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Maternal and Dietary Influences on Offspring Growth and Body Composition among Female Rhesus Macaques (*Macaca mulatta*)

By

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Doctor of Philosophy

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Abstract

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Lifespan health potential originates in the first 1,000 days of human life. The developmental origins of health framework posits that alterations to physiology during this critical period have lasting effects on body form and function that in turn influence susceptibility to chronic disease across the life course. Incorporating evolutionary theory, this project investigated how intergenerational and environmental exposures during this critical period interact to influence fetal and infant growth trajectories as the mechanistic basis of the chronic disease.

Previous research in humans suggest maternal morphology and psychosocial stress as exposures that interact with postnatal feeding strategies to influence growth. These factors are intertwined and reflective of larger societal circumstances in humans; translational animal models can reduce these subjectivities. Within this context, the present dissertation addresses how maternal body size and psychosocial stress, as naturally imposed through social subordination, are reflected in fetal and postnatal growth trajectories among female Rhesus macaques (*Macaca mulatta*), and whether subsequent morphology differs when challenged by a high calorie postnatal dietary intervention. The data used to address these aims came from a longitudinal sample of 35 female Rhesus macaque infants followed from mid gestation to six months of age, using anthropometry and dual energy X-ray absorptiometry (DXA) scanning to assess size and body composition.

The results identified that intrauterine psychosocial stress exposure distinguishes offspring growth trajectories in the form of altered sensitivities to markers of maternal lifespan health (e.g., height, bone mineral content) and current energy balance (e.g., weight, BMI) that are not predicted by birth weight alone. In comparison to their peers, subordinate females challenged by a high calorie diet exhibit accelerated weight gain at the expense of skeletal integrity, setting the stage for susceptibility to overweight and compromised bone health.

These data provide the first prospective longitudinal assessment of fetal and infant growth in Rhesus macaques, documenting an intergenerational pathway influencing the relative growth rates of alternate tissues with potential long-term effects on health. This suggests public health programs targeting girls and young women could have benefits that are measurable at generational timescales in the growth of their children.

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I am grateful for having had the opportunity to be a part of the Emory University community. The six years I spent on campus presented countless occasions for learning and growth, and each of these experiences helped me to develop not only as a researcher and teacher but also as an individual. This process showed me that I am stronger than I imagined, and taught me lessons about relationships, compassion, and leadership that I will always take with me and hope to share with others.

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I had the pleasure of being involved in several training programs, including the Certificate Program for Translational Research and the Molecules to Mankind Program. Both of these experiences offered opportunities to engage with individuals from across the university and expanded my appreciation of the broad range of health sciences research. I especially want to thank current and former directors of the Molecules to Mankind Program, Dr. Nael McCarty, Dr. Julie Gazmararian, and Dr. Ken Brigham, for seeing my potential and providing unwavering encouragement as I made my way through the graduate program.

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INTRODUCTION

Overview of the Problem

Major changes in health have emerged over the last century, as chronic disease surpassed infectious illness as the main cause of global morbidity and mortality. While this change is generally attributable to the rise and distribution of biomedical technologies, including vaccines and antibiotics that prevent or reduce illness burden, a more fundamental question is why chronic disease morbidity and mortality rates burgeoned rather than simply altering longevity. Furthermore, in more recent decades, why has chronic disease morbidity become increasingly common among younger age groups? Explanations range from discussions that focus on the rise in chronic disease morbidity and mortality as an expression of the hygiene hypothesis on immune system function to a focus on behaviors that include the juxtaposition of the modern consumption of 'cheap' calories with sedentary activities. These views are not mutually exclusive, and likely represent the multifactorial and complex nature of the current global health crisis.

Over the last thirty years, a substantial body of evidence arising from studies in both humans and animals point towards the fetal and early postnatal period as pivotal for health potential across the lifespan. When grounded within evolutionary theory, the developmental origins of health framework posits that alterations to physiology during gestation and early life provide a powerful lens for contextualizing both local and global health trends. As these propositions demand intergenerational time to emerge, human documentation is difficult to gather. Importantly, animal models can be leveraged to help understand the impact of social and behavioral interventions on an intergenerational

scale, providing critical information to inform public health policy strategies in ebbing the rise of chronic disease.

Shifting Health- and Diseasescapes and the Origins of Lifespan Health

Evidence spanning from the Paleolithic archeological record to modern clinical databases demonstrate that health and disease trends have not been static, but rather have shifted in response to the dynamic interplay of population movements, demographic transitions, and technological innovations (Harper and Armelagos 2010; McKeown 2009). The most common causes of morbidity and mortality have shifted from those reflecting infectious origins to that of chronic conditions globally (Vos et al. 2015). Low- and middle-income countries face a dual burden (Bygbjerg 2012). This epidemiological transition is predominately attributed to improvements in sanitation and nutrition arising from public health movements and improved infrastructure, bolstered more recently by the emergence of new biomedical technologies. Secular increases in height (Cole 2003) and life expectancy (Kinsella 1992) accompanied the decline of infectious disease morbidity and mortality, and have been interpreted as indicators of an improved healthscape. The reality, however, is not an advance in the spread of overall health, but has instead been a global outbreak of multimorbidity (Atun 2015). That is, while individuals are living longer, increasingly children and adults alike are living with not just a single disease, but instead are facing disability and illness from two or more chronic conditions (Tinetti et al. 2012).

The landscape of changing illness patterns coupled with increasing public health efforts to formulate intervention and/or health promotion strategies fueled the search for identifying risk factors for chronic disease development. An appreciation for the impact

of maternal and broader environmental conditions on offspring morphology and behavioral development has long been present (Lorenz 1935; Stockard 1921), including the observation that life-long health benefits can be achieved by improving early life environmental circumstances among children (Kermack et al. 1934). These early studies have grown into widespread recognition of how social conditions manifest as differences in health status (Berkman and Kawachi 2014), including birth outcomes (Yankauer 1950) and growth trajectories and body size (Tanner 1981). In a related vein, the relationship between maternal body size and perinatal outcomes, in particular offspring growth and body size (McKeown and Record 1954; Ounsted 1965), and their association to later disease risk (Forsdahl 1977; Gennser et al. 1988), became a key area for investigation that was largely popularized through the extensive contributions of David Barker in his work on the 'developmental origins of health and disease' and the mechanistic basis of 'fetal programming' (Barker 2004; Barker 2007; Barker 2012). In combination, these insights reflect the scientific and potential public health gains that can be afforded by the integration of evidence across biological and social sciences, laboratory and population methods.

Barker's initial work leveraged epidemiological data derived from large British population cohorts, including clinical information collected during routine care delivery and from national death registries (Barker et al. 1989a; Barker and Osmond 1986; Barker et al. 1989b; Hales et al. 1991). Subsequently, research by Barker and others have utilized data from several multi-generational cohorts representing not only other European countries (e.g., Boyd et al. 2013; Wijnstok et al. 2013) but also developing regions ranging from South Africa (Adair et al. 2011) to the Philippines (Richter et al. 2007). In

combination, these efforts have overwhelmingly demonstrated that birth weight and early postnatal growth trajectories are associated with several later life health outcomes, including type 2 diabetes, stroke, and osteoporosis (Barker 2012). Importantly, prospective auxological epidemiology is now integrated with physiological measures in attempts to identify the mechanistic basis by which underlying physiological processes manifest within body size and growth trajectory phenotypes and contribute to chronic disease risk (Mummert et al. 2016).

