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Original Article

Transgenerational propensities for infant birth weight reflect fetal growth history of the mother in rhesus monkeys

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ABSTRACT

Birth weight (BW) at delivery is an important developmental milestone indicative of prenatal conditions and portends of the postnatal growth trajectory that will occur during infancy and childhood. Previous research has documented that there are also many physiological and health consequences of being born either small-for-gestational age (SGA) or large-for-gestational age (LGA). Analyses of breeding animals have demonstrated further that a gravid female exerts a strong influence on the size of her infant by term, and this permissiveness or constraint over fetal growth can be transmitted from mothers to their daughters. The following research tested additional hypotheses about matrilineal effects on BW by examining records from a large breeding colony of rhesus monkeys across multiple generations. The analyses utilized BW of 1710 infant monkeys obtained over 4 decades. In addition to determining the association between the BW of a female and her own infants birthed later as a mother, the multi-generational transmission of birth size from a grandmother through her daughters to the next generation was examined. Other maternal influences were evident, including a progressive increase in infant BW with parity, which synergized with matrilineal effects across a female's reproductive life. In addition, our modeling indicated that if an infant's BW was discordant—a SGA female birthing a larger daughter—the discrepant fetal growth pattern could be accentuated in the next generation. Overall, the findings confirm that the size of an infant at term is significantly influenced by a type of gestational imprinting on daughters during the prenatal period, which then continues to shape birth outcomes in subsequent generations.

KEYWORDS: birthweight, infant, inter-generational, rhesus monkey, pregnancy, small-for-gestational age, maternal.

ABBREVIATIONS

BW	:	birthweight
SGA	:	small-for-gestational age
LGA	:	large-for-gestational age
HLM	:	hierarchical linear model
ICC	:	intra-class correlation

INTRODUCTION

The weight of a neonate at delivery is a reflection of that infant's inherent growth potential as well as the availability of nutrients acquired transplacentally and the abundance of the mother's resources [1, 2]. Thus, BW is an indication of the quality of uterine conditions during the prenatal period and serves as a window on the health and wellbeing of the mother [3]. An even broader significance for general health became evident with the realization that BW informs about the regulatory set points for many physiological systems with implications for postnatal growth,

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metabolism, and obesity [4, 5]. Epidemiological studies demonstrated that BW could be linked to risk for several adult-onset illnesses, including type 2 diabetes and cardiovascular disease [6-8]. This larger perspective is often succinctly captured by the term *'fetal programming'*, a viewpoint popularized by the epidemiologist Dr. David Barker. It has been repeatedly documented to be applicable to both humans and animals. Much of the extant research has focused on the impact of being born at the extremes of the BW distribution--either SGA or LGA—but associations have also been found across the entire BW continuum [9-11]. Further, many studies have demonstrated that a significant stunting of fetal growth can continue to have lingering consequences for maternal reproductive health, affecting the pregnancy outcomes of women in subsequent generations [12]. Similarly, there is convincing evidence that a propensity for premature birth can be perpetuated from one generation to the next [13, 14].

In addition to this evidence of clinical importance for maternal and child health, there has also been extensive research in animals because of the relevance for domesticated farm animals and agribusiness. The size of offspring at birth has considerable economic impact when breeding sheep, pigs and cows, because it is associated with infant viability and the pace of postnatal growth, which then affects the age at which animals can first be used as a source of meat, wool or dairy products [15-18]. In addition to the many husbandry factors that influence BW in these species, the number of offspring gestated successfully to term in litter-bearing animals is governed by heritable processes. Especially in mice and rats, it has been possible to selectively breed for litter size and even for the similarity or variance in BW across pups in the same litter [19]. Further, it has been shown that the location of the fetus in the bicornuate uterus of a litter-bearing dam, as well as proximity to a female or male sibling will affect growth and ultimate size at birth [20]. These findings have translational relevance to multiple pregnancies in humans, because the presence of a sibling can modify the growth of the other twin. It has been shown that if two twin sisters are born at different weights, there may be residual inter-generational effects still evident when their own infants are born decades later [21, 22].

