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Allometric metabolic scaling and fetal and placental weight

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Abstract

Background—We tested the hypothesis that the fetal-placental relationship scales allometrically and identified modifying factors of that relationship.

Materials and Methods—Among women delivering after 34 weeks but prior to 43 weeks gestation, 24,601 participants in the Collaborative Perinatal Project (CPP) had complete data for placental gross proportion measures, specifically, placental weight (PW), disk shape, larger and smaller disk diameters and thickness, and umbilical cord length. The allometric metabolic equation was solved for and by rewriting $PW = (BW)^a$ as $\ln(PW) = \ln + [\ln(BW)]$. $\ln(PW)$ was then the dependent variable in regressions with $p < 0.05$ significant.

Results—Mean a was 0.78 ± 0.02 (range 0.66, 0.89), which is consistent with the scaling exponent 0.75 predicted by Kleiber's Law. Gestational age, maternal age, maternal BMI, parity, smoking, socioeconomic status, infant sex, and changes in placental proportions each had independent and significant effects on a .

Conclusions—We find an allometric scaling relation between the placental weight and the birth weight in the CPP cohort with an exponent approximately equal to 0.75, as predicted by Kleiber's Law. This implies that: 1) Placental weight is a justifiable proxy for fetal metabolic rate when other measures of fetal metabolic rate are not available; and 2) The allometric relationship between placental and birth weight is consistent with the hypothesis that the fetal-placental unit functions as a fractal supply limited system. Furthermore, our data suggest that the maternal and fetal variables we examined have at least part of their effects on the normal balance between placental weight and birth weight via effects on gross placental growth dimensions.

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Introduction

The human newborn is entirely composed of nutrients transferred from the maternal to the fetal circulation across the placenta. By extension, birth weight depends on placental function. Physiologic determinants of total placental supply capacity include “driving forces” such as nutrient concentration, charge and oncotic gradients, blood flow (via uterine and umbilical arteries), the physical aspects of the placental villous barrier related to passive permeability (e.g., villous surface area, thickness of the maternal-fetal blood partition, pore size), and transporter function at the microvillous surface. The “net” (or “effective”) placental functional capacity – the nutrients available to the fetus for use in metabolism and, importantly, growth-- would equal the amount of nutrients provided in each fetal-placental cardiac cycle minus the fetal energy costs of placental perfusion and the energy consumed by placental metabolism [1]

The relationship between metabolism and organism size has been repeatedly reduced to the equation **Basal metabolic rate** = **(Body mass)^α** . (e.g.,[2-9] Allometric metabolic scaling (Kleiber's Law) was first conjectured in the 1930's and has proved to be remarkably constant for a wide range of organisms from the smallest microbes (~ 10⁻¹³ g) to the largest vertebrates and plants (~ 10⁸ g,[9]). Allometric scaling is applied to extrapolate human toxic doses from results of experimental models (e.g.,[10]) and the exponent in Kleiber's Law is remarkably constant, between 0.67 and 0.75, Such scaling applies in growing as well as mature organisms. [4] Recent models suggest that allometric scaling can be understood on the basis of supply limitations [9] or as the combined effects of processes that each contribute to regulation of whole-body metabolic rate [2, 7, 8]. In either case, the broad range of observed data underlying the concept that functional capacities are matched to maximum physiological requirements or loads (“symmorphosis” [11]) has been used to propose that such balance was a basic evolutionary requirement.

Ahern in 1966 (as cited in [12] offered a pregnancy-equivalent to the allometric metabolic scaling equation that suggested that the complex relationship between placental function in nutrient transfer and fetal growth could also be parsed allometrically. Explicitly, he substituted placental weight for basal metabolic rate and birth weight body mass, respectively, yielding the following equation:

$$\text{Placental weight} = \alpha (\text{Birth weight})^\beta \text{ or } \text{PW} = \alpha (\text{BW})^\beta \quad [\text{Equation 1.1}]$$

Lackman and colleagues provided justification for the equivalent of fetal growth with fetal oxygen consumption in [13] in their study of over 27,000 sets of umbilical cord blood gas values. They demonstrated that fetal oxygenation is related to size at birth across the entire range of birth weights as studied at term from macrosomic to growth-restricted infants; this conclusion supports oxygen as a primary determinant of fetal growth. Ahern [12] suggested that, based on a “series of ‘normal’ products of conception” that =2/3, consistent with scaling based on volumes and surface areas. However, recently a ¾ scaling has been favored, based on flow theory, in which the rate of delivered materials to cells by the circulation, is constrained by the capacity to deliver materials, or fractal theory (that justifies a ¾ power as the effective surface area optimal to achieve maximum metabolic rate while minimizing internal transport distance) [2-4]. Placental nutrient transfer to the fetus is intimately dependent on placental flow; placental branched growth is essentially fractal. [14] Thus either flow or fractal theory might be applicable to the fetal-placental version of allometric scaling, both supporting a ¾ scale factor.