While the intrauterine environment sets the stage for health opportunities, it interacts with postnatal circumstances to influence outcomes and these modifying effects have been leveraged in support of a life course approach encapsulating both intrauterine and postnatal exposures for understanding disease risk (Power et al. 2013). Postnatal environmental cues come at varying levels (Mummert et al. 2016) ranging from individual and household decisions, such as breast feeding initiation (Wiedmeier et al. 2011) and physical activity (Booth et al. 2012), to distal factors such as economic inequality that influences access to health care and food insecurity (Wilkinson and Pickett 2006). These more distal factors tend to persist intergenerationally, with upwards social mobility infrequent (Bartely et al. 1994; Paneth 1994). The effects of social position on health have been colloquially designated a ‘status syndrome’ (Marmot 2004) based on observations of a strong inverse association between social class and mortality risk, chronic disease rates, and self-reported measures of overall health and well-being among British civil servants participating in the Whitehall Study (Marmot et al. 1991; Reid et al. 1974). Similar results of an effect of social class have been observed using measures of education level and socioeconomic status (Alver et al. 2007; Crandall et al. 2012; Gur et

al. 2004; Ho et al. 2005; Navarro et al. 2009; Varenna et al. 1999), and while universal health insurance diminishes these trends it does not omit them (Banks et al. 2006). In combination, this robust evidence of how maternal conditions and environmental circumstances interact to affect health offers a powerful lens through which we can transform our public health approaches to reducing the burgeoning crisis of multimorbidity (Tinetti et al. 2012).

Leveraging Translational Animal Models

Animal use in biomedical and behavioral research in various capacities has contributed to discoveries that were pivotal for changing diseasescapes over the last century, ranging from Jenner's cowpox inoculation experiments that laid the foundation for the eventual global eradication of smallpox in 1980 (Riedel 2005) to understanding the pathophysiology of, and developing treatments for, cancer and HIV/AIDS (Hatziioannou and Evans 2012; Mukherjee 2011). While traditionally animal models were more heavily utilized in relation to infectious disease, they are increasingly leveraged for improving our understanding of chronic and age-related conditions (Mitchell et al. 2015) and are specifically instrumental for investigating questions within the paradigm of the developmental origins of health (McMullen and Mostyn 2009). Benefits include opportunities for both observational and interventional approaches, with particular gains in species with accelerated life histories that enable the examination of development and intergenerational factors at increased timescales. Further, translational capacity is particularly robust when the animal model of choice has social and behavioral characteristics in common with human traits.

Intergenerational outcomes are currently most understood in rodent models due to their brief gestation periods and rapid time to reproductive maturity (Sengupta 2013), in addition to the relative ease at which they can be handled in laboratory settings. Several studies, for example, have examined the intergenerational impact of food restriction by limiting specific components (e.g., protein) or reducing total calorie intake (e.g., 50% less food) on rodents across as many as 12 generations (Ambegaokar and Chandran 1959; Cesani et al. 2006; Chow and Lee 1964; Gupta and Christie 1968; Pucciarelli et al. 2002; Stewart et al. 1975; Zamenhof and van Marthens 1978). Perhaps most prominent is the study of protein-energy deficiency conducted among 12 generations of black-and-white hooded rats by Stewart et al. (1975), which observed persistent reductions of total litter weights and offspring birth weights of approximately 14% in comparison to controls. Stewart et al. (1975) noted that there was considerable in individual variation within cohorts, with males were more affected than females. Additionally, while birth weights of subsequent generations could be restored to control levels by feeding dams a protein-sufficient diet during gestation, behavioral abnormalities persisted indicating that morphology can mask or obscure underlying physiological changes (Stewart et al. 1973). In a similar vein, a recent study that restricted caloric intake among Wistar rats measured weight, body length, and body mass index (BMI) every ten days from age 20 to 100 days of life across two subsequent generations of offspring (Cesani et al. 2014). They observed compounding decreased weight and length; for example, among males weight was 24% lower and length was 8.6% shorter than controls in the F1 generation, and 29% lower and 9.1% shorter than controls in the F2 generation. In combination, these studies document the importance of intergenerational considerations.

While these rodent studies contributed to our understanding of the role of maternal conditions on offspring health, the use of animal models has been criticized for its translational capacity for making meaningful differences to human health (Akhtar 2015; Greek and Menache 2013; van der Worp et al. 2010). To transcend such limitations, it is vital that the species of interest is ethologically valid for the question at hand. Research involving nonhuman primates has made significant advances for biomedicine (Phillips et al. 2014). The similarities between nonhuman primates and humans span behavioral (Schapiro 2008), genetic (Gibbs et al. 2007; Li and Saunders 2005), and physiological domains (Phillips et al. 2014), with extensive conservation between humans and nonhuman primates in regards to female reproductive biology (Appt and Ethun 2010; Shively and Clarkson 2009) and developmental programming (Dettmer 2013; Weinbauer et al. 2008). Key characteristics that highlight their translational relevance include slower developmental life histories in comparison to other mammals (Charnov and Berrigan 1993; Janson and van Schaik 1993), relatively long periods of gestation with slow fetal growth, singleton births, enriched placentation, and plasticity in growth trajectories (Newell-Morris and Fahrenbruch 1985; Pereira and Leigh 2003; Schneider et al. 1999).

Additionally, the anatomical and behavioral similarities between humans and nonhuman primates make it possible to use research procedures that are either identical or only minimally adapted. The matrilineal hierarchies of some Old World primate species, including the Rhesus macaque *(Macaca mulatta)*, can be leveraged to understand how social class impacts health outcomes independent of human-typical disadvantages like inadequate nutrition or restricted healthcare access that typically accompany low

income. Similarly, within colony groups infant and adult weights have been observed to increase across generations (Hopper et al. 2008; Price and Coe 2000; Price et al. 1999) which can be interpreted as a natural model of our own human obesity epidemic that has emerged within the last century. Developmental studies can specifically examine the role of maternal transmission in this setting. Previous research has demonstrated that involvement in minimally-invasive research procedures during infancy does not have adverse consequences for bio-behavioral development among nonhuman primates (Wilson et al. 1986).

Key Aims and Research Questions

Within this context, the present dissertation addresses how maternal morphology and social rank are reflected in fetal and postnatal growth trajectories among female Rhesus macaques, and whether subsequent morphology is impacted by consumption of a postnatal high calorie diet that mimics what humans typically consume. Research was guided by two primary aims:

1. To identify associations between maternal rank, maternal body composition, and fetal growth and birth weight outcomes
2. To identify associations between maternal rank, maternal body composition, postnatal diet, birth weight and infant growth trajectories during the first six postnatal months.

The data presented herein represent a subset of anthropometric outcome measures that were collected across the 2014 and 2015 breeding seasons at the Yerkes National Primate Research Center as part of larger studies investigating the neurodevelopmental and metabolic mechanisms underlying reproductive maturity and obesity in female

Rhesus macaques. The underlying data represent a rich, interdisciplinary endeavor reflecting the broader community of interests at a university-level, led by Drs. Mark Wilson and Mar Sanchez.

Dissertation Outline

Chapter 1 provides a detailed overview of maternal body composition and behavioral effects on offspring body size and growth trajectories among nonhuman primates in regards to: 1) maternal height, weight, and body composition; 2) social subordination as an analog for chronic psychosocial stress in humans; and 3) 'Western' dietary interventions in the pre- and postnatal period. Chapter 2 includes a description of the study methodology that is specific to the data presented in this dissertation, with Chapter 3 detailing the study aims and subsequent results. Chapter 4 reiterates the main findings, including comparing the results of the present study to outcomes previously documented in both nonhuman primate and human fetuses and infants. In addition, it proposes a physiological mechanism for the key finding of social status-specific physical growth trajectories for postnatal weight gain and BMC accrual that is hypothesized to reflect intrauterine-influenced differentiation potential at the level of the mesenchymal stem cell (MSC). Finally, Chapter 5 describes the contributions of this study to broader questions in anthropology concerning the heritability of skeletal health, in addition to suggesting translational applications of the current findings in the form of public health interventions aiming to increase peak bone mineral content and reduce the physiological side effects of chronic glucocorticoid exposure that could have contributed to the current obesity epidemic.

