birthweight and placental weight. These corrected values were used to calculate the BW:PW ratio, as well as the ratio of $BW^{0.75}$:PW [11]. As an alternative measure of placental efficiency, we also obtained the residuals of the linear regression of corrected birthweight on corrected placental weight using the RESIDUAL statement of proc GLM (SAS, Version 9.4). Because residuals are highly correlated with birthweight, we also used corrected birthweight itself as a measure of placental efficiency, resulting in four measures: BW:PW, $BW^{0.75}$:PW, birthweight and residuals. Each of these measures was standardized to have a mean of 0 and standard deviation of 1 to facilitate comparison.

We tested whether each of the four measures of placental efficiency differed between placentas that would be expected to have a larger functional surface area for exchange (i.e., those with no pathology) and those expected to be less efficient (i.e., those with signs of pathology). We examined aspects of placental pathology previously found to be associated with childhood disease in this cohort [13]: Type of cord insertion, the size of infarcts observed upon gross examination of the placenta and, from microscopic placental examination, the presence of thrombosis or necrosis in the fetal surface vasculature, stromal fibrosis or pathological edema in the terminal villi, and the presence of intervillous thrombi and/or adjacent villous infarction. In addition, we also examined placental pathologies expected to reduce the functional exchange surface: the presence of hemorrhage and/ or decidual necrosis (both observed upon gross examination) and the apparent maturity of the placenta, assessed upon microscopic examination.

Criteria for assessing maturity included the presence of fibrin under the chorionic plate, the presence of cysts on the cut surfaces, the presence of syncytial knots, the lack of the Langhans layer, uniformity of villous size, and the degree of crowding of fetal capillaries within villi [14]. Pathologies associated with inflammation were not analyzed given that these might be associated with recent acute inflammation and/or infection.

The difference between placentas without and with pathology is expected to be positive (i.e., higher measures of placental efficiency in placentas with no pathology) and in standard deviation units (e.g., a difference of 1 indicates that pathological and non-pathological placentas differ in placental efficiency by 1 standard deviation). The difference in measures of placental efficiency between placentas with and without pathology was calculated using the ESTIMATE statement of proc GLM (SAS, Version 9.4). We also used logistic regression (proc LOGISTIC, SAS, Version 9.4) to test whether each of the four measures was associated with neonatal and infant outcomes, i.e., the risk of a poor Apgar score at 1 or 5 minutes, and infant death.

In addition, we assessed whether the allometric scaling exponent was sensitive to the range of gestational ages included in its calculation. The allometric scaling exponent was calculated as the slope of the regression of the natural logarithm of placental weight on the natural logarithm of birthweight, with the widest range of ages included being 34 – 42 weeks, inclusive (as in [11]). For these analyses, we excluded women with any repeat pregnancies in the study, and used raw values (unstandardized and uncorrected for gestational age, sex and race) to be consistent with the previous study [11].

3. Results

3.1. Measures of placental efficiency in term births

The distributions of the BW:PW ratio and the $BW^{0.75}$:PW ratio were slightly positively skewed, while the distributions of birthweight and residuals were closer to normal (Supplementary Figure 1). Among term births, the BW:PW ratio and the residuals of birthweight on placenta weight were significantly higher in placentas without certain pathologies (without infarcts, hemorrhage, intervillous thrombi and/or adjacent villous infarction), as predicted (Table 1). While significant, the differences between placentas with and without pathology were generally very small (< 0.3 standard deviation units). For the type of cord insertion, the residuals were significantly higher in placentas with non-membranous cord insertion, whereas there was no difference in the BW:PW ratio (Table 1). While we excluded births at less than 37 weeks from these analyses, the apparent maturity of some placentas was assessed by microscopic examination to be less than 37 weeks. Placentas assessed to be more mature had significantly higher residuals, as expected, but had significantly lower BW:PW ratios, i.e., placental efficiency, measured using the BW:PW ratio, was lower in placentas that morphologically appeared more mature. To investigate the discrepancy between residuals and BW:PW ratios further, we assessed where mature and immature placentas fell on the plot of birthweight against placental weight (Fig. 2). Not only did those classed as immature placentas result in lower birthweights (Table 1), but placental weight was also significantly lower ($P < 0.0001$, Fig. 2), such that births with immature placentas tended to be towards the lower end of the plot (resulting in higher ratios), but slightly below the regression line (resulting in lower residuals).

Higher BW:PW ratios and residuals were associated with increased odds of good Apgar scores at 1 and 5 minutes, as expected, although there was no association with Apgar scores at 10 minutes (Table 2). Similarly, higher BW:PW ratios and residuals were associated with increased odds of surviving to 120 days of age, although the odds ratio was substantially higher for

residuals than for BW:PW ratios (Table 2). Larger residuals were associated with increased odds of surviving from 121-240 days, whereas there was no association with the BW:PW ratio (Table 2). There was no association between the odds of surviving from 241-365 days with any measure of placental efficiency (Table 2), although only 22 infants died in this interval, and so power to detect association was lower.

3.2. Measures of placental efficiency in preterm births

As at term, the distributions of birthweight and residuals were slightly closer to normal than were those of the BW:PW ratio and the $BW^{0.75}$:PW ratio (Supplementary Figure 2). As described above for term births, among preterm births, BW:PW ratios and residuals were significantly higher in placentas without certain pathologies (Table 3), although the pathologies showing significant differences were not always consistent between term and preterm births. For example, differences in BW:PW ratio between more mature and less mature placentas differed between term and preterm births. Although this analysis included only births at less than 37 weeks, the apparent maturity of some placentas was assessed by microscopic examination to be 37 weeks or greater, potentially reflecting accelerated maturation. Placentas assessed to be more mature had significantly higher residuals and BW:PW ratios, as expected. To investigate this discrepancy in results between term and preterm births, we examined plots of birthweight against placental weight (Supplementary Figure 3). The intercept was substantially lower for preterm births and, as a result, there was better concordance between residuals and BW:PW ratios in preterm than term births (i.e., higher BW:PW ratios above the regression line, lower BW:PW ratios below the regression line). This would explain why residuals and BW:PW ratios yielded similar results for preterm births but not term births.