As investigations of the putative “fetal origins of adult disease” have proliferated, so has the use of birth weight as a proxy for intrauterine “health” (as recently summarized in [15]). Birth weight is currently understood to be a marker of risk for a host of lifelong health risks, but evidence suggests that birth weight *per se* is not the critical exposure. [16] “Fetal origins” investigations would benefit from a clearer understanding of how the placenta, a principal determinant of fetal growth, “translates” its own growth into fetal mass. While reduced placental growth is generally associated with reduced fetal growth, structural changes in the placental vascular distribution system (e.g., abnormal coiling [17], single umbilical artery [18], abnormal umbilical cord insertion [19]) are associated with increased rates of fetal growth restriction. It is likely that finer-level variations in the anatomic architecture of the placental tree, from the larger branches of the umbilical chorionic and fetal stem vessels as well as the distal capillary bed, would also affect the fetal “net benefit” of placental perfusion and alter the birth weight for a given placental weight.

The finer structure of the placenta is difficult to quantify but several proxies exist in a large US birth cohort, the Collaborative Perinatal Project (CPP) [20]. First, measures of the larger and smaller dimension of the chorionic disk describe the area of the uterine lining covered by the placenta. While the uterine spiral artery density likely differs between women, it must be true that, for any one woman, the chorionic plate area would overlay more uteroplacental arteries (and a greater uteroplacental supply) at 300 cm² than at 150 cm². A lesser consideration may be that the chorionic plate area constrains the maximal length of the chorionic plate vessels (possibly altering fetal cardiovascular work since cardiovascular resistance is directly proportional to vessel length). Second, measures of placental disk thickness offer a crude quantification of the depth/extent of villous arborization, not only in terms of villous nutrient exchange surface area but also the fetal stem arterioles, the principal site of placental vascular resistance. Altered proportions of the chorionic plate (a very small chorionic plate area or a very large and expansive chorionic plate) or placental disk thickness (a thin or thick disk) would therefore, in theory, represent very different fetal-placental relationships. The more fetal work involved in perfusing the placenta, the greater “cost” to the fetus of every heart beat and the lesser would be, in theory, the “net” nutrient benefit of each fetal cardiac cycle.

We first determine whether Ahern's equation in fact holds for the largest US birth cohort, and evaluate the scaling factor as estimated in a regression model. A scaling factor within the range of that observed in allometric scaling, a physiologic measure of metabolic rate, then the use of placental weight as a proxy for fetal metabolic rate may, when no other such measures are available, be reasonable. We hypothesize that the mean allometric exponent relating placental and fetal size will approximate that predicted by both flow and fractal theories, $\frac{3}{4}$. If this is true, we then hypothesize that changes in placental three-dimensional shape, the container of the mature and arborized villous tree (estimated by measures of the smaller and larger placental diameters as proxies for the placental chorionic vascular distribution system, and placental disk thickness as proxy for the elaboration of the villous distribution system) will alter the balance between placental weight and fetal weight, in other words, affect the efficiency of placental nutrient transport function. Through the allometric metabolic scaling equation, we can test this hypothesis by assessing whether, and if so, to what degree, these placental growth variables affect coefficient α that reflects the multiplicative constant in the allometric metabolic scaling equation. It should be noted that the numerical value of α in this equation does not have a very intuitive meaning – it is the expected placental weight of a baby whose birth weight is 1.0 (in whatever units birth weight and placental weight are expressed in). Finally, we reconsider what is the most biologically appropriate expression of the feto-placental weight ratio, in light of scaling considerations. The implications of scaling are significant, as a *linear* fetoplacental weight ratio (birth weight/placental weight), which implies $\alpha = 1.0$, is a commonly used clinical tool

for assessing fetal well-being and placental health. If a corrected ratio should be used (e.g., birth weight ^{3/4}/placental weight), this would refine clinical diagnosis of fetal pathology due to placental dysfunction. Deviations from the ratio ^{3/4} could thus also be used as indicators of deviations from normal fetal-placental development.

Materials and Methods

Subjects were a subset of the National Collaborative Perinatal Project (NCPP). Details of the study have been described elsewhere [21, 22] Briefly, from 1959 to 1965, women who attended prenatal care at 12 hospitals were invited to participate in the observational, prospective study. At entry, detailed demographic, socioeconomic and behavioral information was collected by in-person interview. A medical history, physical examination and blood sample were also obtained. In the following prenatal visits, women were repeatedly interviewed and physical findings were recorded. During labor and delivery, placental gross morphology was examined and samples were collected for histologic examination. The children were followed up to seven years of age.