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CHAPTER 1 REVIEW OF THE LITERATURE

Early Life Growth and Body Composition among Old World Monkeys: Responses to Maternal Body Size, Maternal Social Rank, and Exposure to a 'Western Diet'

Introduction

The physical development of children has long served as a barometer of local health conditions (Tanner 1981), with more recent epidemiological evidence linking pre- and postnatal growth to lifespan health (Barker et al. 2013). The relationship between maternal health and well-being and the social and physical environment set the stage for lifespan health through their impact on early life growth (Mummert et al. 2016). Understanding their intersection can contribute to a better understanding of health disparities and empower the development of targeted infrastructure to meet current needs, as well as to anticipate and prepare for future trends in population health. Three key areas of considerable theoretical and research interest for their effect on intrauterine and subsequent postnatal growth include: 1) maternal body size and body composition; 2) maternal experiences of chronic psychosocial stress; and 3) maternal and infant nutrition. Primary themes and key findings related to these issues among humans identify the difficulties in isolating variables sufficiently to permit an unconfounded understanding of how these factors work together. This is an area of inquiry for which studies among nonhuman primates provides a useful translational model for advancing our understanding of human health in an intergenerational perspective.

Maternal Influences on Offspring Growth and Body Composition in Humans

Maternal Body Size

The influence of maternal 'constitutional factors,' including height and weight, on

offspring morphology is well recognized. For example, maternal height and weight are clearly associated with infant birth weight in humans (Kirchengast and Hartman 2003; Niswander and Jackson 1974; Ong et al. 2002; Ounsted et al. 1988). Animal cross-breeding (Joubert and Hammond 1958; Walton and Hammond 1938) and embryo transfer (Allen et al. 2002; Brooks et al. 1995; Ferrell 1991; Jenkinson et al. 2007; Wilson et al. 1998) studies demonstrate that offspring size is more closely matched to recipient size than donor size, emphasizing the translation of maternal size to the prenatal environment and ensuing influences on the growing organism. This effect is emphasized by research documenting the relationship between maternal size and offspring size from the viewpoint of matrilineal inheritance of birth weight (Morton 1955; Price and Coe 2000; Price et al. 1999), proposed as a form of 'maternal constraint,' a non-genetic pathway of inheritance leveraging the phenotypic plasticity of intrauterine growth rate (Ounsted 1965; Ounsted et al. 1986). Anthropologists in particular have invoked this concept in relation to models of an 'obstetrical dilemma' (Washburn 1960) closely tied to the emergence of bipedalism (Krogman 1951) in which maternal constraint over fetal size reduces the risk of cephalopelvic disproportion. This has been extended by a more recent perspective as a mediator of maternal-fetal intrauterine resource competition to maximize fitness (Dunsworth et al. 2012; Fischer and Mitteroecker 2015; Rosenberg and Trevathan 1995; Warrener et al. 2015; Wells et al. 2012).

The dramatic increase in the prevalence of overweight and obesity [body mass index (BMI ≥25)] among women of childbearing age in the last half-century, currently estimated at 58.5% in the United States (Ogden et al. 2014), stimulated a public health interest in understanding the health repercussions of these changes. For example, obesity

is associated with decreased fertility (Sawyer et al. 2006) and poor pregnancy outcomes, including gestational diabetes, pre-eclampsia, and increased occurrence of birth defects with accompanying risks for offspring health (Siega-Riz and King 2009; Waller et al. 2007). Macrosomia is more common among infants born to overweight and obese mothers (Gaudet et al. 2014; Leddy et al. 2008), and at birth these infants exhibit increased ratios of fat to lean tissue (Hull et al. 2008; Sewell et al. 2006). On the opposite end of the spectrum, maternal obesity is also associated with an increased risk of preterm birth and low birth weight (McCance et al. 1994; McDonald et al. 2010; Wei et al. 2003). As both low and high birth weight predicts the risk for chronic disease across the lifespan (Whitaker 2004), there is a sense of urgency to identify the physiological basis underlying these associations.

The relationship between maternal size, body composition, and offspring health is not, however, straightforward, with complexities emerging from sociocultural and environmental conditions on the one hand, and differences in physiology on the other. Maternal constitution itself reflects the summary of her own lifespan exposures, with height representing a salient, static indicator of childhood environmental experience (Cole 2003; Silventoinen et al. 1999). Meanwhile, weight represents the more recent nutritional environment and is a flexible attribute reflecting individual choice in terms of food selection and exercise while also capturing broader sociocultural issues such as food insecurity (Norgan et al. 2012). Further, weight is a nonspecific proxy for body composition and the more specific variables, body fat percentage and distribution, vary globally (Aloia et al. 1999; Rush et al. 2007), and may have implications for how maternal constitution translates into infant health and in turn contribute to persistent

health disparities that are ascribed to categories of race/ethnicity and persist from the perinatal period (Alexander et al. 2003) through old age (Smedley and Nelson 2003).

Maternal Psychosocial Stress

Psychosocial stress is associated with several poor reproductive health outcomes among women of reproductive age, including amenorrhea (Berga 1995), preeclampsia, and gestational diabetes during pregnancy (Landbergis and Hatch 1996; Roy-Matton et al. 2011). Additionally, women reporting higher levels of psychosocial stress deliver a higher proportion of premature (Copper et al. 1996; Dole et al. 2003; McDonald et al. 2014; Tegethoff et al. 2010), intrauterine growth restricted, and low birth weight infants (Borders et al. 2007; Loomans et al. 2013; Strutz et al. 2014; Wadhwa et al. 1993). Further, across infancy and early development, children born to mothers reporting chronic psychosocial stress continue to be at increased risk for adverse physical and mental health outcomes, ranging from asthma to attention deficit/hyperactivity disorder (Cookson et al. 2009; Talge et al. 2007).

Other research, however, has contradicted these trends relating maternal stress and poor reproductive health outcomes. For example, one meta-analysis found psychosocial stress exposure during pregnancy to be only weakly related to the risk for low birth weight (Littleton et al. 2010) and another found no association between adverse perinatal outcomes and maternal report of anxiety-like symptoms (Littleton et al. 2007). The discrepancy in outcomes may reflect, among other research difficulties, heterogeneity in study design, the validity of measurement scales used to capture psychosocial stress, and the timing and severity of the stressor. Additionally, these studies may or may not take into account factors such as maternal weight, parity, and

lifestyle characteristics (e.g., smoking, poor nutrition) that have independent, and possibly synergistic, effects that confound the relationship between maternal psychosocial stress and infant health (Alder et al. 2007; Goedhart et al. 2009).

Maternal Nutritional History and Infant Postnatal Feeding

The effects of undernutrition on maternal and child health are well established (Ramakrishnan et al. 2012; Victora et al. 2008). Perturbations can begin during earliest development, with the importance of perinatal nutrition perhaps most poignantly demonstrated in conditions of famine (Huang et al. 2010; Roseboom et al. 2001), data that offer insight into how the timing of nutritional stressors have specific implications for organ systems. For example, among individuals exposed to famine conditions at different periods of pregnancy in Amsterdam during World War II, fetuses exposed during early gestation have more prominent atherogenic lipid profiles (Roseboom et al. 2000) and a wider array of consequences. Mid-gestational exposure is associated with increased odds of microalbuminuria (Painter et al. 2005), while glucose intolerance has been associated with late exposure (Ravelli et al. 1998). Phenotypic alterations persist intergenerationally, with increased neonatal adiposity observed among the grandchildren of famine exposed women (Painter et al. 2008).

Increasingly, there is more alarm over the long-term effects of over- rather than undernutrition, particularly fetal and early childhood exposure to diets with high calorie or sugar compositions or disproportionate composition in terms of the ratio of fat, protein, and carbohydrates. The evidentiary base in humans is limited, but rapidly expanding. For example, small-for-gestational age and low birth weight are both associated with high maternal sugar consumption (Lenders et al. 1994) and a ‘Western

diet' marked by increased consumption of high-fat dairy products, red and processed meats, refined carbohydrates, and sweets (Knudsen et al. 2008). Postnatal exposure to such a diet could continue via differences in breast milk composition (Nommsen et al. 1991), including alterations in lipid (Park et al. 1999) and fatty acid (Specker et al. 1987) profiles, and subsequently through household feeding decisions (Dettwyler 1989; Losch et al. 1995) that have impacts on growth trajectories and body composition emerging by at least 18 months of age (Thompson and Bentley 2013).