Among infants born preterm, larger BW:PW ratios and residuals were associated with increased odds of good Apgar scores at 1, 5 and 10 minutes (Table 4). Similarly, larger BW:PW ratios and residuals were associated with increased odds of surviving to 120 days of age (Table 4). There was no association between measures of placental efficiency and the odds of surviving from 121-240 days (Table 4), although only 22 infants died in this interval, and so power to detect association was lower.

Where significant differences in placental efficiency were observed between placentas with and without pathology, or between adverse and normal outcomes, the magnitudes of the differences and odds ratios were generally larger for preterm births than for term births.

3.3. Scaling of placental weight with birthweight over different ranges of gestational age

The allometric scaling exponent, calculated as the slope of the regression of the natural logarithm of placental weight on the natural logarithm of birthweight, increased substantially as the range of gestational ages included narrowed around 40 weeks (Fig. 3). When wider ranges of gestational ages were included, the slope of placental weight on birthweight was less steep because low birthweights were associated with heavier placentas than when the range narrowed around 40 weeks (Fig. 3).

4. Discussion

Numerous studies use the size of a fetus or newborn relative to the size of its placenta as a measure of placental efficiency. However, expressing this metric as BW:PW is subject to undesirable properties of ratios that have been described in other fields [7–9]. We compared the standard BW:PW ratio and a modified ratio [11] to an alternative approach using the residuals of the regression of birthweight on placental weight. As expected, ratios and residuals were often

reduced in placentas showing signs of pathology, although many of these effects were small. Pathology associated with ratios and residuals included infarction, hemorrhage and villous dysmaturity (or delayed villous maturation [15]), which are all frequently associated with stillbirth [1]. Ratios and residuals were also lower in newborns with lower Apgar scores and reduced prospects of postnatal survival. Previously, fetal death has been found to be associated with very high and very low BW:PW ratio preterm, and very high BW:PW ratio at term [16] whereas a recent study found that low BW:PW ratio at term was associated with neonatal morbidity (defined in terms of low Apgar score, metabolic acidosis and/or admission to the neonatal unit) [17]. In the present study, residuals almost always showed differences at least as great as the BW:PW ratio in terms of the magnitude of difference between placentas with and without pathology, or between adverse and normal outcomes. For some traits, birthweight alone showed greater differences than any of the measures incorporating placental weight.

In the case of the apparent histological maturity of the placenta, in term placentas the BW:PW ratio produced a counterintuitive result: placental efficiency, measured using the BW:PW ratio, was higher in placentas that morphologically appeared immature. Signs of placental maturity include a lack of Langhans layer (i.e., layer of cytotrophoblast under the syncytiotrophoblast) and crowding of fetal capillaries within villi, such that they are right next to the villous surface [14]. These factors would reduce the distance between fetal and maternal blood, and so mature placentas would be expected to be more efficient. Indeed, increased trophoblast thickness is associated with fetal growth restriction [18,19]. Accelerated placental maturation is potentially a compensatory response to increase the surface area for exchange in pregnancies complicated by placental dysfunction [20,21], although responses at the molecular level are also involved [22,23]. The observation that the BW:PW ratio was increased in

histologically immature term placentas illustrates a known problem with the use of ratios: if the regression of Y on X does not pass through the origin, the Y:X ratio will change for points along the regression line as X increases. In this case, immature placentas were lighter and so had higher BW:PW ratios, even though these births tended to fall below the regression line and so had lower residuals. The increased "efficiency" of immature placentas therefore reflects a mathematical artefact of ratios, and not biological efficiency. This misleading result was not observed among preterm births because of a much lower intercept which reduced the artefact of ratios and led to better concordance between BW:PW ratios and residuals. The artefact of small placentas having large BW:PW ratios may also explain why associations with postnatal death were weaker for BW:PW ratios than for residuals.

It has been proposed that the ratio should be calculated as $BW^{0.75}$:PW on theoretical grounds related to allometric scaling. However, in the present study the $BW^{0.75}$:PW ratio often showed smaller differences between placentas with and without pathology, or between good and bad outcomes, than the BW:PW ratio. Furthermore, this approach assumes a specific allometric scaling exponent. However, we found that this scaling exponent is highly sensitive to the range of gestational ages included in its calculation. When including different ranges of gestational age, the slope of the relationship of placental weight on birthweight is less steep when a wider range of gestational ages is included. This is to be expected: when earlier gestational ages are included, there are more placentas that are relatively large for their babies (because their babies still had some growing to do), which raises the regression line on the left of the plot, leading to a less steep slope. Thus, when including only births within a narrow range of gestational age (40 weeks) the slope reflects an allometric relationship (i.e., variation in size at a specific developmental stage). In contrast, when a wider range of gestational ages is included, the slope is

influenced by the allometric relationship as well as ontogenic changes (i.e., changes with development) and potentially characteristics associated with premature birth.