To more directly model a typical human pregnancy, however, it is of value to investigate species that gestate one infant at a time. A classic study conducted on horses indicated that one key maternal factor accounting for infant size at birth is a type of *uterine constraint* [23]. Using artificial insemination to cross-breed Shire horse-Shetland pony hybrids, Walton and Hammond showed in 1938 that the bigger Shire mare birthed larger foals, whereas the small Shetland mare gestated a little foal even when impregnated by sperm from a large stallion. Although not typically emphasized, this differential growth rate was then perpetuated after birth resulting in hybrid horses that continued to be very different sizes across the first year of life. Research on BW in nonhuman primates has been limited [24, 25], but there is evidence to suggest similar maternal influences on fetal and infant growth in monkeys. Our laboratory had analyzed factors affecting infant BW in a domesticated breeding colony of rhesus monkeys and found evidence for strong heritable trends that were associated with female matrilines [26]. It was of additional interest that neither the BW nor adult size of the fathers seemed to have a significant influence on the BW of their offspring. Further, when focusing exclusively on infant monkeys born at the lower and upper ends of the BW distribution, this maternal effect was especially pronounced among siblings, suggesting a pervasive maternal influence on the majority of her offspring [27]. Finally, a follow-up analysis of the postnatal growth trajectories of 100 female monkeys indicated that small or large size at birth was associated with the female's age at menarche and first conception [28]. Those findings had been reported 2 decades ago. The aims of the current analysis were to replicate the conclusions with new animals born subsequently, and to determine if we could discern transgenerational effects from females through their daughters that continued to influence the BW of later descendants. It seemed that across generations some matrilines might be accentuating the tendency for birthing small and large infants. While this trend proved to be the case overall, one unexpected finding emerged

when occasionally a daughter was born at a larger BW discordant from her mother who had been low BW in the prior generation.

MATERIALS AND METHODS

Subjects

The infant BW data were obtained from a large breeding colony of rhesus monkeys (*Macaca mulatta*). The original founder population had been imported from India over 6 decades ago, but their descendants have been maintained for many generations under standardized conditions at this facility. The monkeys breed both naturally in social groups and as pairs with a timed-mating protocol; 80-100 infants are born annually [29]. The majority are weighed soon after birth. Inclusion criteria for this analysis were: unassisted delivery of a live infant from a singleton, term pregnancy, and neonatal weight acquired within 1 week of delivery. The data span a 45-year period from 1973 to 2018. The total number of infant BWs was 1710, which were used to quantify the average sex difference in BW and to verify that there had not been a simple progressive increase in BW across the years of assessment (although year of birth was still included in many analyses as a covariate). To model one-generation effects, the BWs of 335 dams weighed at birth were compared to the BWs of 1099 infants they delivered. For modeling multi-generation effects, the BWs of 502 triads were evaluated: 107 grandmothers who then birthed 161 daughters that gave birth to 502 female and male offspring, all with accurate BWs meeting the inclusion criteria.

Housing

This monkey colony is housed in a 3-floor vivarium with 28 rooms located in a 31,538 square foot building. All monkeys live in indoor caging with artificial lights on a 14 h light/10 h light dark schedule. The constant photoperiod is used deliberately to override the species tendency to breed seasonally. Thus, infants are conceived and birthed during all months of the year. Previous analyses of the timed-mated multiparous females had documented there isn't seasonal variation in reproductive success or infant birth outcomes [29]. The absence of a seasonal fluctuation in BW was re-affirmed in the current analysis. This consistency in infant BW may be explained further by the maintenance of ambient room temperatures at an average 21 ^{o}C year-round. In addition, the monkeys are fed the same diet everyday (Purina 5LFD, PMI Nutrition International, St Louis), which is supplemented with fresh produce and grains. Long-term use of a controlled diet may account for the stability in infant BW over 4 decades (see Figure 1), enabling us to more clearly delineate the salience of maternal influences.

