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Global population variation in placental size and structure: Evidence from Cebu, Philippines

Julienne N. Rutherford[a,*], Victoria A. deMartelly[b], Haley B. Ragsdale[c], Josephine L. Avila[d], Nanette R. Lee[d], Christopher W. Kuzawa[c,e]

[a] Department of Women, Children, and Family Health, Department of Anthropology, University of Illinois at Chicago, Chicago, IL, USA
[b] University of Chicago, Chicago, IL, USA
[c] Department of Anthropology, Northwestern University, Evanston, IL, USA
[d] USC- Office of Population Studies Foundation, University of San Carlos, Cebu, Philippines
[e] Institute for Policy Research, Northwestern University, Evanston, IL, USA

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ABSTRACT

Introduction: Placental morphology influences the intrauterine environment and fetal growth, which help set life-course health trajectories across generations. Little is known about placental characteristics in populations with chronic nutritional insufficiency where birth weights tend to be lower, and how these relationships between birth and placental weights vary across populations.

Methods: We collected weights and stereologically-determined villous mass and surface area of 21 placentas from offspring of women enrolled in a birth cohort study in metropolitan Cebu, Philippines, a low-income population. We identified 15 samples from other global populations ranging from low to high income that had similar data to ours to assess patterns of variation between birth and placental weights and microscopic characteristics. We ranked the population samples in order for each characteristic.

Results: Mean birth weight in Cebu was 3162 ± 80 g (ranked 9/16) and placental weight was 454 ± 32 g (ranked 12/16). Birth:placental weight ratio was 7.0 (ranked 3/16). Average villous surface area for Cebu placentas was 6.5 m^2 (ranked 9/12); Birth weight:villous surface area was 0.048 g/m^2 (ranked 4/12).

Discussion: Placentas from Cebu produced heavier neonates per units of placental weight and villous surface area than most other populations, despite lower villous surface areas and less complex surface-to-volume topography. This range of placental efficiency spurs questions about the mechanisms by which placental morphology optimizes efficiency in different environmental contexts during gestation. Placental variation both within and across populations is likely due to many intersecting environmental, metabolic, and (epi)genetic factors that will require additional research to clarify.

1. Introduction

Evidence for long-term health impacts of the gestational environment, as often indexed indirectly by fetal growth rate or birth outcomes, has heightened interest in the role of the placenta as a conduit linking maternal characteristics with the gestational milieu experienced by the fetus. Because the placenta is the biological bridge between the maternal and fetal systems, variation in placental structure and function is increasingly recognized as an important influence on fetal development with long-term impacts on health trajectories [1–3].

Studies focused on gross morphological characteristics of the human placenta, such as placental weight, diameter, or linear dimensions, have linked these to both neonatal and long-term disease outcomes [2–10]. These studies reveal complex, and at times contradictory associations between fetal and placental characteristics. For instance, the relationship of birth weight to placental weight is often U-shaped, with lower birth weights associated with both lower [9,11,12] and higher [13,14] placental weights.

Although gross morphological characteristics of the placenta provide important context for interpreting birth outcomes [11,13,15], they are incomplete indicators of the functional properties that influence transfer of nutrients and other resources to the fetus. Microscopic-level morphological variation, which is not reflected in gross measures of placental size, may underlie functional variation in placental characteristics within and between populations, and thus could have important impacts on fetal development and later health. To date, most

* Corresponding author. Department of Women, Children, and Family Health, College of Nursing, 845 S. Damen Avenue, Chicago, IL, 60612, USA.
E-mail address: ruther4d@uic.edu (J.N. Rutherford).

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studies of non-pathological population variation in microscopic structure and functional properties of the human placenta have focused on the effects of high-altitude hypoxia, which places unique demands on placental oxygen transport and fetal oxygen metabolism and can affect fetal growth [16]. This work shows that the extent of proliferation and expansion of the placental villous tree varies according to altitude and ethnicity [17], leading to wide variation in surface area (and thus, nutrient transfer capacity) within the same placental mass.

Comparatively little is currently known about placental characteristics in populations varying in chronic nutritional insufficiency, which can impact fetal growth and birth outcomes and set postnatal risk for a range of cardiometabolic and other diseases [6–8,14,15,18]. Animal model experiments have demonstrated extensive morphological, microscopic, and biochemical changes in the rat, mouse, and sheep placenta in response to undernutrition during gestation [4,19–27]. Experimental work in sheep has indicated that when nutritional stress occurs during the peri-conceptional period, the placenta exhibits a compensatory increase in overall mass [27]. Nutritional stressors occurring during mid-gestation have been observed to drive significant increases or decreases in ovine placental weight, depending upon the degree and composition of nutrient restriction [26]. These findings share similarities with observations among humans exposed to the Dutch Hunger Winter during World War II. In the Dutch population, women experiencing acute nutritional stress in the peri-conceptional period and early gestation gave birth to babies with relatively large placentas, helping to maintain normal birth weights despite severe undernutrition. In contrast, women exposed to famine later in their pregnancies had reduced placental weights [28–31]. Overall, these findings indicate that the timing and type of nutritional stress, both prior to and during gestation, are important in shaping placental responses.