We recommend that the BW:PW ratio not be used as a measure of placental efficiency, and propose the use of the residuals of a regression of birthweight on placental weight as a simple alternative. The use of residuals is closely related to analysis of covariance (ANCOVA) [7–10] and, depending on the research question, ANCOVA or other modeling approaches are also appropriate. For example, rather than testing whether residuals differed between births from complicated pregnancies and controls, one can test whether birthweight differed between complications and controls, with placental weight as a covariate. Additional covariates and cofactors (e.g., gestational age, offspring sex, etc.) can be included easily. Alternatively, logistic regression can be used to model the risk of specific outcomes, e.g., the association between adverse perinatal outcomes and placental weight, adjusting for birthweight [24]. Whereas the BW:PW ratio can be calculated for an individual birth in isolation, the use of residuals requires a sample of births. However, meaningful interpretation of a BW:PW ratio requires a relevant reference population. Furthermore, with a reference population in hand, the regression equation can be used to calculate the predicted birthweight for a given placental weight and, therefore, the residual for an individual birth.

Ratios are known to have undesirable properties [7–10]. In the present study, use of the BW:PW ratio produced an artefact whereby histologically less mature placentas at term appeared to be more “efficient” than mature placentas. Artefacts introduced by the use of ratios may also explain unexpected results such as increases in placental efficiency when birthweight and placental weight are both reduced by glucocorticoid treatment [3]. The increased BW:PW ratio of small placentas is a mathematical feature of ratios resulting from a non-zero intercept (i.e., the

predicted birthweight when placental weight is zero). Small placentas may in fact be more efficient than large placentas, but such a conclusion requires independent assessment of "efficiency" (e.g., measurement of nutrient transport per gram placental tissue) [3–6], and cannot rely on the BW:PW ratio. To study placental efficiency independent of size, the undesirable properties of ratios can be avoided by using residuals. In the present study, residuals showed differences between placentas with and without pathology that were as great as those seen with BW:PW ratios, and often showed stronger associations with adverse outcomes.

Declarations of interest

None.

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Table 1. Associations between measures of placental efficiency and placental morphology/ pathology in term births (37 – 43 weeks). Values are in standard deviation units and indicate the difference (± standard error) between pregnancies where efficiency is expected to be greater (no pathology) and where efficiency is expected to be reduced, i.e., the difference is expected to be positive for all traits. Bold indicates significance at $\alpha = 0.05$.

Trait	Sample size		Difference between no pathology and pathology			
	No pathology	Pathology	BW:PW	$BW^{0.75}$:PW	Birth weight	Residual
Placental examination – Gross						
Type of cord insertion	27180	1168	-0.02 ± 0.03	**-0.07 ± 0.03**	**0.20 ± 0.03**	**0.15 ± 0.03**
Not membranous vs. marginal or membranous						
Cut surface infarct size	27425	934	**0.14 ± 0.03**	**0.10 ± 0.03**	**0.21 ± 0.03**	**0.24 ± 0.03**
Not applicable or all infarcts less than 3 cm vs. at least one infarct measures 3 or more cm						
Hemorrhage	27389	921	**0.12 ± 0.03**	**0.10 ± 0.03**	**0.08 ± 0.03**	**0.11 ± 0.03**
Absent vs. present						
Decidual necrosis	27194	1163	0.03 ± 0.03	0.02 ± 0.03	0.05 ± 0.03	0.05 ± 0.03
Not seen grossly or present, not massive vs. present, massive						
Placental examination - Microscopic						
Fetal surface vascular changes	27799	296	0.06 ± 0.06	0.06 ± 0.06	-0.00 ± 0.06	0.04 ± 0.06
None vs. thrombosis and/or necrosis						
Terminal villi- stromal fibrosis	27155	1056	-0.01 ± 0.03	-0.03 ± 0.03	0.05 ± 0.03	0.03 ± 0.03
Not seen vs. present						
Terminal villi- pathological edema	27194	1019	0.05 ± 0.03	0.05 ± 0.03	-0.03 ± 0.03	0.00 ± 0.03
Not seen vs. present						
Intervillous thrombi and adjacent villous infarction	25714	2482	**0.16 ± 0.02**	**0.17 ± 0.02**	**-0.07 ± 0.02**	**0.05 ± 0.02**
Not seen vs. present						
Apparent maturity of the placenta	26301	1897	**-0.24 ± 0.02**	**-0.32 ± 0.02**	**0.36 ± 0.02**	**0.15 ± 0.02**
37 weeks or over vs. 36 weeks or less						

Table 2. Associations between measures of placental efficiency and perinatal and postnatal outcomes in term births (37 – 43 weeks). Values are odds ratios (and 95% confidence limits) estimating the increase in the odds of the normal outcome per 1 standard deviation increase in placental efficiency, i.e., odds ratios are expected to be greater than 1 for all traits. Bold indicates significance at $\alpha = 0.05$.

Event	Normal outcome	#	Adverse outcome	#	Odds ratio for normal outcome			
					BW:PW	$BW^{0.75}$:PW	Birth weight	Residual
Apgar score at 1 minute	7 or more	21714	3 or less	1330	**1.157 (1.092-1.226)**	**1.117 (1.055-1.182)**	**1.160 (1.096-1.227)**	**1.219 (1.152-1.289)**
Apgar score at 5 minutes	7 or more	26381	3 or less	227	**1.254 (1.093-1.439)**	**1.224 (1.067-1.404)**	**1.144 (1.002-1.306)**	**1.272 (1.115-1.450)**
Apgar score at 10 minutes	7 or more	2720	3 or less	74	1.117 (0.885-1.410)	1.095 (0.867-1.381)	1.128 (0.907-1.401)	1.151 (0.926-1.430)
Infant survival from 0 to 120 days	Survival	28165	Death	240	**1.192 (1.044-1.360)**	1.093 (0.960-1.245)	**1.496 (1.314-1.703)**	**1.494 (1.316-1.695)**
Infant survival from 121-240 days	Survival	28165	Death	70	1.182 (0.926-1.508)	1.114 (0.875-1.418)	1.261 (0.994-1.599)	**1.309 (1.036-1.655)**
Infant survival from 241-365 days	Survival	28165	Death	22	1.332 (0.853-2.080)	1.433 (0.909-2.257)	0.733 (0.486-1.107)	0.943 (0.620-1.433)