Rearing and mating

All infants are raised by their mothers for at least 6-7 months, after which they are weaned into small social groups of similar age juveniles. They remain in these social groups, progressively relocated into larger cages or pens until the birth of their own first infants. Between 5-20 years of age, as multiparous adult females, they are bred using a timed-mating protocol. Their menstrual cycles are monitored, and they are relocated to the cage of a breeder male for 4-7 days during the fertile ovulatory period at mid-cycle. The timed mating program currently consists of approximately 150 females and 16 adult breeder males, all descendants of the original founder population. By standardizing the pregnancy and birthing conditions, it is conducive to discerning maternal influences on infant outcome and lessening the contribution of environmental and dietary factors. The colony is closed to new animals; thus, it was also possible to trace the familial relationships of all females. This information about pedigree was used in our data analysis to determine if females birthing smaller or larger infants were more likely to be genetically related.

Birth weight data

BWs were acquired for both female and male infants. However, for the current analyses, the BWs of males were considered just for determining if a female's BW affected her sons as much as her daughters. For modeling the matrilineal influences from an adult female through her daughters to subsequent offspring, only female BWs were included for the first and second generation. The goal was to predict BW for 228 female and 284 male infants in the third generation. Finally, to examine if dams birthing smaller or larger infants were more likely to be genetically related, only

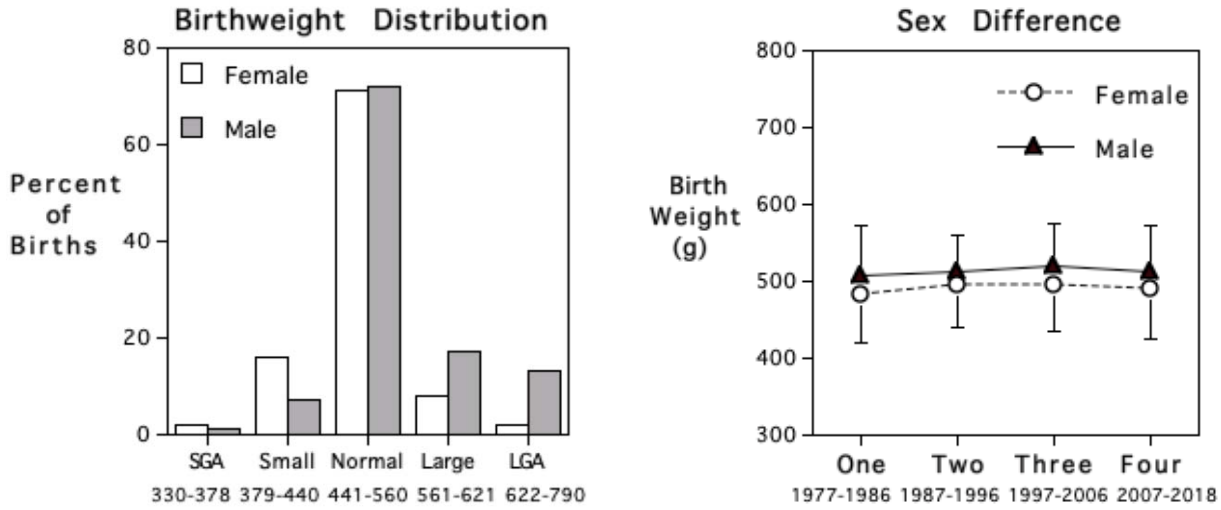

Figure 1. Distribution of birth weights across the normal range from 330-790 g in rhesus monkeys illustrating the percent of females and males in 5 weight categories (SGA [< 2 SD], small, normal [mean +/- 1 SD], large, LGA [> 2 SD]). **A**. Females and males were equally represented in each subgroup. **B**. Stability of infant BW across 4 decades, as well as the consistent sex difference of 21-24 g between female and male infants.

adult females were included in that associational analysis. The familial background and genetic relatedness of 20 females who birthed small infants was determined and compared to how related they were to 20 different females who birthed large infants. Relatedness scores were based on parental ancestry records going back many generations and derived with Kintraks Breeding software. Because relatedness scores were not normally distributed and could range from 0.5 (mother-daughter) to 0.25 (half sibling with different father) and down to less than 0.01, the nonparametric Kruskal-Wallis test was used to determine if females birthing SGA and LGA infants were descended from different matrilineal pedigrees.