The predictive power of the birth:placental weight ratio for reflecting functional nutrient transfer is strongly supported by animal models; however these relationships are less clear in humans [32]. Laga et al. [33] observed striking differences in gross morphological and microscopic placental characteristics between a middle-class American cohort and a low SES Guatemalan cohort. Average placental weight, birth weight, villous mass, trophoblast mass, and both peripheral and capillary villous surfaces were all considerably reduced in the Guatemalan sample compared to the American sample. A later comparison of both a high and low SES cohort within Guatemala found lower average placental weights and reduced nutrient transport in the women with low SES and associated malnutrition [34]. More recent work has identified indirect associations between maternal chronic or lifetime nutritional status and fetal growth [35–37], placental weight [9], and placental nutrient transport [5,35,37].

Maternal nutritional influences on placental characteristics may be particularly important as influences of offspring health in populations where widespread low birth weights are linked with rising rates of cardiovascular disease in the context of the nutrition transition. Indeed, there is evidence that the deleterious long-term health impacts of being born small may be particularly harmful in populations in which lower mean birth weight is followed by relatively rapid weight gain later in life [13,15,32]. In this context, fetal nutrient supply may have particularly important long-term effects on population-level health. However, to date, little is known about placental characteristics in such populations.

In this paper we describe gross and microscopic characteristics of the placenta in a population with a relatively low mean birth weight and in which cardiovascular disease is now on the rise. We report on a subsample of a birth cohort of women from the Cebu Longitudinal Health and Nutrition Survey (CLHNS), from metropolitan Cebu, Philippines, in which early life nutritional stress is common [38], and stunting affects up to 69% of rural children by the age of two [39]. The Philippines is a lower-middle income nation undergoing significant economic, dietary, and lifestyle changes, and exemplifies current global trends towards rising prevalence of overweight, cardiovascular disease, and the metabolic syndrome [40,41]. Working with this population, we have shown that maternal third trimester nutritional status and offspring birth outcomes predict offspring growth, adiposity, blood pressure, lipid profiles, and immunity [42–44]. As the original cohort members have reached adulthood and begun families of their own, the survey collected information on birth outcomes in the third generation, allowing evaluation of the intergenerational effects of nutrition [45].

In order to explore the hypothesis that there is population variation in the ratio of birth weight to placental weight, we describe gross and microscopic characteristics of placentas from a subset of the women in the CLHNS cohort and compare our findings to reports from other populations, ranging from low to high economic income status.

2. Materials and methods

2.1. Study population

We collected 22 placentas from 22 women enrolled in the CLHNS. The criteria for inclusion included being enrolled in the CLHNS since birth, pregnant at the time of interview in 2011, and likely to deliver at one of 5 clinical sites. At enrollment there were no exclusion criteria. Collection of birth weights and placentas occurred from July 2011 to January 2013. Exclusion criteria for analysis included multiple births; diagnoses of pre-eclampsia, preterm delivery, and/or gestational diabetes; stillbirth; or other fetal/neonatal complications. We excluded one placenta from a twin pregnancy, yielding a total of 21 placentas in the analysis sample. There were no diagnoses of maternal and/or fetal/neonatal complications. All data and sample collection at Cebu were conducted under conditions of written informed consent with approval from the Institutional Review Board of Northwestern University and University of Illinois at Chicago. More information on tracking of pregnancies and in-home interviews is reported elsewhere [46].

2.2. Collection procedures

Placentas were collected at 5 locations in metropolitan Cebu, Philippines, and with approval of, and in collaboration with, hospital/clinic staff: Cebu City Medical Center, Vicente Sotto Memorial Medical Center, Eversley Child's Sanitarium, Cebu Maternity House and Puericulture Center, and Star Birthing Clinic. Women enrolled in the study texted research personnel to alert them to the labor and the location of the birth. In all 5 sites, vaginally-delivered placentas were collected after the umbilical cord was clamped within minutes of delivery and processed in an adjoining room by research personnel. Placentas were processed as quickly as possible after research personnel received them (time from delivery: 11–43 min, mean = 21.9 min). The placentas were passively drained of accumulated blood, i.e., no pressure was applied to the outer surface; attached but loose membranes and the umbilical cord were trimmed flush to the placental surface. The adherent amnion on the chorionic plate was left intact. The placenta was rinsed, gently patted with paper towels, and then weighed in a plastic weigh boat to the nearest whole gram on a tared digital scale with a 3 kg capacity. Placental volume was measured via fluid displacement in a clear plastic 2 L graduated pitcher to the nearest mL; the pitcher was filled up to the 1 L mark with available tap water and the entire placenta was placed in the pitcher.