Table 3. Associations between measures of placental efficiency and placental morphology/ pathology in preterm births (24 – 36 weeks). Values are in standard deviation units and indicate the difference (± standard error) between pregnancies where efficiency is expected to be greater (no pathology) and where efficiency is expected to be reduced, i.e., the difference is expected to be positive for all traits. Bold indicates significance at $\alpha = 0.05$.

Trait	Sample size		Difference between no pathology and pathology			
	No pathology	Pathology	BW:PW	$BW^{0.75}$:PW	Birth weight	Residual
Placental examination - Gross						
Type of cord insertion	4387	210	-0.01 ± 0.07	-0.06 ± 0.07	**0.15 ± 0.07**	0.04 ± 0.07
Not membranous vs. marginal or membranous						
Cut surface infarct size	4482	143	0.16 ± 0.08	0.13 ± 0.08	0.13 ± 0.08	**0.17 ± 0.08**
Not applicable or all infarcts less than 3 cm vs. at least one infarct measures 3 or more cm						
Hemorrhage	4386	219	**0.45 ± 0.07**	**0.26 ± 0.07**	**0.69 ± 0.07**	**0.58 ± 0.07**
Absent vs. present						
Decidual necrosis	4317	301	**0.18 ± 0.06**	**0.13 ± 0.06**	**0.20 ± 0.06**	**0.21 ± 0.06**
Not seen grossly or present, not massive vs. present, massive						
Placental examination - Microscopic						
Fetal surface vascular changes	4530	47	**0.55 ± 0.15**	**0.41 ± 0.15**	**0.58 ± 0.15**	**0.61 ± 0.15**
None vs. thrombosis and/or necrosis						
Terminal villi- stromal fibrosis	4459	134	-0.10 ± 0.09	-0.15 ± 0.09	0.08 ± 0.09	-0.04 ± 0.09
Not seen vs. present						
Terminal villi- pathological edema	4392	201	**0.19 ± 0.07**	0.12 ± 0.07	**0.27 ± 0.07**	**0.28 ± 0.07**
Not seen vs. present						
Intervillous thrombi and adjacent villous infarction	4225	366	0.02 ± 0.05	0.04 ± 0.05	-0.05 ± 0.05	-0.01 ± 0.05
Not seen vs. present						
Apparent maturity of the placenta	3535	1052	**0.31 ± 0.03**	0.06 ± 0.04	**0.83 ± 0.03**	**0.56 ± 0.03**
37 weeks or over vs. 36 weeks or less						

Table 4. Associations between measures of placental efficiency and perinatal and postnatal outcomes in preterm births (24 – 36 weeks). Values are odds ratios (and 95% confidence limits) estimating the increase in the odds of the normal outcome per 1 standard deviation increase in placental efficiency, i.e., odds ratios are expected to be greater than 1 for all traits. Bold indicates significance at $\alpha = 0.05$. There were only 6 deaths from 241-365 days of age and so analyses of this age range were not performed.

Event	Normal outcome	#	Adverse outcome	#	Odds ratio for normal outcome			
					BW:PW	$BW^{0.75}$:PW	Birth weight	Residual
Apgar score at 1 minute	7 or more	3100	3 or less	449	**1.989 (1.768-2.238)**	**1.404 (1.258-1.566)**	**3.165 (2.789-3.592)**	**2.382 (2.125-2.671)**
Apgar score at 5 minutes	7 or more	3848	3 or less	191	**2.527 (2.124-3.007)**	**1.564 (1.330-1.840)**	**5.222 (4.256-6.408)**	**3.025 (2.572-3.559)**
Apgar score at 10 minutes	7 or more	617	3 or less	104	**2.057 (1.602-2.642)**	**1.324 (1.052-1.665)**	**4.036 (2.988-5.452)**	**2.552 (1.994-3.265)**
Infant survival from 0 to 120 days	Survival	4276	Death	341	**2.664 (2.323-3.055)**	**1.676 (1.477-1.901)**	**4.659 (3.990-5.440)**	**3.154 (2.764-3.600)**
Infant survival from 121-240 days	Survival	4276	Death	22	1.244 (0.794-1.949)	1.282 (0.815-2.018)	0.925 (0.595-1.439)	1.158 (0.752-1.784)