Higher order data analytical strategy

A 2-level hierarchical linear model (HLM) was constructed from dyads with valid BWs for both the dam (N = 353) and her infants (N = 1099). Infant-specific (level 1) and family-specific (level 2) predictors of infant BW were examined. The intra-class correlation (ICC) confirmed that infants birthed to the same dam (i.e., siblings) were more likely to have similar BWs. Infant-specific predictors included sex, birth order, and year of birth. These 3 variables were statistically controlled in all subsequent analyses. Dam-specific predictors of infant BW included dam BW and maternal age at which each offspring was birthed because of the likely influence of maternal parity on BW. Exploratory analyses also considered whether very small (<378 g) or large infants (>622 g) evinced stronger associations with their mother's BW than found for the overall cohort. Next, to delineate transgenerational effects further, a 3-level HLM examined a subsample with triadic records: grandmothers (N = 107), dams (N = 161), and their descendants (N = 502). The ICC distinguished variance in infant BW that could be attributed to the grandmother and dam or was inherent to the infant. This analysis specifically parsed the relative contribution of the BW of grandmother and dam to the BWs of their descendants. A test of the cross-generation interaction then determined whether considering the two-generational influence together was more predictive of infant BW. The analyses controlled for the sex of the infant because females tended to be born smaller than male infants (see Figure 1B).

RESULTS

Stability of sex difference in BW over time

An analysis of variance comparing the BW of 1710 infants born across 4 decades from 1977 to 2018 indicated there had not been a simple

progressive change in BW over time (Figure 1). However, there was a significant average difference of 21-24 g in the BW of females and males, which was stably present ($F[1,1703] = 49.2$, $p < 0.0001$). Variation in infant BW was also evaluated by categorizing BW into 5 subgroups with respect to the overall mean and standard deviation (>2 SD: SGA and LGA; >1 SD: small and large; mean + 1 SD: normal). Females and males were equally represented in each subgroup, and the average weight of a female and male in each subgroup was similar (Figure 1).

Influence of infant sex, birth order, and temporal trends on BW

In keeping with the *a priori* predictions, and based on the 2-level HLM analysis, we found the BWs of infants from the same mother were similar, $\chi^2(352) = 923.27$, $p < .001$; 35% of the total variance in infant BW was due to shared dam-level variance and the remaining 65% due to infant-specific factors. Infant specific factors included: 1) sex, $\beta = -24.07$, $t(745) = 7.20$, $p < .001$, because males weighed more than female infants, and 2) the effect of birth order on BW, $\beta = 4.85$, $t(352) = 5.95$, $p < .001$. Each later offspring was approximately 5 g larger than the prior one. Lastly, within this model based on the subgroup with BW for dams and infants, there was a modest central tendency for a small increase in BW over time, $\beta = .487$, $t(352) = 2.01$, $p = .045$. However, the temporal effect also varied significantly across the dams, $\chi2(182) = 227.58$, $p = .012$. After controlling for parity, the temporal trend no longer retained statistical significance, leaving only the significant variation across females. As portrayed in Figure 2, there appeared to be increasing dispersion in infant BWs, suggesting weights were increasing for some lineages, whereas infant BW was decreasing for other females. As can be seen in Figure 2, there was a clear upward or downward trend evident in different females, suggesting that parity was accentuating the inherent propensity as multiparous dams birthed additional infants. The length of each line reflects the number of offspring birthed by each female.

Significant association between maternal and infant BW

Even after statistically controlling for sex, birth order, and the temporal trends, the BW of infants was still highly correlated with the BW at which