Examining dietary influences on fetal and postnatal development is challenging in part by limitations related to measuring dietary intake. For example, how well a three-to-seven day recall survey represents an individuals' typical diet and whether people accurately report serving sizes is questionable. In particular, research among infants is subject to conflicts over how to define feeding behaviors, including concepts such as the duration and exclusivity of breast feeding (Noel-Weiss et al. 2012). Additionally, it is clear that individual variation exists in terms of the physiological response to foods, reflecting a combination of factors including genetics (Mootha and Hirschhorn 2010), the microbiome (Devaraj et al. 2013), and body composition (Johnstone et al. 2005).

Translational Aspects of Nonhuman Primate Models for Understanding the Developmental Origins of Health

The physiological and developmental differences between rodents and humans, in addition to differences in experimental and observational study designs, suggest careful consideration for the limitations of translational applications (Beydoun et al. 2010), particularly for research questions related to the developmental origins of health. For example, while the influence of maternal diet on offspring development has been

investigated in rodent models, the translational relevance may be limited given that the neurological circuits regulating metabolism, satiety, and appetite develop prenatally in humans but postnatally in rodents (Bouret et al. 2004; Grayson et al. 2006; Grove et al. 2003; Koutcherov et al. 2002). Similarly, while the absolute length of rodent long bones eventually stops increasing, growth cessation occurs well after adulthood has been reached and the growth plate itself does not fuse between the metaphysis and the epiphysis, while in rabbits growth plate fusion occurs well in advance of reaching puberty (Kilborn et al. 2002). In combination, these examples highlight limitations that are specific to questions concerning the influence of diet and other exposures on physical growth outcomes.

A nonhuman primate model can be effective for overcoming some of these barriers, though limitations do still remain. For example, New World monkeys, including marmosets (*Callithrix jacchus*), nearly always give birth to twins or triplets and likely have specific placental mechanisms to support this litter size (Rutherford 2009). Other, more subtle differences, such as the earlier and more superficial trophoblast invasion of the spiral arteries among macaques (genus *Macaca*) compared to humans (which may be related to their comparatively shorter gestation lengths, de Ruk and van Esch 2008), may have effects on the translational capacity of research. Thus, while nonhuman primates are argued to be the most physiologically and genetically similar translational animal model for humans (see review in Phillips et al. 2014), these key differences in physiology must be taken under consideration when applying these studies as human analogs for insights into the developmental origins of health.

In addition to physiological similarities to humans, nonhuman primates are leveraged in translational research for their behavioral likeness to humans and the relative ease at which research procedures originally developed for humans can be used among nonhuman primates and vice versa. For example, they tend to exhibit complex social behaviors which include a high-degree of maternal-infant contact and resource sharing (Maestripieri 1999), and in colony settings their complex social network can be systematically observed over time (Altmann 1974) or experimentally manipulated (Jarrell et al. 2008) to examine how changing social circumstances influence health status.

Taking the similarities and differences into consideration, nonhuman primate models can be leveraged for understanding the developmental origins of health related to how maternal morphology, chronic psychosocial stress, and high fat diet exposures affect physical growth trajectories.

Body Size and Obesity in Old World Primates

The same anthropometric and body composition assessment methods can be used in human and nonhuman primate research alike. For example, reports including relatively non-invasive anthropometry such as weighing and measuring crown-heel length in living (e.g., Walker et al. 1984) and recently deceased (e.g., Rutenberg et al. 1987) animals are common in the literature. Additionally, to address questions related to body composition several techniques have been routinely utilized, including calculating BMI from measures of weight and either crown- rump (CRL) or crown-heel length (CHL) (Bercovitch et al. 2000), measuring skinfold thickness (Bercovitch 1987), total body electroconductivity (Power et al. 2001), isotope-labeled water (Altmann et al. 1993; Garcia et al. 2011), computed tomography (CT) (Laber-Laird et al. 1991), and dual energy X-ray

absorptiometry (DXA) (Hamada et al. 2003; Takahashi et al. 2006). These measures have been demonstrated to offer comparative assessments of body composition (Walker et al. 1984) and noted for their contributions to translational research (Bauer et al. 2011).

While obesity is infrequent in wild nonhuman primates (Banks et al. 2003; Banks et al. 2001), it emerges naturally within provisioned, captive breeding colonies (Bodkin et al. 1993; Chen et al. 2003; Chen et al. 2002; Comuzzie et al. 2003; Goodchild and Schwitzer 2008; Hansen and Bodkin 1986; Hotta et al. 2001). More arboreal nonhuman primates, including macaques, tend to be relatively lean with fat pads that are generally: 1) distributed primarily intra-abdominally along the central ventral portion of the torso; 2) minimally stored in peripheral subcutaneous depots; 3) balanced between the anterior and posterior aspects of the trunk; and 4) absent in the distal limbs and tail (Dittus 2013). Further, animals who are considered to be storing fat healthily deposit peripheral and intra-abdominal adipose tissue ventrally and maintain arboreal mobility (Garber 2011). Definitions of obesity have varied across studies, with proposed cut-points based on percentage body fat (30%, Hansen and Bodkin 1986; 22%, Hotta et al. 2001; 25%, Jen et al. 1985; 35%, Raman et al. 2005) or two standard deviations above a sex-specific population mean (Kemnitz et al. 1989; Rivera et al. 2015). When adiposity accumulates excessively in nonhuman primates, the tissue accumulates superficially towards the central ventral paunch, in the forward and rear axillas and groin (Kemnitz and Francken 1986; Kemnitz et al. 1989). Pereira (1995) observed that in excess, this accumulated fat mass hinders mobility.

Body fat sexual dimorphism is generally low among wild nonhuman primates, though a pattern whereby females exhibit increased fatness relative to males is observed

among food provisioned animals ranging from colony (Goodchild and Schwitzer 2008) and supplementary feeding (Altmann and Alberts 2005) settings to areas in which troops live in close proximity to human spaces (reviewed in Dittus 2013; Schwartz and Kemnitz 1992). The morphology of nonhuman primates in captive settings is more analogous to body fat sexual dimorphism among humans, whereby in well-nourished populations females have considerably more body fat than males (Lohman 1981; Wells 2007). This is a pattern exhibited at least marginally among hunter-gather groups as well (Abbie 1967; Truswell and Hansen 1976). Dimorphism in fat percentage is evident already at birth (Guihard-Costa et al. 2002; Ibanez et al. 2008; Lampl et al. 2012) and dimorphic fat distribution patterns become magnified during and after puberty in humans (Staiano and Katzmarzyk 2012; Taylor et al. 2010), with females exhibiting increased peripheral/subcutaneous fat accumulation whereas males tend to have increased visceral adiposity (Kuk et al. 2005; Malina 1996; Seidell et al. 1988; Wells 2007). Patterns of age-related increases in relative fat mass and distribution are shared between humans and nonhuman primates (Raman et al. 2005; Ramsey et al. 2000; Tigno et al. 2004).

While striking similarities in the adiposity phenotype between humans and captive nonhuman primates have been reported, a central difference remains during the early developmental period. Nonhuman primate neonates exhibit virtually no body fat at birth (Adolph and Heggeness 1971; Lewis et al. 1983), with intrauterine fat deposition considered by Widdowson (1974) a uniquely human adaptation. Theoretically this increased fatness among human infants has been proposed as a means for survival advantages in the face of nutritional uncertainty and infection risks (Kuzawa 1998; Wells 2009), and as a physiological adaptation linking decreased gut size (Aiello and Wheeler

1995; Snodgrass et al. 2009) to encephalization (Kuzawa 1998; Prechtl 1986) with adiposity buffering the metabolic costs associated with larger brains (Leonard et al. 2003).