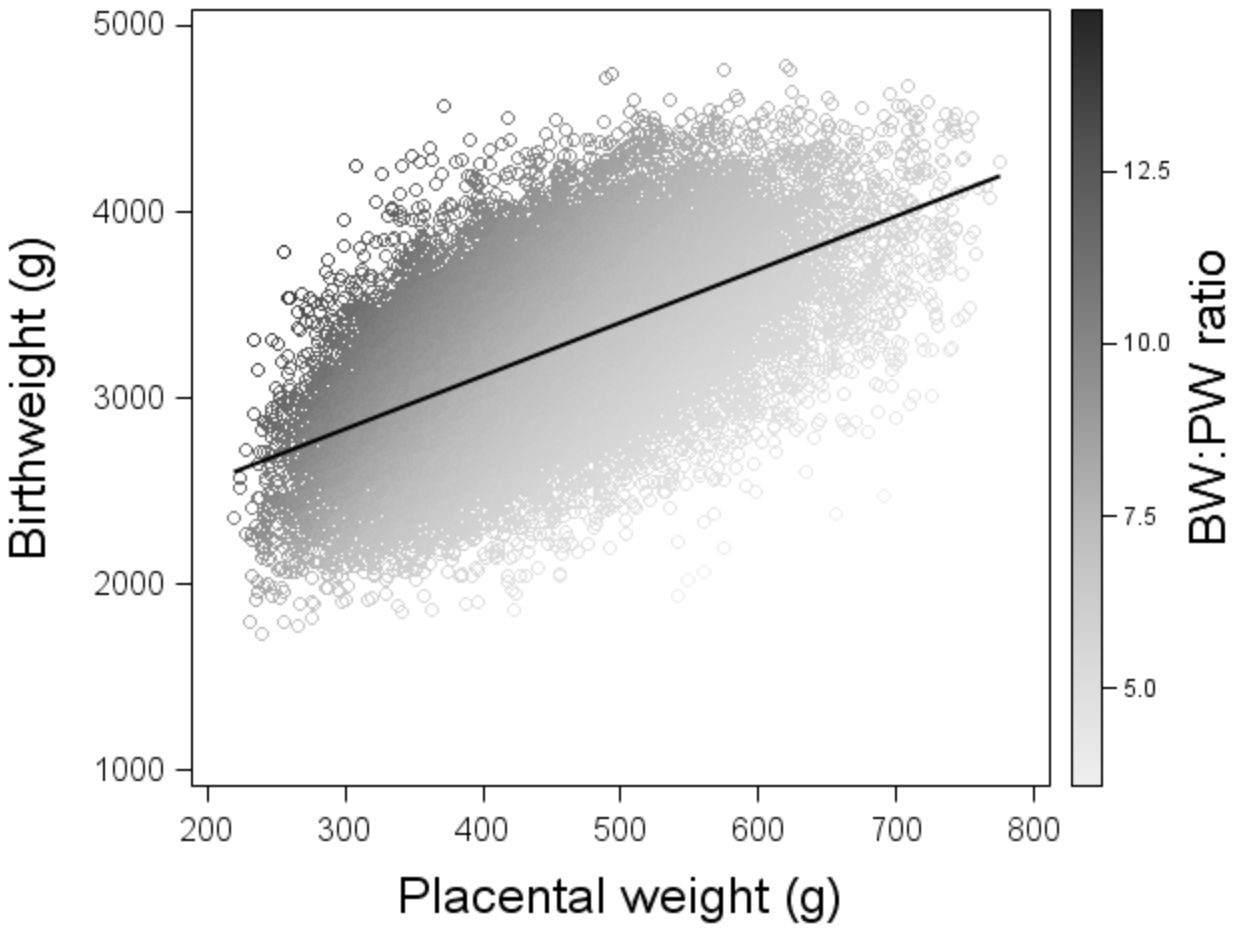


Figure 1. The relationship between birthweight and placental weight among births between 37 and 43 weeks, inclusive (N = 28497). Symbols are shaded according to the BW:PW ratio, and the line is from least-squares regression.