For stereological analyses, a systematic random sampling protocol was employed. A 12" by 12" wire grid made from construction cloth was gently laid on top of the placenta ensuring no compression of the tissue. Each cell of the grid was approximately 0.5 square inches. A four-sided die was thrown to determine the first cell of the grid to be sampled. Once selected, that cell was marked with tissue biopsy dye as were every 6th cell following, moving in rows from left to right then right to left in a continuous zig-zag row to row. The grid was removed and full depth vertical cores of tissue with ~0.5 inch circumference were removed using a scalpel and surgical scissors. These core samples were immersed in 10% NB formalin for up to 24 h to complete fixation. Once fully fixed, the cores were removed from fixative, wrapped in formalin-moistened paper towels and placed in plastic bags to keep them moist, then shipped from the USC Office of Population Studies at the University of San Carlos in Cebu City to the Rutherford laboratory at UIC.

2.3. Stereological analyses

At the Rutherford laboratory VAD bisected the cores longitudinally and randomly chose one to be processed for histology. Cores that were too long for one cassette were bisected crosswise and those bisections were randomly chosen for histology. Two slides were made for each core sample, and again one was randomly selected for stereological analysis. Depending on the size of the placenta, the sampling grain employed yielded a mean of 4.35 samples per placenta, in turn yielding an average of 30.5 microscopic fields.

StereoInvestigator, v. 11 (MBF Bioscience, Williston, VT) was used to measure placental compartment volumes using counting grids and to measure surface area using cycloid arcs as described in Ref. [47] and summarized here:

2.3.1. Absolute volumes of villi, intervillous space, and fetal capillaries

Counts of villi, intervillous space, and fetal capillaries were summed for all fields of view per placenta and evaluated as ratios to total placental counts to generate volume densities. The fractional volume of compartment c of a reference r is thus estimated:

$$\text{estV}(c) \;/\; \text{V}(r) = \Sigma P(c) \;/\; \Sigma P(r)$$

Where *P(c)* and *P(r)* are the sums of positive test hits divided by the sum of all possible test points of that reference, overall fields of view of all sections taken from a given placenta. Fractional volumes are converted to absolute volume estimates by multiplication by placental volumes determined using fluid displacement. Volume units are cubic centimeters (cm^3).

2.3.2. Surface area of the villi

Surface density is estimated from vertical samples by the intersection of software-generated cycloid arcs of known length with profiles of the compartment of interest, in reference to the entire reference space. The equation for estimating surface area density follows:

$$\text{estS}_v = 2l \;/\; ((l/p)(P))$$

Where *I* is the sum of intersections between cycloid arcs and compartment profile, *l/p* is the length of the cycloid per test line, and *P* is the number of points hitting the reference volume. Estimation of absolute surface area is calculated by multiplication by total placental volume. Surface area units are reported as square meters (m^2).

2.3.3. Isomorphy coefficient

The isomorphy coefficient relates an exponent of surface area to volume [48]:

$$\text{Isomorphy coefficient} = S^{3/2}/V$$

Linking surface to volume in this way provides a means for tracking disproportionate growth between groups. If the coefficient is larger in one group, this suggests that there has been a relative increase in surface area compared to volume. Therefore, the isomorphy coefficient yields a means of assessing differences in growth patterns rather than just growth endpoints. A decrease in surface area compared to a relatively static volume suggests some decrease in topographic complexity as well, hence the description of the isomorphy coefficient as a "shape factor". Because surface area is raised to the 1.5 power, the isomorphy coefficient units are cubic centimeters per cubic centimeters (cm^3/cm^3).

2.4. Shrinkage correction

The comparison of maternal erythrocyte diameter from fresh blood smears to the erythrocyte diameter of fixed placentas has frequently been used to determine the shrinkage due to histological tissue processing [49,50]. In this study, a more direct method was adopted, as described elsewhere [47]. In a subset of samples (n = 46 samples from 21 placentas), once the biopsy sample was collected, its diameter was measured using sliding calipers. Each sample was measured individually and placed individually in a labeled plastic cassette. The cassettes were then processed prior to embedding, and the biopsies were embedded in numerical order in a single paraffin block. Once processed to slides, the biopsy diameters were remeasured using the same sliding calipers used to initially measure the biopsies prior to processing, and an average linear shrinkage rate of 18.4% was calculated, similar to the low end of the range of 20–30% linear shrinkage reported for maternal erythrocyte diameters calculated for processed samples of human placenta [49,50]. After the volume and surface area values were calculated according to the methods described, they were converted via the shrinkage factor to represent measures of unprocessed tissue.