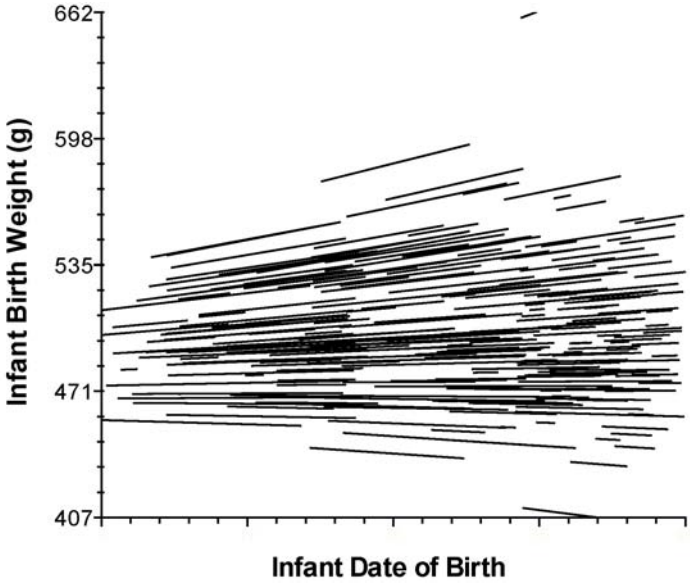

Figure 2. The influence of the dam's BW on all infants she delivered as an adult. Matrilineal effects synergized with the influence of parity, resulting in more dispersion of BW over time, impacting both smaller and larger infants in this breeding colony of rhesus monkeys. The length of each line reflects multiple offspring; a single dot indicates the dam had only one infant.

their mothers had been born, $\gamma = .179$, $t(351) = 4.39$, $p < .001$. The BW of an infant was predicted to be 2 g heavier for every 10 g increment in the mother's BW. This significant linkage was evident in both female and male offspring and is illustrated in Figure 3. We then tested if infants born very small (SGA <378 grams, N = 36) were more likely to be born to especially low BW dams (i.e., lower than expected by the linear association with infant BW). However, this analysis of extreme SGA infants did not indicate they had been delivered by dams that had been born particularly small, $\gamma = -.003$, $t(389) = 1.75$, $p = .24$. Similarly, infants born LGA >562 g, N = 43) were also not more likely to have been delivered by mothers born extremely large. In fact, the trend was for those larger BW dams to regress back toward the normal range and central tendency for BW, $\gamma = -.006$, $t(389) = 2.07$, $p = .039$.

Transgenerational effect of grandmother to her descendants

The ICC values in the 3-level HLM indicated that the grandmother accounted for 9% of the variance in her later descendants, $\chi^2(106) = 138.21$, $p = .019$. An additional 21% of the variance in infant BW was attributed more directly to the dam, $\chi^2(54) = 95.99$, $p < 0.001$. As found in the 2-level HLM, female infants were born smaller than males, $\gamma = -23.70$, $t(232) = 4.02$, $p < .001$; therefore, the models controlled for infant sex. In keeping with the 2-level HLM, a mother's BW predicted her infant's BW, $\gamma = 0.24$, $t(53) = 4.14$, $p < .001$. However, the grandmother's BW did not directly determine the BW of her more distant descendants, $\gamma = 0.064$, $t(105) = .994$, $p = 0.3$. This modeling suggested the intermediate generation was the more influential conduit mediating the transgenerational effect. After accounting for the direct effects of the dam, the influence of a grandmother on her later descendants no longer attained statistical significance.

Transgenerational effects after a discordant BW

Although the matrilineal effect indicated dams born small or large tended to pass this trait onto their offspring, there were some exceptions when a female was occasionally delivered with a BW discrepant from her mother. The 3-level HLM enabled us to identify this subset of dams born at a larger BW than their mother. The interactive effect is portrayed in Figure 4. While the BW of dams tended overall to reflect the grandmother's BW, if a dam had been born at a larger weight than expected, this effect was perpetuated further in her descendants. This summative outcome for the next generation is illustrated by the higher mean BW of 515 g for infants descended from a small BW grandmother and a larger BW mother. The infants with a discordant matrilineal history