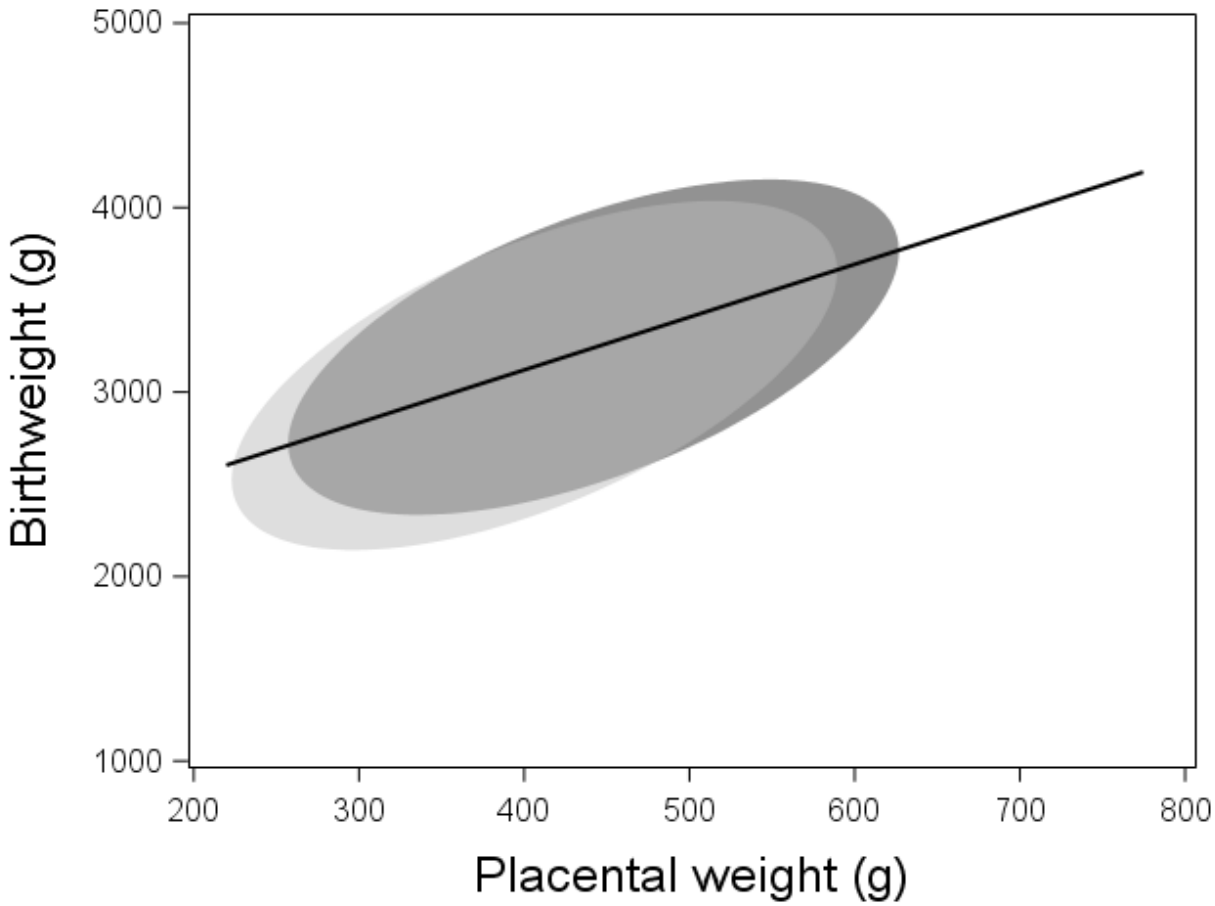


Figure 2. The relationship between birthweight and placental weight among mature (darker grey) and immature (lighter grey) placentas from births between 37 and 43 weeks. Data are presented as 90% confidence ellipses (ELLIPSE statement in proc SGPLOT, SAS, Version 9.4) with the overall least-squares regression line.