2.5. Comparison to other populations

We searched the literature for studies in which at least birth and placental weights were reported, excluding studies of pathological conditions, e.g. preterm, infection, pre-eclampsia, etc. Because of the relatively low number of studies and because of the great variation in sample sizes and types of data collected, we elected not to perform a systematic review or statistically-driven meta-analysis of the literature. We began by searching references in Zamudio 2007. We then forward searched papers that referenced Mayhew 1996, Zamudio 2007, and Alwasel et al., 2010. We also searched for papers with the term "placenta" in combination with the terms "global," "population," "variation," and "normal." These two approaches yielded an overlapping set of 7 studies, representing 15 samples. Further, 11 samples from 5 studies provided data on microscopic placental characteristics. Only the Colorado study reported household income data and education level at the time of the pregnancy. That said, the samples ranged from relatively affluent communities of European descent, to reasonably affluent communities in Saudi Arabia and Tunisia, to lower income communities in Bolivia. A study from Nottingham, UK that included samples of both neonates born at normal birth weights and neonates diagnosed as IUGR was included in the comparisons because the reported values were similar to those summarized in the seminal textbook on placental norms and pathology [51] and values from growth-restricted neonates may be a valuable comparison to Cebu and other lower-income locales with a lower mean birth weight. Specific altitudes were reported in some studies in the sample, while others were approximated using publicly available data. The studies from Bolivia identified specific ethnic groups but others did not. We describe birth weights as "normal" if they fell within 2500 and 4000 g, in accordance with WHO guidelines [52]. In all studies, birth weight was recorded immediately after birth. Placentas were confirmed as having been trimmed prior to weighing except in Saudi Arabia, where placental weights were recorded from hospital records with no description of hospital protocol. No published studies but that from Colorado reported a specific timing of placental weighing; in Colorado they were weighed 10–30 min after birth, similar to our study. Confirmed pre-pregnancy weight and thus BMI was available only from Colorado.

For several samples, published data were sufficient to allow calculation of the birth:placental weight ratio (i.e., placental efficiency), birth weight:villous surface area ratio (i.e. villous surface efficiency), and the isomorphy coefficient. The ratio of birth weight to placental weight indicates how many grams of neonate is produced by one gram of placenta. The higher the ratio, the higher the birth weight per gram

Table 1
Maternal characteristics for several populations, listed alphabetically.

Country: Ethnicity	N	Age (yrs)	Stature (cm)	Weight (kg)	BMI	Education (yrs)	Income (USD)	Reference
Bolivia: Mestizo/European (high altitude) [a]	54	–	152.7 [b]	–	–	–	–	Haas et al. 1980
Bolivia: Mestizo/European (low altitude) [a]	46	–	155.3 [b]	–	–	–	–	Haas et al. 1980
Bolivia: Quechua/Aymara (high altitude) [a]	51	–	149.7 [b]	–	–	–	–	Haas et al. 1980
Bolivia: Quechua/Aymara (low altitude) [a]	31	–	151.8 [b]	–	–	–	–	Haas et al. 1980
Cebu [c]	21	27.0	150.9 [c]	–	20.1 [c]	–	$429.35 (USD)[c]	Current study
Colorado (high)	13	29.2	–	61.7 [d]	21.8 [d]	17.4	$67K ± $36K (USD)	Van Patot, et al. 2003
Colorado (low)	19	27.0	–	63.0 [d]	22.5 [d]	14.4	$47K ± $51K (USD)	Van Patot, et al. 2003
Kyrgyzstan[e]	30	25.4	–	–	–	–	–	Reshetnikova et al., 1994
Nottingham (control)	9	30.9	–	64.3 [b]	24.1 [b]	–	–	Mayhew et al. 2003
Nottingham (IUGR)	5	36.2	–	76.1 [b]	31.0 [b]	–	–	Mayhew et al. 2003
Saudi Arabia	967	29.4	158 [b]	77.3 [b]	31.0 [b]	–	–	Alwasel et al. 2011
Tunisia	1321	30.7	162 [b]	66.3 [b]	25.2 [b]	–	–	Alwasel et al. 2013

[a] From Haas (1980), of which the multiple Bolivian studies in Table 2 are a subset.
[b] Not specified as pre-pregnant value.
[c] 2005 data; study dates 2011–2012.
[d] Specified as pre-pregnant value.
[e] Maternal data not reported by altitude.

of placenta. By extension, the higher the ratio, the larger the fetus is relative to its placenta. Because of inconsistencies in the ways the data were reported across studies, it was not possible to statistically evaluate differences. Instead, the data are presented to allow visual exploration of patterns of variation.

3. Results

Table 1 summarizes maternal characteristics (e.g., age, height, weight, education) of the samples under consideration, in alphabetical order. Such data are incompletely represented across studies, barring robust comparison. Further, the maternal characteristics for the Bolivian studies cited in Table 2 come from Haas et al., 1980 [55]; the Kyrgyzstan study did not report maternal characteristics by altitude [56]. Table 2 summarizes key placental characteristics from Cebu along with the comparative data from published studies, presented in order of lowest to highest birth weight. All phenotypic categories are ranked, with a rank of one being the largest/heaviest. Only the Nottingham IUGR population exhibited an average birth weight that met the clinical criterion for low birth weight. Among the other populations, mean birth weights ranged from a low of 2925 g (among high altitude Mestizos/Europeans from Bolivia) to 3605 g (in the normal weight Nottingham sample). The median of the mean birth weights for all populations was 3215 g. Mean Cebu birth weights were on the lower end of the range at 3162 g, and all populations (other than IUGR Nottingham) with birth weights lower than those found in Cebu were located in high-altitude regions.