Social Dominance Hierarchies as a Model of Chronic Psychosocial Stress

The social practices of nonhuman primates serve as a powerful model for examining the effects of psychosocial stress in both naturalistic and experimental laboratory settings (Sapolsky 2005; Sapolsky 2011). Old World monkeys, including macaques, baboons (genus *Papio)*, and mandrills (genus *Mandrillus*), organize into hierarchical social groups containing more females than males with a dominant male performing a 'control role' (Oswald and Erwin 1976) that reduces overall aggression within the group (Smith 1973; Tokuda and Jensen 1968) by limiting the frequency and duration of female aggressive encounters (Bernstein and Sharpe 1964; Erwin and Sackett 1990). Rank is socially inherited through the matriline (Pereira 1995), remaining generally stable across development and adulthood (Pereira 1995; Walters and Seyfarth 1987) until older adult females concede rank to their mature daughters (Combes and Altmann 2001). Such hierarchies are reinforced through the combination of affiliative and agnostic behaviors. In macaques specifically, subordinate status is primarily maintained through aggressive threats and harassment from higher ranking animals, with lower ranking animals ending aggressive encounters by emitting submissive behaviors (Bernstein 1976; Bernstein and Gordon 1974). In cases of group reorganization, whether by overthrow or fission, when a high-ranking adult female loses position her immature daughters similarly assume a more subordinate place within the larger social hierarchy (Bernstein 1969; Gouzoules 1980). The importance of maternal presence for rank

acquisition and maintenance extends across the lifespan, with longitudinal studies demonstrating that mothers affiliate more with their own adult female offspring than with unrelated adult females and attenuate their agnostic conflicts with other group members (Fairbanks 2000). These processes contribute to the intergenerational inheritance of distinct social experiences that expose the effect of social hierarchy on health outcomes.

Prior work has described discrete physiological differences related to social rank in adult nonhuman primates, including increased risks for cardiovascular disease (Shively et al. 2009b) and alternations to immune system activation and inflammation (Tung et al. 2012). Further, low social rank is associated with a hyporesponsive limbic-hypothalamic-pituitary adrenal (LHPA) axis characterized by weakened glucocorticoid negative feedback and reduced cortisol secretion (Michopoulos et al. 2012a; Michopoulos et al. 2012b) accompanied by differences in hormone signaling across several systems, including sex steroid, dopamine, and serotonin regulation (Michopoulos et al. 2011; Morgan et al. 2002). Metabolically, previous research found dominant adult female Rhesus macaques (*M. mulatta*) living in small, experimentally formed groups to have increased weight and bone mass with increased leptin and decreased adiponectin levels in comparison to subordinates (Michopoulos et al. 2012a). What is less clear is whether these health disparities exist in early in life, or if they emerge across development in response to the postnatal experience of chronic social subordination. The body of evidence documenting that acute and chronic stress exposure during gestation and the early perinatal period has lasting impacts on the offspring brain, temperament, and learning capacity in nonhuman primates (Lupien et al. 2009; Spinelli et al. 2009) suggests that morphological differences may also be evident in early life.

The effect of social subordination on reproductive outcomes has been a long-standing area of investigation in groups of nonhuman primates in relation to social hierarchies, though differences not only between species but also in the heterogeneity of study designs highlight the complexity of this paradigm. For example, debate is ongoing regarding the relationship between social rank and female fertility among nonhuman primates, particularly in naturalistic versus laboratory settings (Altmann et al. 2004; Deutsch and Lee 1991; Harcourt 1987; Packer et al. 1995; Wasser 1996). Key differences in reproductive health include delayed ovulation and shortened interbirth intervals and gestation length. Lower ranking Rhesus macaques, for example, experience more years of early adult sterility (Wilson 1981), delayed first birth (Bercovitch and Berard 1993), and heightened infant mortality (Wilson et al. 1978) in comparison to higher ranking females. Such distinctions may underlie differences in lifetime reproductive success (though see Chalyan et al. 1991; Gouzoules et al. 1982). As another example, gestation length is reduced by approximately seven days among low ranked as compared to high ranked olive baboons (*P. hamadryas anubis*) (Garcia et al. 2009; Garcia et al. 2006). In combination, these differences in reproductive outcomes point towards the possibility of rank-based health phenotypes that emerge early in development.

'Western Diets' and Controlled Dietary Interventions

Access to nutrition is a key confounder increasing the complexity in interpretations of reported research on nonhuman primate health outcomes. Inconsistencies between findings from captive and free- or semi free-ranging animals of the same species may represent differences stemming from the availability of a stable food base, the energtic consequencies of food acquisition and travel, and supplementatal

nutrition from humans (Altmann and Samuels 1992; Isbell et al. 1999; Pontzer and Wrangham 2004). In order to advance understanding of effects from exposure to a 'Western diet' on infant health and development, research needs to be confined to laboratory settings where feeding can be controlled. While such studies have been possible in nonhuman primate colonies for several decades (e.g., Schwartz et al. 1988), recent advances in automated feeders provide a unique opportunity to quantitate actual individual intakes of variable dietary options such as low- versus high-calorie foods (e.g., Wilson et al. 2008). This paradigm of 'choice' access has substantial benefits for translational aspects of this research, as the dietary environment more closely approximates the human-like condition of deciding what to consume at each meal. Further, studies across several species clearly indicate that a dietary choice sustains consumption of an obesogenic diet (la Fleur et al. 2011; Pandit et al. 2012).

Research to date has documented that among subordinate adult female macaques, exposure to a 'Western diet' has induced increased visceral obesity and heightened risk for cardiovascular disease (Shively et al. 2009a), in addition to an overall increase in total calorie intake (Arce et al. 2010). While in the presence of a high calorie dietary alternative, both high and low ranked animals ate more frequently and increased their per-day calorie intake (Moore et al. 2013). After access to the high calorie diet was removed, chronic hyperphagia was maintained among subordinates (Arce et al. 2010; Michopoulos et al. 2012c; Moore et al. 2013). Combined with the previously described work regarding the physiological differences between low and high-ranked adult nonhuman primates, these nutritionally-based distinctions suggest that early life exposure to a high calorie diet could influence body size and growth outcomes through a

combination of altered physiology and modified eating behaviors.

Review of Previous Work

A review of previous studies among Old World monkeys reporting on infant through adolescent anthropometry and body composition in relation to three areas: 1) maternal size and body composition, 2) maternal social rank, and 3) dietary interventions that manipulated fat and/or calorie content to mimic a 'Western' diet or overfeeding, identified work among three genuses: *Macaca, Papio,* and *Mandrillus*.

Maternal Morphology Effects on Offspring Size and Growth Trajectories

Ten publications describing 30 analyses related to maternal body size and body composition influences on offspring size and growth trajectories among two species of macaques [*M. macaca,* (Bercovitch et al. 2000; Bowman and Lee 1995; Hinde et al. 2009; Hopper et al. 2008; Johnson and Kapsalis 1995; Price and Coe 2000; Price et al. 1999); *M. fuscata,* (Rivera et al. 2015)], olive baboons [*P. h. anubis,* (Garcia et al. 2009)], and mandrills [*M. sphinx,* (Setchell et al. 2001)]. Across these studies, measures of maternal size included: weight (own birth weight, pre-gravid, at one month postpartum, at the conclusion of postpartum amenorrhea, and at the time of reconception); gestational weight gain; and assessments of body composition via body fat percentage using DXA and by proxy using BMI. The influence of maternal size on offspring weight and height pre-pubertally are described below, separated by sex where available (Tables 1.1, 1.2, and 1.3).

Offspring Weight

Males and Females Combined

A number of studies assessed relationships between maternal size at birth, her

pre-gravid weight and pregnancy weight gain, and both offspring birth weight and postnatal size without differentiating for effects related to sex (Table 1.1). This makes it difficult to assess whether differences in outcomes may reflect confounding from sexual dimorphism.