The data for the present analysis was derived from all liveborn singletons. To control for correlated observations the sample was restricted to only or first singleton live births to a single mother. Among 41,970 women who provided eligible singleton births, 36,017 contributed placenta data. The sample was further restricted to those with complete data on the six placental gross measures (described below), placental weight, and birth weight, of known gestational age between 34 weeks and 42 6/7 (less than 43) completed weeks (N=24,152). Gestational age was calculated from the last menstrual period in rounded weeks. The 34 week cut off was selected because gestations younger than this age were less likely to survive. Gestational lengths as great as 54 weeks were also reported; these were clearly in error and were also excluded. Finally, the lowest 0.5% of placental variables was excluded, as biologically implausible, leaving a final analytic sample of 24,061. There were no exclusions for diagnoses of diabetes, preeclampsia or other maternal medical conditions.

Placental gross measures included placental disk shape, relative centrality of the umbilical cord insertion, estimated chorionic plate area, disk eccentricity, placental disk thickness, placental weight, and umbilical cord length, measured according to a standard protocol [20, 23] Gestational age was calculated based on the last menstrual period in rounded weeks The analytic sample was restricted to those with complete data on the six placental gross measures, placental weight and birth weight, of gestational ages ≥ 34 weeks (younger infants having been unlikely to survive) and less than 43 completed weeks (given that gestations were assigned implausible gestational lengths up to 54 weeks, N=24,061). The original coding of placental measures and the recoding used for this analysis follow:

- **Chorionic disk shape** coding was based on the gross examination of the delivered placenta. Shapes included round-to-oval, and a variety of atypical shapes (e.g., bipartite, tripartite, succenturiate, membranous, crescent or “irregular”). For this analysis, the shape measure was recoded as a binary variable with “round-to-oval” as “0” and “other than round-to-oval” as “1”.
- **Relative centrality of the umbilical cord insertion** was calculated from two variables recorded in the original data set. The *distance from the cord insertion to the closest placental margin* was recorded to the nearest cm. The *type of umbilical cord insertion* was coded as membranous (velamentous), marginal or normal (inserted onto the chorionic disk). We combined these two variables into a single distance measure, by recoding velamentous cord insertions as negative values, cords inserted at the placental margin as “0” and progressively more central cords as “1” to “9” (overall scale range -13 to 13). For example, a cord inserted

velamentously 5 cm from the nearest margin was scored “-5”, while a cord inserted on the chorionic plate 5 cm from the edge was scored “5”. Then this distance was divided by the mean radius, calculated as (larger diameter + smaller diameter)/4.

- **Estimated chorionic plate area** was calculated as the area of an ellipse from two variables recorded in the original data set, the *larger diameter* and *smaller diameter of the chorionic disc*. These two measures, taken perpendicular to each other, were recorded in cm. **Disk eccentricity** was calculated as the ratio of the larger and smaller diameters. Both the **chorionic plate area** and **disk eccentricity** could be cast as “interaction term”, specific mathematical formulations of the possible interactions between larger and smaller diameters with specific anatomic interpretations.
- **Placental thickness** at the center of the chorionic disc was recorded in units of 0.1 cm, by piercing the disc with a knitting needle on which millimeter marks were inscribed.
- **Placental weight (PW)** was measured to the nearest 10 grams; this variable was converted to grams.
- The **fetoplacental weight ratio** was calculated as birth weight divided by the placental weight, and is a value generally considered to reflect a physiologic state of balance between fetal and placental growth.
- **Umbilical cord length** was analyzed as it was measured in the Labor and Delivery Room.

Maternal characteristics were recorded at enrollment and throughout pregnancy by study interviewers. Maternal age was coded as age at (enrollment) in years, and maternal height was measured in inches. Maternal weight prior to pregnancy was self-reported in pounds. Body mass index (BMI) was calculated from maternal height and weight. Parity counted all delivered live born offspring and did not include miscarriages/early pregnancy losses. Socioeconomic status index was a combined score for education, occupation and family income as scaled by the US Bureau of the Census. [24] Mother's race was coded as a binary variable denoting African-American as “1” and all others as “0”; original data coded race as Caucasian, African American, and “other”, most of whom were Puerto Ricans (9.2 percent). Cigarette use was coded by maternal self report at enrollment as non-smoker (coded as <1 cigarette per day), or by the self-reported number of cigarettes smoked daily grouped as 1-9, 10-20, and >20 (greater than one pack per day).