Mean placental weights varied greatly across samples, with the lightest placentas coming from low altitude Mestizo/European Bolivia (452 g) and the heaviest from normal weight Nottingham (637 g). Cebu placentas again were on the lower end of the range at 454 g (28.7% lighter than those from Nottingham). There was also great variation in placental phenotypes even for those groups with mean birth weights below the median. For example, although birth weight in Saudi Arabia was only 48 g (1.5%) greater than that of next-ranked Cebu, placentas weighed 88 g, or 19.4%, greater. This disproportion is reflected in the birth:placental weight ratio (Fig. 1). The data are arrayed from the lightest birth weights at the top to the heaviest on the bottom, as in Table 2, with Cebu hatch-marked; the variation in placental efficiency is apparent.

Placentas from Cebu produced a higher birth weight per unit placental weight compared to most populations, ranking 3rd of 16, behind low altitude Aymara/Quechua and European/Mestizo from Bolivia. For 12 of the 16 samples we were able to calculate the amount of birth weight each square centimeter of villous surface area supports (i.e., "villous surface efficiency"). This feature was chosen because nutrient transport occurs across the villous surface area. Cebu ranked 4th. High altitude Kyrgyzstan ranked the highest, with high and low altitude Bolivian Aymara/Quechua ranked 2nd and 3rd. In Fig. 2, the data are again arrayed from the lightest birth weights at the top to the heaviest on the bottom with Cebu hatch-marked; there is marked variation in the amount of birth weight supported by villous surface area even when birth weights are similar. Similarly, for these same 12 populations, we calculated and compared their villous surface efficiencies, that is, the amount of birth weight each unit of placental surface area supports. For 8 of the populations we could calculate and compare their isomorphy coefficients, which again yielded great variation. Cebu had by far the lowest coefficient. Placentas with lower isomorphy coefficients tended to produce higher birth weight per unit of surface area.

4. Discussion

The weights of Cebu placentas from uncomplicated pregnancies fall within the range of published values from studies from several other populations. However, within this range, Cebu birth weights are distinguished as being among the lowest reported in the literature (from those studies that also published placental weights), as are placental weights at Cebu. The only populations with lower average weight neonates are those described as living in high altitude conditions, which has long been associated with lower birth weight and alterations in placental microarchitecture and function, such as a reduction of spiral artery remodeling [17] and uterine artery blood flow [16]. Cebu placentas are similar in weight and in relationship with birth weight to those from low-income, high-altitude populations of various ethnicities, in which both placentas and birth weights are relatively small. Our findings indicate that placentas from Cebu possess simpler topography and reduced surface areas, yet greater efficiency for their weight.

Population variation in the relationship between placental characteristics and birth weight highlights that prenatal environments vary widely. For example, in Saudi Arabia Alwasel et al. [58] found that while birth weights did not vary much from those reported in European samples, placental weights were smaller and thus the overall placental efficiency was higher, ranging from 6.29 to 6.40. In contrast, a Norwegian study [61] of 6515 births found that at term, the placental efficiency for babies born at weights between the 10th and 90th percentiles ranged from 4.61 to 6.76, with those at the 50th having a placental efficiency ratio of 5.43–5.46. This is similar to the ratio of 5.7 reported for the normal weight infants in the Nottingham study [53], and 5.6 reported for normal weight infants born between 38 and 40 weeks in Israel [62]. The findings of such a range of placental

Table 2

Birth weight and placental characteristics for several populations, ranked in order of lowest to highest birth weight[a].