Maternal size at birth showed no correlations between infant outcome and continuous maternal variables (Price et al. 1999), but analyzing *tertiles of maternal size at birth* identified increased birth weights among late-for-date offspring born to late-for-date mothers, and decreased birth weights among small-for-date offspring born to small-for-date mothers (Price and Coe 2000). *Maternal pre-gravid weight* was associated with increasing birth weight (Bowman and Lee 1995; Price et al. 1999), and increased rate of weight gain across the first 12 and 24 months among Rhesus macaques (Bowman and Lee 1995); weight among Japanese macaques at 7.5 months (Rivera et al. 2015) and weight at age 12 months among a combined population of captive and free-ranging Rhesus macaques (Bercovitch et al. 2000). Similar relationships were not found among a sample of mandrills up to age eight months (Setchell et al. 2001). *Heighted maternal gestational weight gain* was associated with increased birth weight among Rhesus macaques (Price et al. 1999). *Increased maternal weight at one month postpartum* positively predicted heighted offspring weight at one and 3.5 months of age (Hinde et al. 2009), and similarly weight-for-age was increased among olive baboon offspring in relation to their mother's weight at the end of her own postpartum amenorrhea (Garcia et al. 2009). *Pre-gravid maternal body fat percentage* was positively correlated with infant weight at 7.5 months (Rivera et al. 2015), though findings in response to maternal BMI are contradictory. While no significant differences in offspring weight-for-age through

eight postnatal months were observed by Setchell et al. (2001) among mandrills, *greater maternal BMI* predicted increased weight-for-age among a Rhesus macaque sample examined by Johnson and Kapsalis (1995).

Males Only

Two studies reported four separate analyses describing relationships between maternal body size and male offspring size (Table 1.2). Both *maternal weight and crown-rump length* were positively correlated with birth weight among a sample of Rhesus macaques (Bowman and Lee 1995), but no significant effects from either maternal pre-gravid weight or BMI were observed on weight-for-age among male mandrills aged one to ten years (Setchell et al. 2001).

Females Only

Two studies reported three separate analyses describing relationships between maternal body size and female offspring weight (Table 1.3). While no significant differences in weight-for-age among female mandrills aged one to seven years were predicted by maternal pre-gravid weight or BMI (Setchell et al. 2001), *maternal crown-rump-length* was positively correlated with female birth weight (Bowman and Lee 1995).

Offspring Crown-Rump Length and Body Composition

Effects on offspring crown-rump length outcome in response to maternal body size characteristics are less frequent in the literature, with descriptive results only reported in the study of mandrills by Setchell et al. (2001) (Tables 1.1, 1.2, and 1.3). In separate analyses, no significant differences in crown-rump-length-for-age were predicted by maternal pre-gravid weight or BMI among a mixed-sex cohort of mandrills under eight months of age, males aged one to ten years, or females aged one to seven

years (Setchell et al. 2001). No studies reporting on offspring infant to adolescent body composition outcomes in response to maternal morphology were identified.

Table 1.1 Maternal Morphology Influences on Offspring Growth and Body Composition: Both Sexes Combined

Habitat and Species	Age	N (F)	Maternal Body Size Measures	Result	Citation
Infant Outcome: Weight					
Captive[1] *M. mulatta*	Birth	195	Dam birth weight	NS correlation between offspring birth weight and dam birth weight	(Hopper et al. 2008)
Captive *M. mulatta*	Birth[2]	1321	Pre-gravid weight, Gestational weight gain	+ birth weight among offspring born to heavier dams[3] + birth weight among offspring born to dams with greater gestational weight gain[3]	(Price et al. 1999)
Captive *M. mulatta*	Birth	2170	Dam birth weight[4]	+ birth weight among LFD offspring born to dams who were also LFD[5] - birth weight among SFD offspring who were born to dams who were also SFD[5]	(Price and Coe 2000)
Captive *M. mulatta*	Birth-12 months	32	Pre-gravid weight, BMI	+ birth weight among offspring born to heavier dams + weight growth rate among offspring born to heavier dams	(Bowman and Lee 1995)
Captive *M. sphinx*	Birth-8 months	64 (38)	Pre-gravid weight, BMI	NSD offspring weight-for-age by dam weight[6] NSD offspring weight-for-age by dam BMI[6]	(Setchell et al. 2001)
Captive *M. mulatta*	1-4 months	58 (36)	Weight at 1month postpartum	+ weight at 1 and 3.5 months of age among offspring of heavier dams[7]	(Hinde et al. 2009)
Captive *M. fuscata*	7.5 months	32 (16)	Pre-gravid weight, Body fat (DXA), Gestational weight gain	Positive correlation between offspring weight and dam weight[8]	(Rivera et al. 2015)

Habitat and Species	Age	N (F)	Maternal Body Size Measures	Result	Citation
				Positive correlation between offspring weight and dam body fat[8] NSD offspring weight by dam gestational weight gain[8]	
Captive *P. h. anubis*	1-24 months	23 (10)	Weight at end of postpartum amenorrhea, Weight at reconception	+ weight-for-age among offspring of heavier dams at the end of postpartum amenorrhea + weight growth rate among offspring of heavier dams at reconception	(Garcia et al. 2009)
Captive/ Free-Ranging *M. mulatta*	12 months	279 (123)[9]	Pre-gravid weight	+ weight at 12 months of age among offspring of heavier dams	(Bercovitch et al. 2000)
Free-Ranging *M. mulatta*	1-24 months	38 (14)	BMI	+ weight-for-age for offspring of dams with higher BMI	(Johnson and Kapsalis 1995)
Infant Outcome: Height					
Semi Free-Ranging *M. sphinx*	Birth-8 months	64 (38)	Pre-gravid weight, BMI	NSD offspring CRL-for-age by dam weight[6] NSD offspring CRL-for-age by dam BMI[6]	(Setchell et al. 2001)

[1]Includes both single- and socially-housed animals, as well as animals that were SRV positive
[2]Analysis restricted to animals deemed "appropriate for gestational age", that is, the top 5% and bottom 5% for their sex and gestational age were eliminated from the sample.
[3]Model included temporal variables (year of birth, maternal and paternal generation), maternal/paternal variables (matriline, parity, pre-gravid weight, weight gain, patriline), infant variables (sex, gestational age), and interaction term of sex by maternal generation.
[4]Dams own birth weight was categorized as small-for-date (SFD), average-for-date (AFD), and large-for-date (LFD)
[5]Controlling for gestational age
[6]Controlling for maternal age
[7]Regression model includes milk yield, infant sex, and maternal weight
[8]Dams were participating in a dietary intervention whereby they had consumed either a control (15% calories from fat) or high fat diet (37% calories from fat) for between two

and seven years prior to the current pregnancy. Their dietary assignment was maintained through gestation and lactation of the current pregnancy.
[9]Study group includes both captive subjects at the Sabana Seca Field Station (N=162, F=72) and Cayo Santiago Island (N=117, F=51), both in Puerto Rico.

Table 1.2 Maternal Morphology Influences on Offspring Growth and Body Composition: Males

Species and Habitat	Age	N	Maternal Body Size Measures	Result	Citation
Infant Outcome: Weight					
Captive *M. mulatta*	Birth-12 months	32	Pre-gravid weight, CRL, BMI	Positive correlation between birth weight of sons and dam weight Positive correlation between birth weight of sons and dam CRL	(Bowman and Lee 1995)
Semi Free-Ranging *M. sphinx*	1-10 years	87[1]	Pre-gravid weight, BMI	NSD offspring mass-for-age by dam weight[2] NSD offspring mass-for-age by dam BMI[2]	(Setchell et al. 2001)
Infant Outcome: Height					
Semi Free-Ranging *M. sphinx*	1-10 years	86[1]	Pre-gravid weight, BMI	NSD offspring CRL-for-age by dam weight[2] NSD offspring CRL-for-age by dam BMI[2]	(Setchell et al. 2001)

[1]Total study sample was provided, with no discernable breakdown between males and females
[2]Controlling for maternal age

Table 1.3 Maternal Morphology Influences on Offspring Growth and Body Composition: Females

Species and Habitat	Age	N	Maternal Body Size Measures	Result	Citation
Infant Outcome: Weight					
Captive *M. mulatta*	Birth-12 months	32	CRL	Positive correlation between maternal CRL birth weight of daughters	(Bowman and Lee 1995)
Semi Free-Ranging *M. sphinx*	1-7 years	87[1]	Pre-gravid weight, BMI	NSD offspring mass-for-age by dam weight[2] NSD offspring mass-for-age by dam BMI[2]	(Setchell et al. 2001)