Fitting and applying the metabolic scaling equation

Consistent with the usual techniques for allometric regression, Ahern's power-function relationship:

$$PW = \alpha(BW)^\beta \quad [\text{Equation 1.1}]$$

was recast into linear form by taking (natural) logarithms of the independent and dependent variables:

$$\ln(PW) = \ln(\alpha) + \beta \ln(BW) \quad [\text{Equation 1.2}]$$

which was then fitted to the data by ordinary linear least-squares regression. Having determined β for the fitted equation, it was then possible to calculate, for each baby (denoted by the subscript i), a “baby-specific” α_i value,

$$\ln(\alpha_i) = \ln(PW_i) - \beta \ln(BW_i) \quad [\text{Equation 1.3}]$$

which will tend to be slightly greater or less than the regression α value, depending on whether that baby's placenta is heavier or lighter, respectively, than what would be expected based on the fitted allometric equation. For example, a baby whose α_i value was +0.2 would have a placenta that was about 22% heavier than expected, based on that baby's weight, according to the fitted allometric equation. (The 22% comes from the fact that $e^{+0.2} = 1.22$, approximately.) These α_i values (both raw and as logarithms) were used as the dependent variable in subsequent analyses.

Testing for significant influences on α_i

Multivariate regression were used to determine significant associations with $\ln(\alpha_i)$. $P < 0.05$ was considered significant throughout. Three analyses were run. Model 1 included all placental variables; thus the point-estimate of effect for each placental variable is adjusted for the presence of the others, and is presented in Column 1 of Table 3. Model 2 included all maternal and fetal variables; again, data presented reflect effects adjusted for the presence of the other maternal variables (Column 2, Table 3). Model 3 included all variables (placental, maternal and fetal, Column 3, Table 3).

Results

Descriptive Statistics

Population descriptors are presented in Table 1 and Table 2.

Solving for α_i and β

The mean (exponentiated) α and β were (respectively) 1.03 ± 0.17 (range 0.38, 2.42), and 0.78 ± 0.02 (range 0.66- 0.89), the latter 104% of the allometric exponent predicted in a supply-limited fractal system, 0.75. [2, 4]

Placental gross growth dimension variables: effects on α_i (Table 3, Column 1)

After adjustment for placental weight, α_i was greater in irregularly shaped placentas and increased as placental larger and smaller placental diameters, disk thickness and umbilical cord length increased. Chorionic plate area, in effect, a multiplicative interaction term of the larger and smaller diameters, was inversely correlated with α_i , suggesting a negative effect on placental efficiency at extreme chorionic plate sizes. Thus, the placental dimensions of shape, chorionic plate (area and the larger and smaller diameters individually), disk thickness, and cord length had separate significant effects on the extent to which placental weight represents fetal metabolic rate. The placental gross growth dimensions accounted for 24% of α_i variance ($r=0.49$). Analyses of $\ln \alpha_i$ (as expected) yielded slightly different point estimates of effect, but there were no changes in statistical significance, in terms of either presence or degree, but r was slightly higher (0.509 , $r^2=0.26$).

Maternal and fetal factor effects on α_i (Table 3, Column 2)

Higher doses of maternal smoking was associated with greater α_i . Male infants had lower α_i than female infants. No difference in α_i was seen between Caucasians and African-Americans. α_i was positively correlated with birth length and inversely correlated with

maternal BMI ($r=0.035$ and $r=0.08$, respectively). Gestational age also was inversely correlated with $\ln \beta_1$. All the maternal and fetal factors considered in this analysis accounted for 3.6% of $\ln \beta_1$ variance ($r=0.19$). Again, analyses of $\ln \beta_1$ (as expected) yielded slightly different point estimates of effect, but there were no changes in statistical significance, in terms of either presence or degree. Correlation ($r=0.19$) and r^2 (0.03) were also unchanged.

Do placental measures mediate effects of maternal and infant variables on α_1 (Table 3, Column 3)?

After adjustment for placental variables, increasing maternal age, parity and African-American race (not associated with $\ln \beta_1$ independent of the inclusion of placental variables, **Column 1**) were significantly associated with $\ln \beta_1$, indicating that these variables impact $\ln \beta_1$ via effects on one or more placental variables. In particular, the point-estimate of effect of African-American race increased 10-fold after inclusion of placental variables (0.002, p ns, v. 0.023, $p<0.0001$). The effect of birth length on $\ln \beta_1$ reversed sign and increased 5-fold (0.020, $p<0.0001$ v. -0.011 , $p<0.0001$). The effect of maternal smoking on $\ln \beta_1$ was little changed by inclusion of placental variables (0.022, $p<0.0001$ v. 0.017, $p<0.0001$). Again, analysis of $\ln \beta_1$ (as expected) yielded slightly different point estimates of effect, but there were no changes in statistical significance, in terms of either presence or degree.