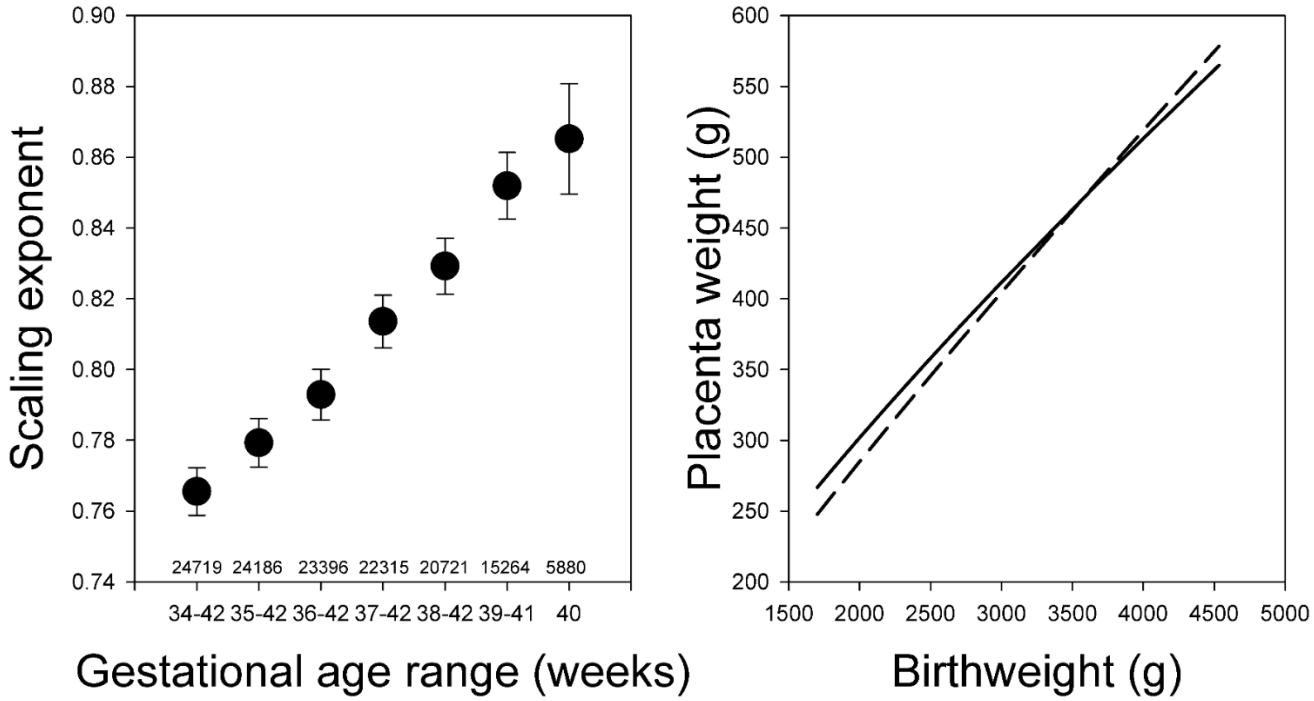
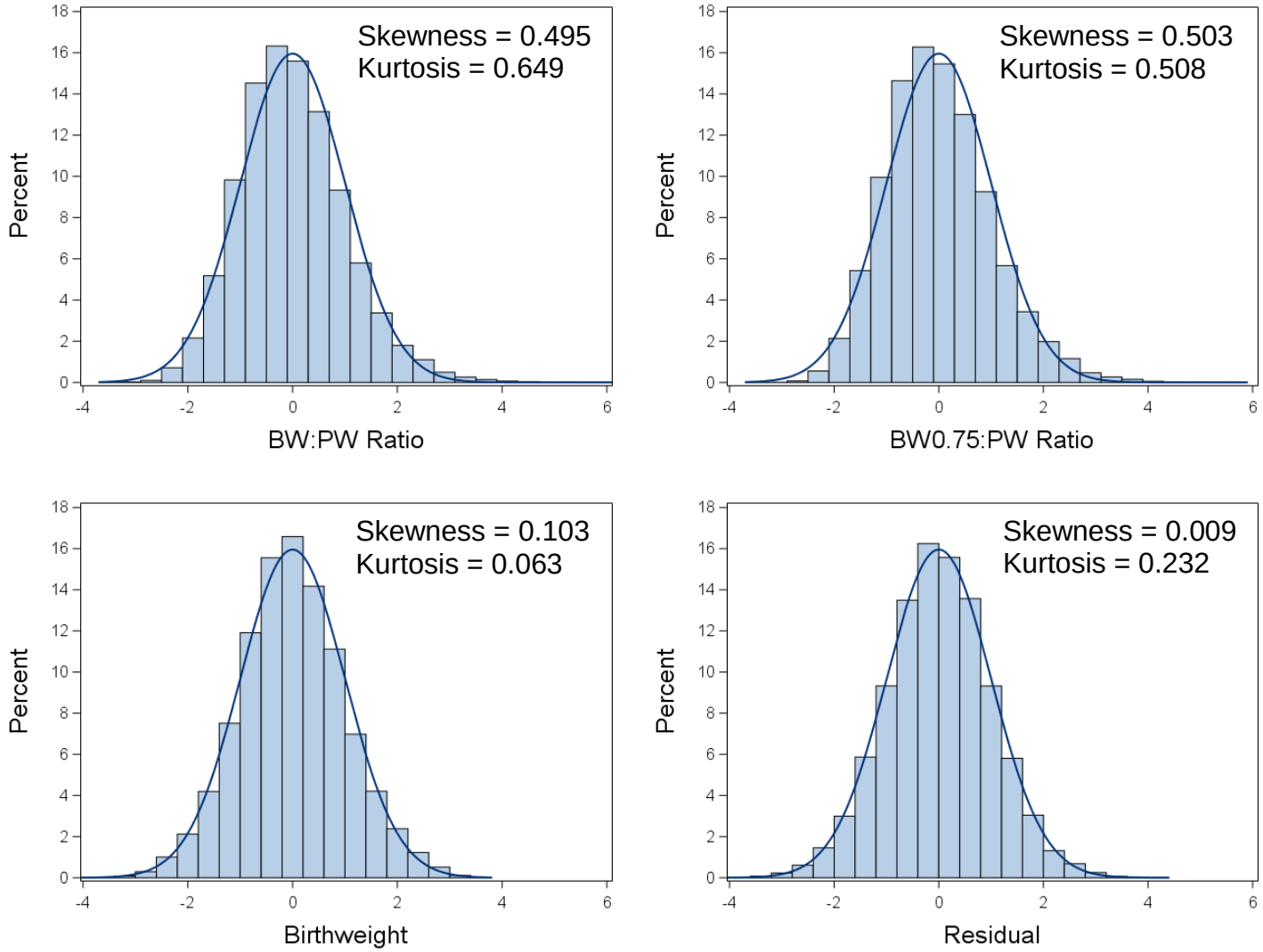
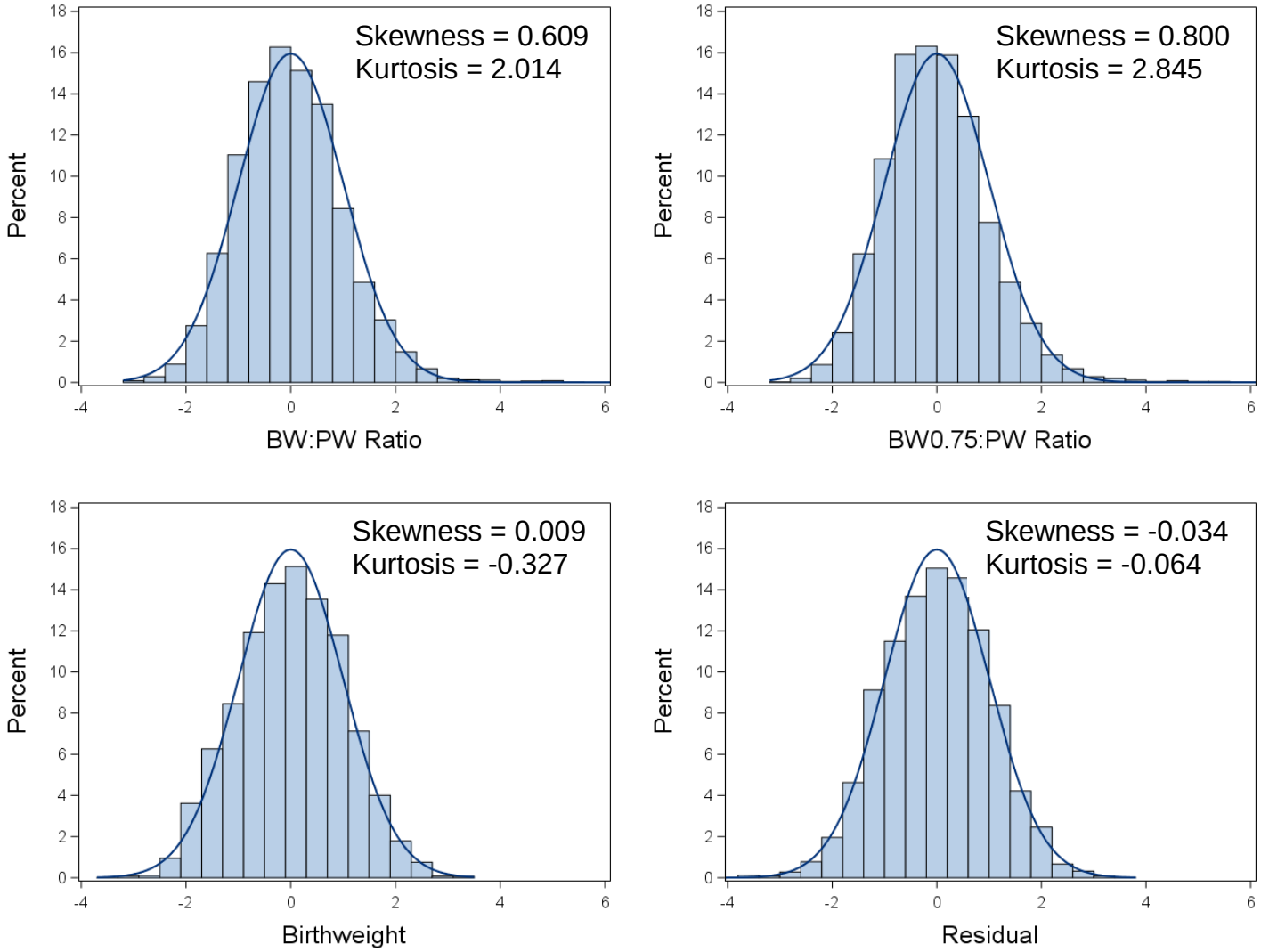