Species and Habitat	Age	N	Maternal Body Size Measures	Result	Citation
Infant Outcome: Height					
Semi Free-Ranging *M. sphinx*	1-7 years	86[1]	Pre-gravid weight, BMI	NSD offspring CRL-for-age by dam weight[2] NSD offspring CRL-for-age by dam BMI[2]	(Setchell et al. 2001)

[1]Total study sample was provided, with no discernable breakdown between males and females
[2]Controlling for maternal age

Methodological Considerations Comparing Previous Work on Maternal Morphological Influences on Offspring Weight, Height, and Body Composition

The body of literature describing offspring weight during early development in response to maternal morphology is limited, encompassing 30 analyses in ten publications (Bercovitch et al. 2000; Bowman and Lee 1995; Garcia et al. 2009; Hinde et al. 2009; Hopper et al. 2008; Johnson and Kapsalis 1995; Price and Coe 2000; Price et al. 1999; Rivera et al. 2015; Setchell et al. 2001). Limited samples in variable contexts make comparisons difficult. Seven of the ten publications described captive populations of macaques, and nearly half of the analyses stem from a single publication reporting on outcomes among a population of semi free-ranging mandrills at the International Medical Research Center in Franceville (CIMRCF), Gabon (Setchell et al. 2001). The majority of studies were cross-sectional in nature; for example, Johnson and Kapsalis (1995) reported on offspring weight at 12 months of age, while Hinde (2009) described offspring weight at one and 3.5 months in mixed-sex cohorts of Rhesus macaques. This makes longitudinal inferences impossible.

Less than one-third of these analyses were conducted in a sex-specific manner. Seven of the analyses combined male and female subjects in their analytics under the

assumption that males and females grow at similar rates during early development. There is no evidentiary base for this assumption among nonhuman primates and is an area in need of further clarification given observations of sex-specific growth trajectories among humans during fetal (Lampl et al. 2010) and postnatal life (Veldhuis et al. 2005), in addition to the clear sexual dimorphism within several species of Old World nonhuman primates (Badyaev 2002).

Crown-rump length outcomes were described only for the semi-free ranging mandrill population observed by Setchell et al. (2001). The nature of the data required the sample to be treated as semi-longitudinal, with substantial variation in the total number of individual-specific measurements. No reports of offspring body composition in relation to maternal body size were located. The influence of maternal morphology on offspring skeletal size and body composition represents a substantial area in need of additional research.

The limited nature of findings involving the skeletal system and body composition can be, at least partially, attributed to the difficulties of working with nonhuman primates and a general prioritization of minimizing human-nonhuman primate contact, particularly among semi-free ranging and wild populations. This is suggested by the disproportionate number of reports on weight relative to height and body composition, whereby body mass can be assessed by performing frequent observations to record weight as an animal approaches a baited or non-baited scale (e.g., Johnson and Kapsalis 1995).

Maternal Social Rank Effects on Offspring Size and Growth Trajectories

Fifteen publications describe offspring size and growth trajectories in relation to maternal rank among three species of baboons [*P. h. cynocephalus,* (Altmann and Alberts 1987; Altmann and Alberts 2005)*; P. h. ursinus,* (Johnson 2003); *P. h. anubis,* (Garcia et al. 2009)], three species of macaques [*M. mulatta,* (Bercovitch et al. 2000; Bowman and Lee 1995; Dixson and Nevison 1997; Hinde et al. 2009; Mann et al. 1998; Zehr et al. 2005)*; M. fuscata,* (Mori and Watanabe 2003); *M. tonkeana,* (Sanna et al. 2015)], and mandrills [*M. sphinx,* (Setchell and Dixson 2002; Setchell et al. 2006; Setchell et al. 2001)] (Tables 1.4, 1.5, and 1.6). Across these studies, social rank was classified in one of three ways, all based on systematic observations of aggressive and affiliative behavior following approaches championed by Altmann (1974). Some research groups adopted a continuous proportional rank approach whereby the focal infant's mother was assigned a relative position within the larger social hierarchy of the group (e.g., Garcia et al. 2009). Alternately, others assigned individual subjects to either dichotomous (low/high) or tertile (low/middle/high) rank categories based on either the focal infant's mothers' proportional rank position within the entire group or the relative rank of her matriline (e.g., Johnson 2003; Setchell et al. 2001). Finally, in smaller groups of captive animals, a single alpha was designated as high ranked and all others assigned across middle and low categories (e.g., Bowman and Lee 1995). This variation in the operational definition of maternal rank complicates comparisons among study results.

Offspring Weight

Males and Females Combined

Influences of maternal rank were reported for males and females combined in five studies (Altmann and Alberts 1987; Bowman and Lee 1995; Hinde 2009; Sanna et al.

2015; Setchell et al. 2001) (Table 1.4). Among yellow baboons, no effect of maternal rank was observed when examining offspring weight-for-age or the rate of weight accumulation from birth through age 36 months (Altmann and Alberts 1987). Similarly, among Tonkean macaques examined longitudinally from six to 36 months (Sanna et al 2015) and in Rhesus macaques studied at one and 3.5 months (Hinde 2009), offspring weight was not predicted by maternal rank. In contrast, the studies that focused on infant weight during the first year of life documented maternal rank-based differences (Bowman and Lee 1995; Setchell et al. 2001). Among mandrills observed through age eight months, increased weight was observed among the *infants of high ranked dams* compared to those born to low ranked dams, when controlling for infant and maternal age (Setchell et al. 2001). Among Rhesus macaques, meanwhile, *high ranked dams* gave birth to heavier infants that then accumulated weight at a slower rate over the first year of life in comparison to offspring born to low and middle ranked females (Bowman and Lee 1995).

Males Only

Eleven studies reported on the effects of maternal rank on male offspring weight from infancy through late adolescence representing a range of habitats and species (Altmann and Alberts 2005; Bercovitch et al. 2000; Bowman and Lee 1995; Dixson and Nevison 1997; Garcia et al. 2009; Johnson 2003; Mann et al. 1998; Mori and Watanabe 2003; Setchell and Dixson 2002; Setchell et al. 2006; Setchell et al. 2001) (Table 1.5). Four studies, representing captive, semi free-ranging, and free-ranging habitats, found no significant maternal rank effects on male weight when assessed from the peri-pubertal period through late adolescence (Dixson and Nevison 1997; Johnson 2003; Mann et al. 1998; Mori and Watanabe 2003). The effects of maternal rank on male juvenile and

adolescent body weight in yellow baboons observed by Altmann and Alberts (2005) conflicted depending on their food source. No differences in weight were observed among those raised with access to a 'food-enhanced' environment, while the *sons of high-ranked dams without supplemental nutrition* had increased weight-for-age compared to sons of low ranked dams. In all seven studies where maternal rank predicted male weight, body mass was elevated in the sons of high compared to low ranked mothers (Altmann and Alberts 2005; Bercovitch et al. 2000; Bowman and Lee 1995; Garcia et al. 2009; Setchell and Dixson 2002; Setchell et al. 2006; Setchell et al. 2001).

Females Only

Five reports assessed maternal rank effects on female weight from infancy through late adolescence (Altmann and Alberts 2005; Garcia et al. 2009; Johnson 2003; Setchell et al. 2001; Zehr et al. 2005) (Table 1.6). Weight-for-age was not predicted by maternal rank among female mandrills (Setchell et al. 2001), while all other studies observed maternal influences on female body size, although the outcomes were not consistent. *High maternal rank* predicted increased weight-for-age among wild female chacma and yellow baboons, but only in the absence of supplemental nutrition programs (Altmann and Alberts 2005; Johnson 2003).