Country: Ethnicity[reference]	N	Altitude (m)	Birth weight (g)	Birth weight rank	Placental weight (g)	Placental weight rank	Placental efficiency[c]	Placental efficiency rank	Villous volume (cm^3)	Villous volume rank	Villous surface area (m^2)	Villous surface rank	Villous surface efficiency[d]	Villous surface efficiency rank	Isomorphy coefficient	Coefficient rank
Nottingham: European (IUGR)[53]	5	60[b]	2360	16	409	16	5.77	13	–	–	6.47	10	365	7	–	–
Bolivia: Mestizo/ European (high altitude)[54a,b,55]	28	3600	2925	15	457	12	6.40	9	115.0	7	5.25	12	557	1	104602	7
Kyrgyzstan: Kyrgyz (high altitude) [56]	10	2200–2800	2975	14	467	10	6.37	10	131.7	3	13.40	1	222	12	372453	1
Bolivian: Aymara (high altitude) [57]	10	3600	2994	13	459	11	6.52	8	–	–	9.07	5	330	8	–	–
Colorado: European (high altitude) [17]	19	3100	3123	12	605	2	5.16	16	–	–	–	–	–	–	–	–
Bolivia: Aymara or Quechua (high altitude)[54a,b,55]	16	3600	3155	11	480	8	6.57	7	101.4	8	6.30	11	501	3	155946	5
Philippines: Cebuano (this study)	**21**	**40**[b]	**3162**	**10**	**454**	**14**	**6.96**	**3**	**180.5**	**1**	**6.51**	**9**	**486**	**4**	**92023**	**8**
Saudi Arabia: not reported [58]	967	670[b]	3210	9	542	5	5.92	12	–	–	–	–	–	–	–	–
Bolivia: Mestizo/ European (low altitude)[54a,b,55]	14	400	3220	8	452	15	7.12	2	115.0	6	7.02	7	459	5	161736	4
Bolivian: Aymara (low altitude) [57]	14	400	3251	7	480	7	6.77	6	–	–	8.83	6	368	6	–	–
Kyrgyzstan: Kyrgyz (middle altitude) [56]	10	2020	3275	6	472	9	6.94	4	131.7	4	11.20	3	292	10	284604	3
Colorado: European (low altitude) [17]	13	1600	3359	5	542	4	6.20	11	–	–	–	–	–	–	–	–
Tunisia: not reported [59,60]	1321	300[b]	3392	4	594	3	5.71	14	–	–	–	–	–	–	–	–
Bolivia: Aymara or Quechua (low altitude)[54a,b,55]	10	400	3415	3	454	13	7.52	1	117.8	5	6.56	8	521	2	142630	6
Kyrgyzstan: Kyrgyz (low altitude) [56]	10	760	3506	2	510	6	6.87	5	152.1	2	12.60	2	278	11	294054	2
Nottingham: European (normal birthweight) [53]	9	60[b]	3605	1	637	1	5.66	15	–	–	11.00	4	328	9	–	n/a

[a] Only means reported here.
[b] Estimated elevation not reported in original citation.
[c] Placental efficiency = fetal weight/placental weight (g/g).
[d] Villous efficiency = fetal weight/villous surface area (kg/m^2).