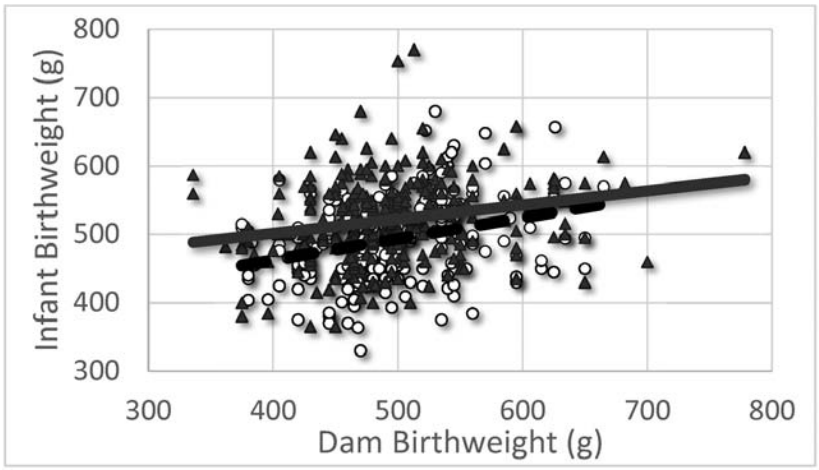

Figure 3. Significant correlation between the infants' BW and the BW at which their mother had been born. The influence of a dam's BW on her offspring was similar for female and male infants, as evidenced by the scatterplots and slopes of the regression lines. Female infant (circle), male infant (triangle).

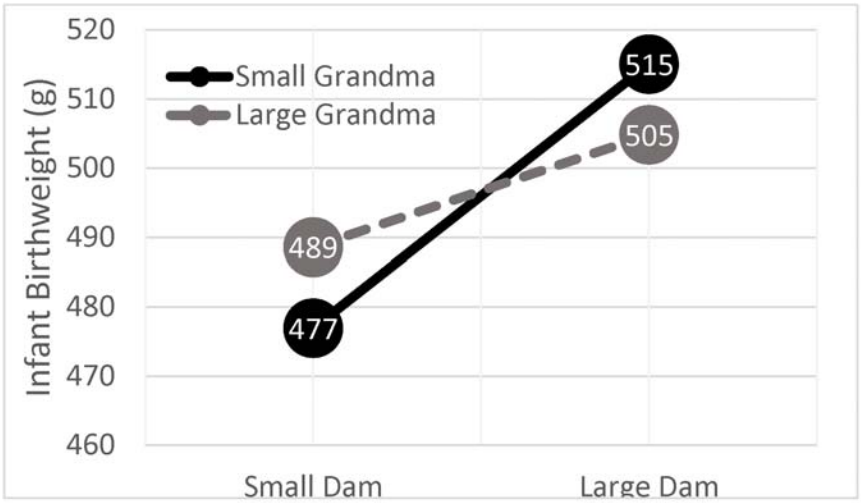

Figure 4. Interactive effect of grandmother's and mother's BW on the BW of their descendants. In general, mothers born small (dams) delivered infants of a lower BW, whereas females larger at birth continued to have bigger infants. However, if a dam was born at a discordant weight –larger than the grandmother born small -- this discrepant outcome was accentuated further in the next generation. The heaviest mean BW in descendants was from dams with a larger BW who had been birthed by grandmother born small. This effect is evinced by the mean BW of 515 g for offspring of the female lineages with a small BW grandmother and larger BW dam.

were noticeably larger at birth than those from a concordant matriline with a small BW grandmother and small BW dam (i.e., resulting in a mean BW of 477 g for their descendants).

Relatedness of dams birthing infants at the extremes of the BW continuum

The final analysis examined whether these maternal influences on infant BW could be attributed to the emergence of inbred female lineages in this colony due to an inadvertent selection process over time. Twenty females that birthed extremely small infants at the low end of the distribution were selected (BW <420 g) and their relatedness compared to 20 different females birthing much larger infants (BW >575 g). Because the familial ancestry of all monkeys was known, it was possible to quantify their relatedness, ranging from 0.5 (mother-daughter) and 0.25 (half sibling with a different father), down to less than 0.01%. However, all mother-daughter pairs were then excluded from this analysis because of the previously demonstrated gestational influences on the daughter. As can be seen in Figure 5, females were not more likely to be more related on the basis of their infants' BWs than they were to the dams birthing infants at the other end of the weight continuum. Because the relatedness scores did not have a normal distribution, they were compared with a non-parametric Kruskal Wallis test. The pairwise comparisons, with an adjusted significance threshold of P = 0.017 because of the 3-way testing, indicated that females birthing SGA infants were actually less related to one another (P = 0.136) than were females who birthed LGA infants.