Discussion

The allometric exponent, and the relationship of placental weight to birth weight

Our results demonstrate that in this population predominantly delivered at term, placental weight scales to birth weight to the $3/4$ power, from which we suggest the following:

1. Placental weight is a justifiable proxy for fetal metabolic rate when other measures of fetal metabolic rate are not available.
2. The allometric relationship between placental and birth weight is consistent with the hypothesis that the fetal-placental unit functions as a fractal supply limited system.

To our knowledge, only one other study of placental allometry has been carried out [25] that focused on the allometry of various placental compartments from 10-41 weeks gestation. This work supports our findings that there exist various fetal-placental allometric scaling relations different from a simple dimensional proportionality.

We have recently developed a dynamical model of placental vascular growth [14, 26, 27] which relates the spatial shape of the placenta with the structure of the underlying vascular fractal. This model recapitulates many of the known variant placental shapes (bilobate, multilobate, irregular or “scalloped”) by a change of the fractal structure of the vasculature at a specific time instance. In a modern cohort with more precise chorionic plate measures than were collected in the CPP, we have confirmed that such placental shape variance is associated with changes in the allometric scaling relation of fetus and placenta. Specifically, deviations from spatially filling symmetric fractal vascular growth are associated with reduced placental vascular efficiency, that is, a smaller birth weight than predicted by the allometric scaling for the given placental weight [14] These findings are consistent with a connection between the allometric fetoplacental scaling and the fractal structure of the vascular supply system.

We anticipate that future investigations may further improve these estimates of placental function by including other measures of placental growth, e.g., arborization density, enzyme activity (17 β -hydroxysteroid dihydrogenase), and microvillus transport capacity.) We explicitly included all CPP cases with complete placental data; we did not exclude cases of

diabetes, preeclampsia or abruption, as one purpose of the present effort was to determine whether, as a general principle, placental weight scaled to birth weight. Deviations from a $3/4$ scale in the context of maternal medical conditions may help better understand how maternal diseases, via effects on placental growth and, by extension, placental function affect the fetus.

Optimal transport and placental anatomy

Placental arborization is an essentially random process of fractal growth influenced by permissive and restrictive genetic and environmental factors. Our results suggest that, in general terms, the relationship between placental structure and placental function (in terms of nutrient transport allowing fetal growth) fits an allometric scaling model. The apparent universality of scaling among living organisms has been tied to the idea that evolution also drives optimality of structure, such an “optimal structure” having no excess structures relative to its maximal function (e.g., O_2 flux in the lungs, blood flow in the vascular tree, etc.) [11] Optimization theory has been used to analyze a number of biological relationships over the years, from feeding strategies to locomotor gaits (recently reviewed by [28]). In this light, our findings suggest that, in general, and in a predominantly term birth cohort, placental structure is optimized. Likewise, in this light, our findings that changes in placental shape and placental dimensions—independent of their associations with placental weight—affect the balance between placental weight and birth weight can be interpreted as those changes in shape and dimension reflecting deviations from optimal placental structure.

We speculate that these changes in placental shape and dimension are the physical manifestations of altered placental growth necessitated by the intrauterine environment. Using more precise measures of the chorionic shape, we have demonstrated that the radial standard deviation from the umbilical cord insertion is significantly correlated with λ , [14, 26] further albeit indirect evidence that abnormal chorionic surface perimeters, the “errors in outline” acknowledged by Drs Benirschke and Kaufmann, [29] reflect a placental architecture in which function (of nutrient and oxygen transport) is no longer maximized.

Influences on placental-fetal scaling

Placental gross growth measures and several maternal characteristics influence placental-fetal scaling. An increase in λ implies a larger placenta for a given birth weight, and a lower fetoplacental weight ratio, and a smaller birth weight for any given placental weight. The “optimal” result of placental growth should be to yield greater fetal nutrient transfer and a larger baby, rather than a larger placenta. Our data suggest that the maternal and fetal variables we examined have at least part of their effects on the normal balance between placental weight and birth weight via effects on gross placental growth dimensions. As noted above, the fact that placental growth parameters also affect λ independent of placental weight is consistent with our hypothesis that early gestational constraints that yield variant shapes and dimensions of the mature arborized placental villous tree have a permanent effect on the delivered birth weight. Gestational age also showed a significant effect on scaling, despite the admittedly problematic estimation of gestational age by last menstrual period in this cohort. Gestational age should not, in and of itself, affect the $3/4$ power relationship between placental weight and birth weight. That there is a significant association of even poorly measured gestational age on the scaling relationship suggests that the pathology(ies) that underlie shortened gestational lengths may have (chronic) effects on placental vascular/fractal structure. This is consistent with many studies that have associated chronic placental pathologies with preterm birth. [30-34]

Should the fetoplacental weight ratio calculation be modified to scale placental weight to the $\frac{3}{4}$ power?