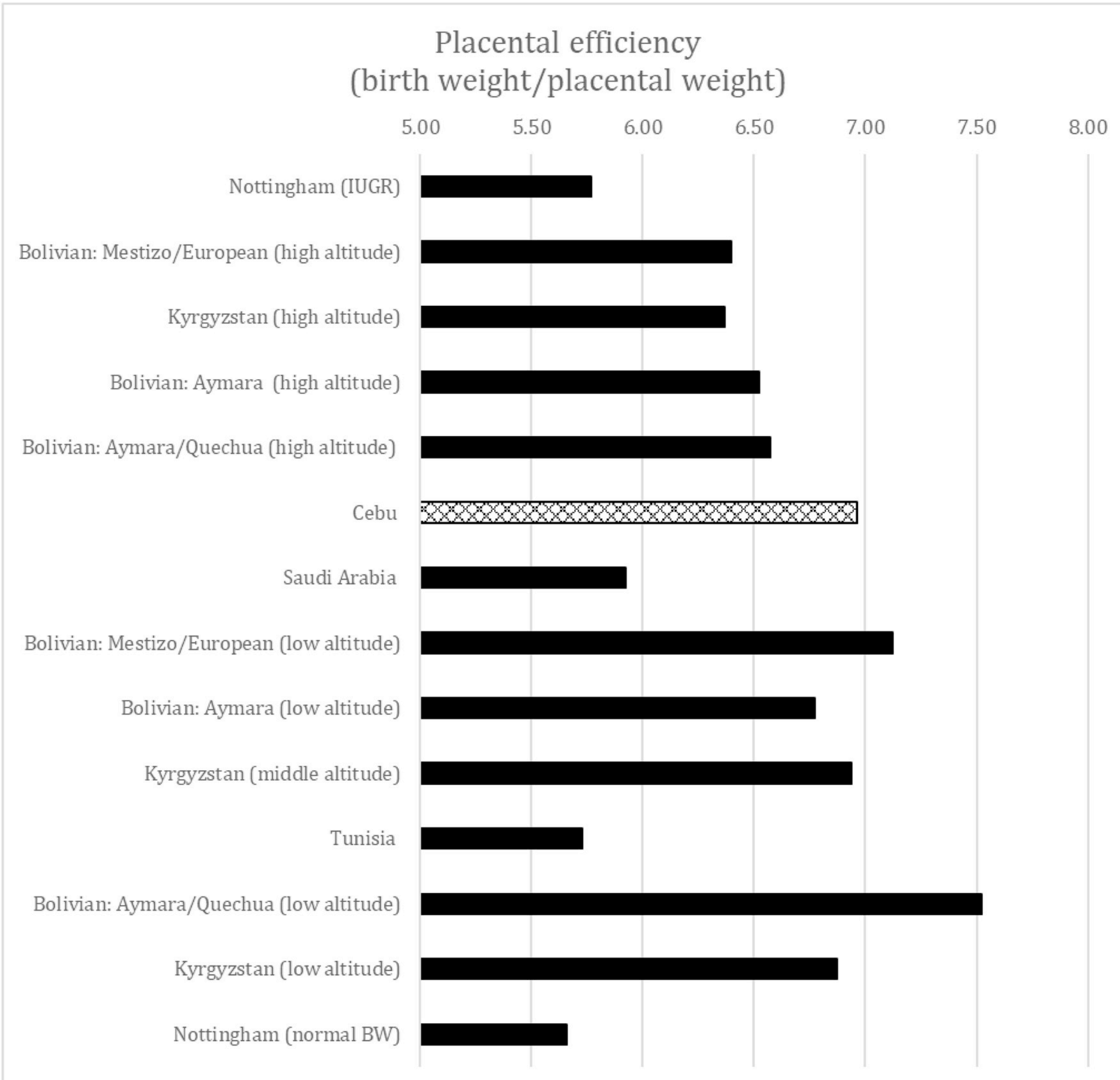

Fig. 1. Population variation in the birth:placental weight ratio, from lowest to highest birth weight.

characteristics underlying 'normal' birth weights further erodes the utility of 'universal' standards based largely on affluent populations of European descent. Thus, in situations in which birth weights are similar but birth and later health outcomes are not, it may be important to consider underlying factors such as influences on placental development and function.

The relationship between birth weight and placental weight offers clues about placental function, and the production of fetal mass. We find that Cebu placentas produce a higher birth weight per unit placental weight than do placentas from most other locations, particularly those that are relatively affluent (e.g. Saudi Arabia, Colorado, Nottingham). One possible mechanism underlying the ability of the relatively small placentas at Cebu to support a high level of fetal growth is their comparably large placental villous volume. Cebu placentas rank 1st in this microscopic compartment. The placental villus is the functional unit of the placenta, housing the fetal capillaries which convey nutrients taken up from maternal circulation, and covered by a thin layer of placental cells, the cytotrophoblast (CT) and syncytiotrophoblast (SCT) [63]. The SCT is a highly specialized layer of cells engaged predominantly in nutrient uptake from maternal blood as well as hormonal signaling back into maternal blood. Interestingly, the villous surface area – an indirect measure of the SCT and thus transport capacity – is relatively small in placentas from Cebu, compared to other populations, yielding a low isomorphy coefficient, which is suggestive of a relatively less complex microarchitecture overall [47]. It is thus possible that the placentas from Cebu achieve relatively high production of fetal mass through the activity of a greater number or volume of fetal capillaries within the villus to maximize uptake from the available stores being transported by a relatively smaller surface area. In addition, alterations to glucose and amino acid transport systems have been observed in nutritionally stressed animal models [19,23,64–66], and are also potential drivers of increased placental efficiency in Cebu. In comparison, the sample with placentas with the greatest surface area both absolutely and relatively (in the form of the isomorphy coefficient) is from the high-altitude Kyrgyz population, which is associated with the second lowest non-IUGR birth weights.

There are multiple ways to increase nutrient transport to the fetus that are not captured directly by the morphometric characteristics presented here. Either alone or in concert with an increased surface area, the thickness of the membrane separating fetal capillaries and maternal blood, formed in part by the SCT, is highly variable. A thinner membrane facilitates passive diffusion more efficiently [49]; this is another possible mechanism contributing to relatively high fetal growth for a given unit of placenta at Cebu. However, due to a lack of comparative data, we did not examine this compartment in the current study.