DISCUSSION

These results replicate previous findings of a strong maternal influence on infant BW and extend the observation to relatives within matrilines of rhesus monkeys [27]. Infants born from the same mother were similar in size reflecting the pervasive influence of that mother's BW. This association was also transmissible across at least 2 generations, but not strictly heritable. Many studies in humans have indicated that a congruent pattern of BWs can be seen in families and across generations, but the relative contribution of heritable vs environmental factors is still not fully resolved [30-34]. Specifically, in our analysis of familial relatedness among female monkeys birthing very small or very large infants, we did not

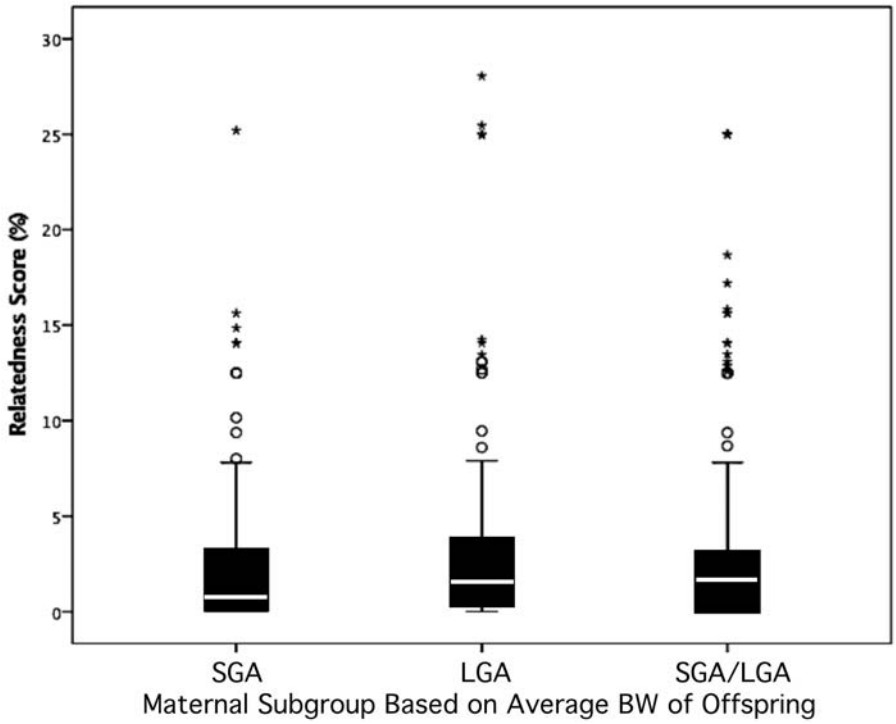

Figure 5. Genetic relatedness of 20 female monkeys birthing very small infants (<420 g) compared to 20 dams birthing large infants (>575 g). Family pedigrees were used to calculate percent relatedness. There was no evidence for inbreeding and inadvertent selection as the explanation for birthing SGA or LGA infants. Females birthing SGA vs LGA infants were not more likely to be distantly related (SGA/LGA).

find evidence that they were more genetically related than would be expected by chance in this breeding colony. Moreover, the transgenerational model that examined whether an infant's grandmother impacted the BW of her descendants suggested there could be a surprising divergence if a dam in the intermediate generation had been born at a discordant BW. This conclusion about the relative importance of the gestational experience and the lesser significance of underlying genetic factors may differ for other animal species. However, in many of those studies, the data were generated from litter-bearing animals that were selectively inbred, and the appearance of effects on neonatal BW may partially reflect the heritable influences on litter size [35]. When multiple fetuses are gestating in utero together, litter size would affect the growth trajectories of all infants.

We had first reported on maternal effects on infant BW in monkeys over 20 years ago [27]. The current analysis indicates these transgenerational trends have now persisted over a 40-year period and are continuing to affect the descendants of that earlier cohort of animals. The previous modeling had definitively shown that paternal influences on infant BW were negligible, even though male infants are impacted by the fetal growth propensities manifest in their mothers. Male infants are born heavier than females-- by 21-24 g--but both sexes are similarly represented across the BW continuum, and neither sex is more likely to be SGA or LGA. Nevertheless, the gestational imprinting and transmission of fetal growth is perpetuated primarily through the female relatives within matrilines. This conclusion about the predominance of a female influence in the rhesus monkey does differ from a number of analyses in humans that reported a paternal contribution, although it is always smaller than the maternal influence [36, 37].