The ratio of birth to placental weight is the common yardstick used in clinical assessment of the appropriateness of placental function (in terms of providing the fetus with nutrients and allowing fetal growth) to the placental mass. Our data suggest that the relationship between birthweight as a measure of placental function and placental weight is not linear but instead scales to the $\frac{3}{4}$ power predicted by both flow and fractal theories. While this calculation is more cumbersome, deviations from ranges presented in Table 4 may be most clinically precise as they would identify placentas with truly altered flow patterns or fractal structure. Importantly, instead of a range of fetoplacental weight ratios, our data suggest that, at least at term, the fetoplacental weight ratio, appropriately scaled, should be 1.

In summary, data from the Collaborative Perinatal Project demonstrate that placental weight and birth weight in the mid-late third trimester scale consistent with allometric scaling power laws. We hypothesize that maternal and/or fetal pathologies (e.g., preeclampsia) known to modify either branch calibers or the branching structure *per se* will yield “suboptimal” placentas, in terms of birth weight. Better characterization of the branching growth of the placenta may be facilitated by allometric modeling, to develop computer models of placental structure that reflect placental function, and potentially to provide a feasible model for branching growth of other fetal viscera.

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Descriptives of the National Collaborative Perinatal Project subsample with placental data, children in placenta analysis (N=24,061).