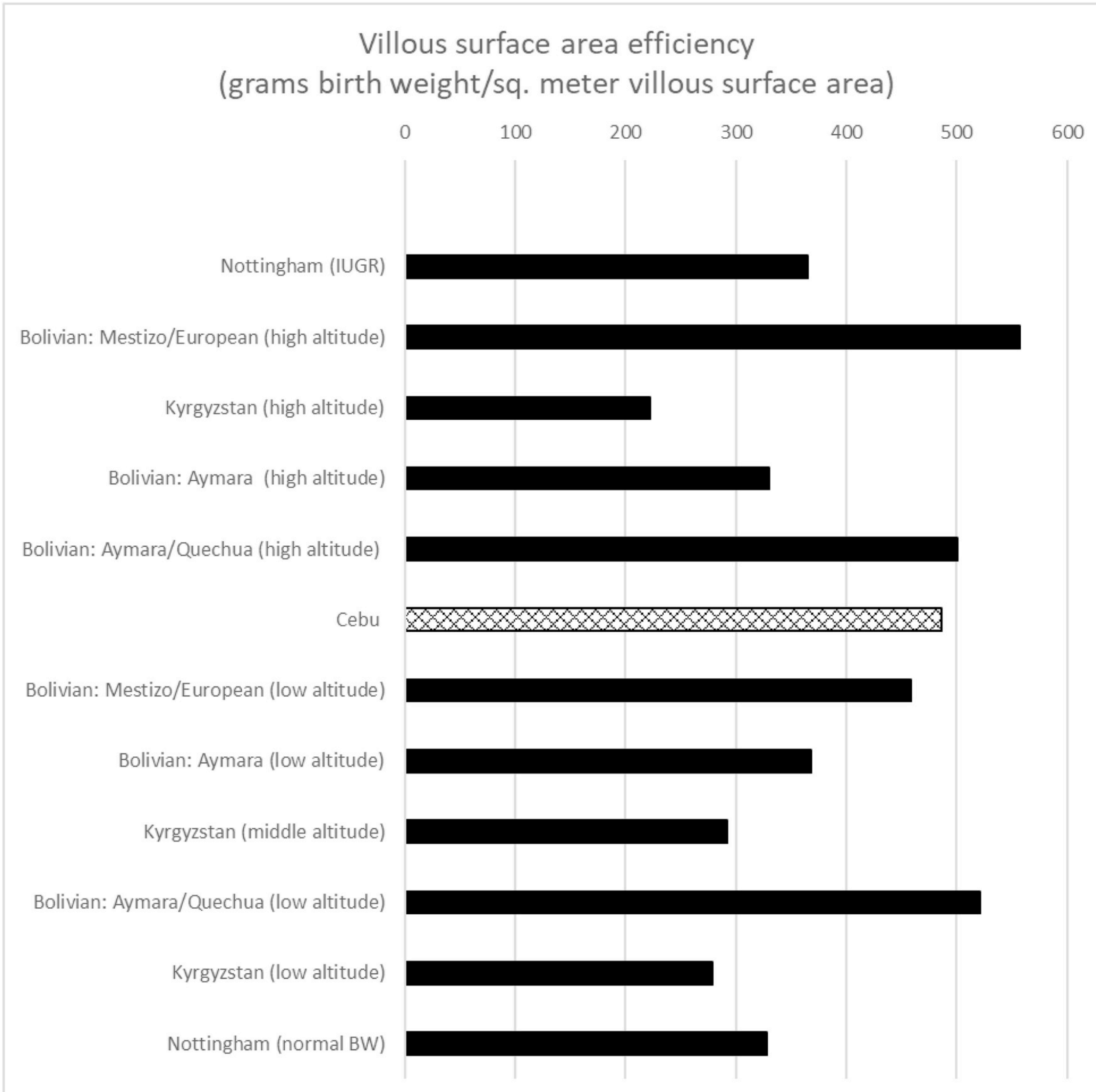

Fig. 2. Population variation in villous surface area efficiency, from lowest to highest birth weight.

Beyond physical properties of the microscopic elements of the placenta, other sources of variability to be addressed in future analyses of population variation may occur at the ultrastructural and molecular, including epigenetic, levels. Flexibility of placental 'strategy' supports optimal fetal growth within particular environmental contexts in such a way that, as Lumey [30] states, "birthweight is not an appropriate proxy measure of undernutrition for all pregnancy trimesters" (p. 110). In sum, placental variation both within and across populations is likely due to many intersecting environmental, metabolic, economic, and (epi)genetic factors that will require additional research to clarify.

The study of placentas from Cebu is subject to some limitations. Our sample consisted of just 21 placentas. Although small, this sample compares favorably to most other studies of placental microstructure. We pooled males and females in our analyses, in part owing to the relatively small sample size. There is evidence that male and female fetuses and their placentas grow at different rates to different maxima at term, with males typically being born at slightly higher birth weights with slightly heavier placentas, yet with lower birth:placental weight ratios [61,67,68]. There were 16 male offspring (76%), and 5 female offspring (24%) in our sample. Because our sample was predominantly male, it is possible that our mean placental characteristics are inflated beyond the overall population mean for Cebu and that a more sex-balanced sample would be associated with even smaller placentas and thus higher placental efficiencies. A larger concern is that of comparing birth and placental weights across several studies, many with low sample sizes themselves and incomplete descriptions of how placentas were processed and maternal characteristics. It is possible that some of the variation our comparison reveals is due to variation in methodologies rather than variation in placental structure and function. This limitation is a call for more systematic approaches to collecting and processing placentas in different clinical and research settings to aid in more refined and reliable population comparisons.

5. Conclusions

In sum, we find that placentas in a population characterized by lower birth weights, widespread childhood stunting, and moderate nutritional insufficiency are relatively small, and have low villous surface area and less complex surface to volume topography. Although average birth weights at Cebu were low, placentas were even smaller relative to birth weights, yielding a high efficiency of birth weight to placental weight. Overall surface area of the placental villi was low compared to most other populations, but it yielded a relatively high plane of support for fetal growth. This could be due to modifications to the thickness of the membrane separating maternal and fetal circulations and/or increased fetal capillary volume or surface area within the villi to maximize nutrient uptake. Our findings in Cebu demonstrate there is wide variability across populations, even those of similar economic and nutritional status, in placental structure and function underlying normal birth weights from uncomplicated pregnancies. These findings underscore the need for additional work aimed at documenting normal variability in placental characteristics in human populations, and the factors experienced during and prior to pregnancy, that contribute to this variation. Understanding the environments that differentiate placental development and function may be an important step in uncovering the sources of population-level developmental disparities that persist across the life course.

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Competing interests

The authors have no competing interests to declare.

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