Because of the standardized diet and living conditions in this monkey colony, the BW of a female continues to affect her postnatal growth, as well as her age at menarche and first

conception [28]. This linkage between BW and age at puberty has also been documented in humans and many other animals because larger size usually results in an earlier puberty [38]. The association underscores the economic implications for agribusiness where husbandry practices can affect BW in domesticated farm animals. In many litter-bearing species, a low BW is also often a determinant of infant survival [39]. Using experimental manipulations of litter size and BW in baby rabbits, it was found that both variation in kit weight within a litter and small kit size are associated with a higher mortality [40]. In contrast, among humans there can often be very different health-related concerns associated with growth propensity because the availability of high calorie and high fat food options leads to a differential postnatal risk for obesity and the adult-onset diseases associated with Metabolic Syndrome [5].

The present results also extend "*litter*" effects to "*sibling*" effects by demonstrating the significant shared variance within families: 35% of the total variance in infant BW was shared by their siblings. The "*sibling*" effect also extended across generations to what could be called an "*aunt*" effect. Sisters from the same mother then delivered infants with a similar BW. In essence, the sibling effect in the 2-generation model (accounting for 35% of the total variance) agreed with the conclusion from the 3-generation model in which 21% of the total BW variance was shared between infants from the same mother. An additional 9% of the similarity extended back to the earlier generation of their grandmother.

One of the more novel findings from modeling the effect across 2 generations was that if a daughter did have a discordant BW, it could have a sustained influence on her descendants. If the first dam in a matriline had been born at a low BW, but then had a daughter in the normal or larger BW range, this discrepancy was accentuated in the next generation. While we did not definitively identify the cause of this compensatory response affecting the next generation, there have been analogous reports in humans when the growth of a female baby is stunted by being gestated in a twin pregnancy. She may then give birth to a larger than expected infant, or at least a heavier infant than the nieces or nephews born to her larger twin sister [41]. One possible contributing factor could be persistent differences in gestational weight gain. We had demonstrated previously that gravid female monkeys who gain more weight – more than 2.5 kg – will typically deliver larger infants. This influence of a female's preconception weight and her weight gain while pregnant also probably accounts for the finding that infant BW typically increases with age and maternal parity in monkeys. Although in the current analysis we also identified some bidirectional trends because parity acted synergistically with the matrilineal effect. That is, maternal parity resulted in a larger BW in the offspring of dams who birthed larger infants, while it reinforced the tendency for smaller infants from mothers on the low end of the BW continuum.

Several inclusion criteria for this analysis should be restated. All infants had to be from term pregnancies and unassisted deliveries. Therefore, preterm births and caesarian deliveries were excluded. Many epidemiological studies have had to consider the effects of low birth weight in humans along with the influence of a shorter gestational length [42, 43]. This potential confound is important to consider because the propensity for premature birth is also passed from one generation to the next, although it likely involves other risk factors beyond the ones influencing fetal growth. Many maternal conditions, including gestational hypertension and diabetes, as well as infections and inflammatory responses, can contribute to a premature delivery [44, 45].

CONCLUSION

There is a strong maternal influence on infant BW in monkeys, which can be transmitted across generations. The propensity appeared to be mediated proximally by the gestational experience of the female while in utero. This fetal imprinting has sometimes been described as a type of *uterine constraint*, but it is probably not due to the physical dimensions of the uterus or the size of the pelvic opening [46], but rather to processes that govern the energetic and metabolic set points for fetal growth [47]. The evidence for direct genetic effects on fetal growth in humans indicates that the heritable influence is stronger in early gestation and less prominent in the third trimester,

when metabolic mediators may become more influential [48]. Similarly, the research on BW outcomes after *in vitro* fertilization in women have indicated that the infant's BW is more associated with the gestating mother than with the BW of the biological mother and father who were the donors of the egg and sperm. Finally, it is also important to consider that maternal caregiving and nursing styles can be passed from mother to daughter in monkeys [49]. Thus, different growth trajectories initiated in the prenatal period can be accentuated or moderated by postnatal rearing [50], which could extend the influence of fetal growth or lessen its impact on adult reproductive health and physical wellbeing.

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CONFLICT OF INTEREST STATEMENT

None of the authors have any COI to disclose.

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