Table 1

		Birth Weight		Placental Weight		Disk Shape "not round"		Larger Diameter (cm)		Smaller Diameter (cm)		Disk Thickness (mm)		Umbilical Cord Length (cms)		Distance from cord insertion to nearest disk margin (cms)	
		Number (%)	Mean (SD)	Mean (SD)	Mean (SD)	Number (%)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Maternal race	White	11713 (48.7)	3285.1 (489.0)	446.1 (92.4)		576 (4.9)	19.2 (2.1)	16.5 (1.9)				23.3 (4.1)	59.3 (13.3)			4.6 (2.3)	
	Black	10134 (42.1)	3095.6 (483.2)	426.3 (90.0)		275 (2.7)	18.9 (2.2)	16.4 (1.9)				20.3 (4.6)	58.7 (13.3)			5.1 (2.2)	
	Other	2214 (9.2)	3161.2 (465.3)	435.6 (91.4)		79 (3.6)	19.0 (2.2)	16.2 (1.9)				20.9 (4.5)	57.0 (13.0)			4.8 (2.2)	
Maternal socioeconomic status (SES)	0-1.9	1660 (6.9)	3087 (487.0)	420.8 (90.0)		45 (2.7)	18.8 (2.1)	16.3 (1.9)				20.5 (4.6)	57.6 (13.1)			5.0 (2.2)	
	2.0-3.9	6968 (29.0)	3147.4 (498.2)	432.3 (92.1)		200 (2.9)	18.9 (2.2)	16.4 (1.9)				20.9 (4.6)	58.1 (13.3)			5.0 (2.2)	
	4.0-5.9	7156 (29.7)	3183.7 (492.4)	438.3 (92.7)		267 (3.7)	19.1 (2.1)	16.4 (1.9)				21.6 (4.6)	58.9 (13.4)			4.9 (2.2)	
Previous births (parity)	6.0-7.9	4827 (20.1)	3239.9 (487.5)	442.6 (91.7)		211 (4.4)	19.1 (2.1)	16.4 (1.9)				22.7 (4.4)	59.8 (13.3)			4.7 (2.3)	
	8.0-9.5	3048 (12.7)	3311.3 (454.8)	442.4 (87.4)		186 (6.1)	19.3 (2.0)	16.6 (1.8)				24.0 (3.8)	60.0 (12.9)			4.5 (2.4)	
	Unknown	402 (1.7)	3181.6 (551.2)	441.6 (98.8)		21 (5.2)	19.3 (2.2)	16.8 (2.0)				21.1 (4.6)	56.6 (12.8)			5.0 (2.4)	
Maternal cigarette use (cigarettes/day)	None	9515 (39.6)	3152.1 (469.5)	427.9 (87.3)		304 (3.2)	19.0 (2.0)	16.3 (1.9)				22.0 (4.4)	58.4 (13.1)			4.7 (2.2)	
	1	5062 (21.0)	3208.9 (471.4)	440 (90.5)		202 (4.0)	19.0 (2.1)	16.5 (1.9)				21.9 (4.7)	58.2 (13.0)			4.9 (2.3)	
	2	3334 (13.9)	3200.9 (499.3)	439.6 (92.5)		157 (4.7)	19.1 (2.2)	16.5 (1.9)				21.8 (4.7)	59.5 (13.6)			4.8 (2.4)	
Maternal Age	3-9	5995 (24.9)	3241.5 (534.5)	446.2 (97.7)		261 (4.4)	19.1 (2.3)	16.5 (1.9)				21.5 (4.8)	59.7 (13.6)			5.0 (2.3)	
	10	127 (0.5)	3321.4 (553.3)	459.5 (102.0)		5 (3.9)	19.5 (2.4)	16.6 (2.1)				20.9 (5.1)	60.1 (14.0)			5.0 (2.2)	
	Unknown	28 (0.1)	3073.9 (466.8)	443.2 (89.5)		1 (3.6)	18.6 (2.0)	16.6 (2.3)				23.3 (4.2)	60.5 (15.6)			5.3 (2.2)	
Maternal weight	Non-smoker	13132 (54.6)	3268.5 (483.7)	436.8 (92.0)		519 (4.0)	19.0 (2.1)	16.4 (1.9)				21.9 (4.7)	59.2 (13.5)			4.8 (2.3)	
	1-9	4262 (17.7)	3121.4 (492.2)	430.2 (88.9)		145 (3.4)	19.0 (2.2)	16.4 (1.9)				21.3 (4.6)	58.3 (13.1)			4.9 (2.2)	
	10-19	3047 (12.7)	3101.8 (481.8)	439.8 (93.7)		112 (3.7)	19.1 (2.1)	16.5 (1.9)				21.9 (4.5)	58.5 (13.0)			4.9 (2.2)	
Maternal cigarette use (cigarettes/day)	>=20	3490 (14.5)	3080.4 (488.1)	442.3 (92.3)		145 (4.2)	19.2 (2.1)	16.5 (1.9)				22.2 (4.4)	58.5 (13.1)			4.8 (2.3)	
	Unknown	130 (0.5)	3239.5 (521.5)	437.9 (88.5)		9 (6.9)	19.3 (2.4)	16.6 (2.1)				21.9 (4.5)	56.7 (12.6)			5.1 (2.0)	
	<20	5967 (24.8)	3113.5 (472.1)	426.3 (87.9)		124 (2.1)	18.8 (2.0)	16.3 (1.8)				21.5 (4.5)	57.6 (13.1)			4.9 (2.2)	
Maternal weight	20-29	13840 (57.5)	3208.6 (481.6)	437.3 (90.7)		520 (3.8)	19.0 (2.1)	16.4 (1.9)				22.0 (4.6)	58.7 (13.1)			4.8 (2.3)	
	30-39	3882 (16.1)	3262.3 (535.6)	450 (97.0)		252 (6.5)	19.5 (2.3)	16.7 (2.0)				21.8 (4.8)	61.1 (13.8)			4.9 (2.3)	
	>=40	372 (1.6)	3221.6 (594.6)	446.9 (113.7)		34 (9.1)	19.6 (2.7)	16.7 (2.3)				21.6 (5.0)	61.0 (13.6)			4.8 (2.5)	
Maternal weight	<100	1423 (5.9)	2945.6 (457.4)	400.4 (80.1)		60 (4.2)	18.7 (2.1)	16.1 (1.9)				21.0 (4.4)	54.8 (12.3)			4.7 (2.3)	
	100-149	18214 (75.7)	3178.6 (477.8)	433.6 (89.3)		712 (3.9)	19.0 (2.1)	16.4 (1.9)				21.8 (4.5)	58.5 (13.1)			4.8 (2.3)	
	150-199	3381 (14.1)	3353.3 (500.5)	463.3 (96.9)		112 (3.3)	19.4 (2.2)	16.7 (1.9)				22.1 (4.9)	62.0 (13.7)			5.0 (2.3)	