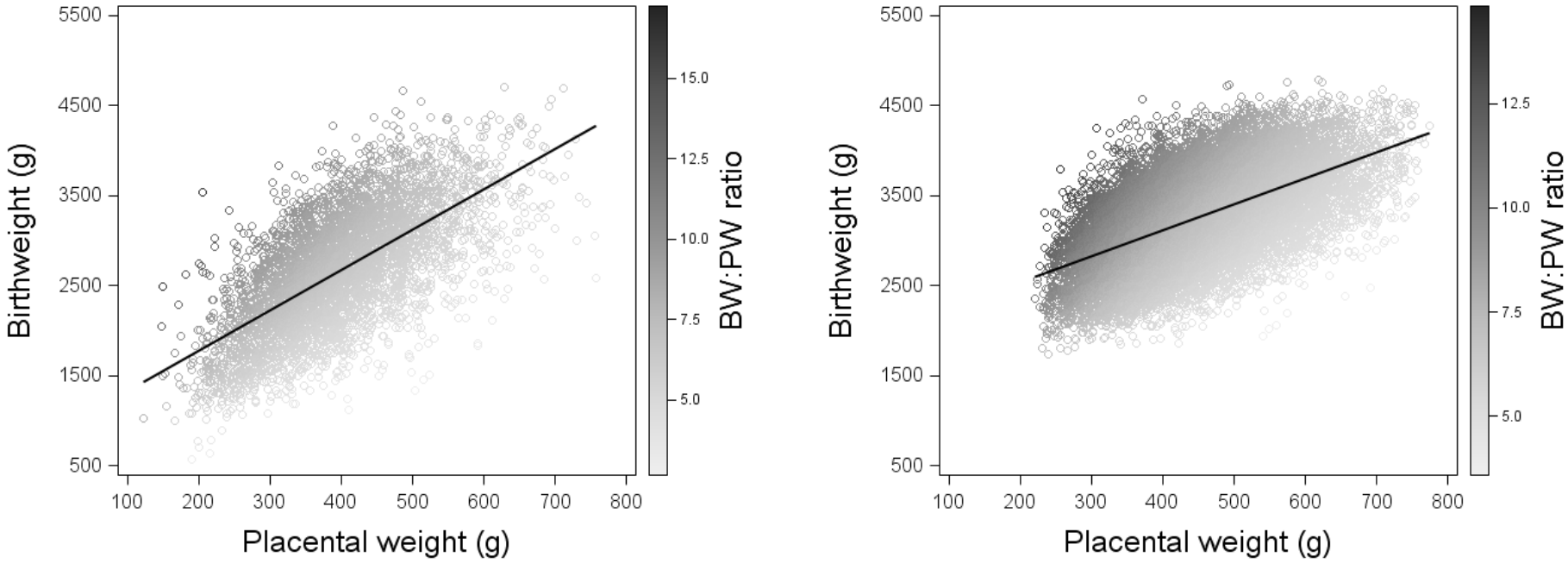
Figure 3. The effect of gestational age range on the allometric scaling exponent. The scaling exponent (± standard error), calculated as the slope of the regression of the natural logarithm of placental weight on the natural logarithm of birthweight, rises as the range of gestational ages narrows (left panel). Sample sizes are shown above the x-axis. The best-fit line from the regression of the natural logarithm of placental weight on the natural logarithm of birthweight (right panel), showing the steepest line from the narrowest range of gestational ages (40 weeks only, dashed line) compared with the least steep line from widest range of gestational ages (34-42 weeks, solid line). Births at 40 weeks had among the smallest and largest placentas and babies, therefore the extremes for birth and placenta weights were the same for all gestational age ranges.



Supplemental Figure 1. Distribution of variables for term births (histograms). Curves are normal density estimates (DENSITY statement in proc SGPLOT, SAS, Version 9.4). Skewness and kurtosis are expected to be zero for a normal distribution (the kurtosis provided is the excess kurtosis).



Supplemental Figure 2. Distribution of variables for preterm births (histograms). Curves are normal density estimates (DENSITY statement in proc SGPLOT, SAS, Version 9.4). Skewness and kurtosis are expected to be zero for a normal distribution (the kurtosis provided is the excess kurtosis).



Supplemental Figure 3. The relationship between birthweight and placental weight among preterm (24 – 36 weeks, N = 4645, left panel) and term (37 – 43 weeks, N = 28497, right panel) births. Symbols are shaded according to the BW:PW ratio, and the line is from least-squares regression.