		Birth Weight		Placental Weight		Disk Shape “not round”		Larger Diameter (cm)		Smaller Diameter (cm)		Disk Thickness (mm)		Umbilical Cord Length (cms)		Distance from cord insertion to nearest disk margin (cms)	
		Number (%)	Mean (SD)	Mean (SD)	Mean (SD)	Number (%)	Number (%)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Maternal BMI	>=200	483 (2.0)	3443.3 (573.8)	480.2 (107.6)		21 (4.4)		19.5 (2.2)		16.8 (2.0)		22.2 (4.8)		63.8 (14.2)		5.1 (2.4)	
	Unknown	560 (2.3)	3144.6 (556.3)	436.6 (101.4)		24 (4.3)		19.0 (2.3)		16.2 (2.0)		22.0 (5.2)		58.5 (13.4)		4.6 (2.4)	
	<20	6067 (25.2)	3084.5 (475.2)	417.6 (85.8)		226 (3.7)		18.8 (2.1)		16.2 (1.9)		21.6		57.1 (13.0)		4.7 (2.2)	
	20-30	14820 (61.6)	3219.4 (485.6)	441.2 (91.5)		578 (3.9)		19.1 (2.1)		16.5 (1.9)		21.8		59.2 (13.3)		4.9 (2.3)	
	>30	1321 (5.5)	3351.1 (531.5)	467.5 (102.1)		49 (3.7)		19.4 (2.2)		16.7 (2.0)		21.9		61.7 (13.8)		5.1 (2.3)	
	Unknown	1853 (7.7)	3236.4 (513.7)	442.8 (94.3)		77 (4.2)		19.2 (2.1)		16.2 (1.8)		23.0		59.7 (13.5)		4.7 (2.3)	
Infant gender	Male	12298 (51.1)	3251.3 (496.7)	439.2 (91.4)		462 (3.8)		19.1 (2.1)		16.5 (1.9)		21.8		60.1 (13.5)		4.9 (2.3)	
	Female	11763 (48.9)	3133.9 (481.5)	434.3 (92.1)		468 (4.0)		19.0 (2.1)		16.4 (1.9)		21.8		57.6 (12.9)		4.8 (2.3)	

Table 2

Descriptives of the placental measures (N=24,061).

	Overall Population	
	Mean (SD)	Range
(exponentiated)	1.03 (1.18)	0.38, 2.42
	0.78 (0.02)	0.66, 0.89
Umbilical cord length	58.8 (13.4)	7, 98
Cord insertion to margin (cm)	4.8 (2.3)	-13, 13
Largest diameter of placenta (cm)	19.0 (2.1)	12, 30
Smallest diameter of placenta (cm)	16.5 (1.9)	9, 25
Chorionic plate area (cm ²)	247.7 (50)	77, 569
Placental thickness (cm)	2.2 (0.5)	0.4, 4.5
Placental weight (g)	437 (92)	90, 1100
Birthweight (g)	3194 (493)	1219, 5613

Table 3

Placental, maternal and fetal influences on

Variable		Model 1 Multivariate model-lacental variables only (N=24,061)	Model 2 Multivariate model-Maternal and fetal variables only (N=21,603)	Model 3 Multivariate model - All variables (N=21,603)
Placental shape	Round-oval (23,131)	-0.021 (0.005) ***		-0.020 (0.005) ***
	Other than round/oval (930)			
Chorionic plate area		-0.001 (0.000) *		-0.001 (0.000) ***
Disk ellipsivity		0.17 (0.004) ***		0.16 (0.03) ***
Larger diameter		0.017 (0.004) ***		0.030 (0.004) ***
Smaller diameter		0.042 (0.004) ***		0.054 (0.004) ***
Disc thickness		0.010 (0.000) ***		0.012 (0.000) ***
Cord length		0.001 (0.000) ***		0.001 (0.000) ***
Relative cord eccentricity		0.014 (0.007) *		0.008 (0.007)
Maternal age			0.000 (0.000)	-0.001 (0.000) **
Parity			0.000 (0.000)	0.001 (0.001) *
Smoking			0.022 (0.001) ***	0.017 (0.001) ***
Infant gender			0.020 (0.002) ***	0.017 (0.002) ***
Birth length			0.003 (0.000) ***	-0.011 (0.000) ***
Maternal BMI			-0.001 (0.000) ***	-0.001 (0.000) ***
Socioeconomic status			0.000 (0.001)	-0.007 (0.001) ***
African-American race			0.002 (0.003)	0.022 (0.002) ***
Gestational age			-0.007 (0.001) ***	-0.009 (0.001) ***

*** P < 0.0001 bolded and italicized;

** P < 0.001;

* P<0.05;

Not bolded, P>0.05.

Three analyses were run. Model 1 included all placental variables; thus the point-estimate of effect for each placental variable is adjusted for the presence of the others, and is presented in Column 1 of Table 3. Model 2 included all maternal and fetal variables; again, data presented reflect effects adjusted for the presence of the other maternal variables (Column 2, Table 3). Model 3 included all variables (placental, maternal and fetal, Column 3, Table 3).