Among captive animals, maternal rank had varying effects on female offspring body weight. When assessed at the end of their mother's postpartum amenorrhea, weight-for-age was lower among the *daughters of high ranking* olive baboons (Garcia et al. 2009). Among a sample of adolescent female Rhesus macaques, the *daughters of middle-ranked dams* were heaviest at age 24 months, the *daughters of low ranked females* were lightest at age 30 months, maternal-rank influences were absent by age 36 months (Zehr

et al. 2005). In combination, there was no clear pattern of maternal rank influences on their daughter's body weight by age or habitat.

Offspring Crown-Rump Length

Males and Females Combined

One study examined maternal rank effects on CRL-for-age in a combined sample of male and female mandrills from birth to eight months (Setchell et al. 2001) (Table 1.4). In this report, no significant differences were observed between infants born to high versus low ranked mothers (Setchell et al. 2001).

Males Only

No differences in CRL-for-age were observed among male mandrills based on maternal rank when reported separately for a cohort of one to ten year olds (Setchell et al. 2001) or a cohort of two to seven year olds (Setchell and Dixson 2002) (Table 1.5). Taking a different approach, Setchell et al. (2006) examined maternal influences on male mandrill CRL using principal components analysis (PCA). Here, CRL was part of a suite of traits used as a marker of maturation, including weight, testis volume, canine height, and time spent solitary, wherein *adolescent sons of high ranked females* matured earlier than those born to low ranked females.

Females Only

Two studies reported both CRL- and CHL-for-age outcomes among females. Zehr et al. (2005) examined CRL at three time points among captive adolescent female Rhesus macaques (Table 1.6). In this cohort, maternal rank was categorized into tertiles, with the *daughters of middle ranked females* exhibiting a statistically significantly longer CRL at age 24 months compared to those born to low or high ranked dams. No differences were

observed by maternal rank for CRL at 30 or 36 months, or for CHL at any of the time points. Similar observations were reported by Setchell et al. (2001), where no rank-related differences in CRL-for-age were observed among female mandrills.

Offspring Body Composition

One publication was identified that described offspring body composition in relation to maternal social rank, which included three specific findings from a mixed sample of older adolescent captive and free-ranging male Rhesus macaques (Bercovitch et al. 2000) (Table 1.5). Among captive six year old males, BMI was not significantly different for offspring born to low, middle, or high ranking females (Bercovitch et al. 2000). In contrast, among free-ranging males of the same age, both BMI and abdominal skinfold thickness was statistically significantly greater *among those born to high* as compared to low ranked mothers (Bercovitch et al. 2000). No reports of maternal social rank effects on female offspring body composition were identified.

Table 1.4 Maternal Rank as a Gradient of Psychosocial Stress Influences on Offspring Growth and Body Composition: Both Sexes Combined

Habitat and Species	Age	N (F)	Maternal Rank Definition	Result	Citation
Infant Outcome: Weight					
Captive *M. mulatta*	Birth-12 months	32	Single High Female, then equally divided into Middle/High	+ birth weight of infants of high ranked dams - weight gain from birth to 12 weeks among infants of high ranked dams	(Bowman and Lee 1995)
Captive *M. mulatta*	1-4 months	58 (36)	High/Middle/Low, by tertile	NSD weight at age 1 month or 3-4 months by maternal rank	(Hinde et al. 2009)
Captive *M. tonkeana*	6-36 months	23	High/Low	NSD weight by maternal rank	(Sanna et al. 2015)

Habitat and Species	Age	N (F)	Maternal Rank Definition	Result	Citation
Semi Free-Ranging *M. sphinx*	Birth-8 months	64 (38)	Upper quartile = High, IQR = Middle, Lowest quartile = Low	+ weight-for-age among infants of high ranked dams[1]	(Setchell et al. 2001)
Captive *P. h. cynocephalus*	>36 months	56	High/Low	NSD weight-for-age by maternal rank	(Altmann and Alberts 1987)
Captive *P. h. cynocephalus*	>36 months	38	High/Low	NSD weight-for-age growth rate by maternal rank	(Altmann and Alberts 1987)
Infant Outcome: Height					
Semi Free-Ranging *M. sphinx*	Birth-8 months	31	Upper quartile = High, IQR = Middle, Lowest quartile = Low	NSD CRL-for-age by maternal rank[1]	(Setchell et al. 2001)

[1]Controlling for maternal age

Table 1.5 Maternal Rank as a Gradient of Psychosocial Stress Influences on Offspring Growth and Body Composition: Males

Habitat and Species	Age	N	Maternal Rank Definition	Result	Citation
Infant Outcome: Weight					
Captive *M. mulatta*	Birth-12 months	16	Single High female, then Middle/Low	+ birth weight for sons of alpha mothers	(Bowman and Lee 1995)
Captive *M. mulatta*	4 years	22[2]	High/Low	NSD for weight by maternal rank	(Mann et al. 1998)
Captive *M. mulatta*	>5 years	8	High/Middle/Low by tertile	NSD for weight loss across mating season by maternal rank	(Dixson and Nevison 1997)
Captive *M. mulatta*	6 years	90	High/Middle/Low, by tertiles	+ weight for sons of high ranked dams at age 6	(Bercovitch et al. 2000)
Captive *P. h. anubis*	Birth-24 months	13	Upper quartile = High, IQR = Middle, Lowest quartile = Low	+ weight-for-age at end of dam's postpartum amenorrhea for sons of high ranked dams	(Garcia et al. 2009)
Semi Free-Ranging *M. sphinx*	1-10 years	87[3]	Upper quartile = High, IQR = Middle, Lowest quartile = Low	+ weight-for-age for sons of high ranked dams[1]	(Setchell et al. 2001)

Habitat and Species	Age	N	Maternal Rank Definition	Result	Citation
Semi Free-Ranging *M. sphinx*	2-7 years	13	Upper tertile =High, Middle and lower tertile =Low	+ weight-for-age for sons of high ranked dams	(Setchell and Dixson 2002)
Semi Free-Ranging *M. sphinx*	6-9 years	82	Upper quartile = High, IQR = Middle, Lowest quartile = Low	+ maturation (PCA factor including body mass, CRL, testis volume, canine height, and time spent solitary) for sons of high ranked dams	(Setchell et al. 2006)
Free-Ranging *M. fuscata*	3 and 6 years	57	High/Middle/Low, by tertiles	NSD for weight at 3 and 6 months by maternal rank	(Mori and Watanabe 2003)
Free-Ranging *P. h. ursinus*	~5 months - 8 years	17	High/Low	NSD for weight-for-age by maternal rank	(Johnson 2003)
Free-Ranging *P. h. anubis*	~16 months - 8 years	29	High/Low	+ weight-for-age for sons of high ranked dams	(Altmann and Alberts 2005)
Free-Ranging *P. h. anubis*	~16 months - 8 years	19[4]	High/Low	NSD for weight-for-age by maternal rank	Altmann and Alberts (2005)
Infant Outcome: Height					
Semi Free-Ranging *M. sphinx*	1-10 years	86[3]	Upper quartile = High, IQR = Middle, Lowest quartile = Low	NSD for CRL-for-age by maternal rank[1]	(Setchell et al. 2001)
Semi Free-Ranging *M. sphinx*	2-7 years	13	Upper tertile =High, Middle and lower tertile =Low	NSD for CRL-for-age by maternal rank	(Setchell and Dixson 2002)
Semi Free-Ranging *M. sphinx*	6-9 years	82	Upper quartile = High, IQR = Middle, Lowest quartile = Low	+ maturation (PCA factor including body mass, CRL, testis volume, canine height, and time spent solitary) for sons of high ranked dams	(Setchell et al. 2006)
Infant Outcome: Body Composition					

Habitat and Species	Age	N	Maternal Rank Definition	Result	Citation
Captive *M. mulatta*	6 years	90	High/Middle/Low, by tertiles	NSD BMI by maternal rank at age 6 years	(Bercovitch et al. 2000)
Free-Ranging *M. mulatta*	6 years	66	High/Low	+ BMI among sons of high ranked dams at age 6 + abdominal skinfold thickness among sons of high ranked dams at age 6	(Bercovitch et al. 2000)

[1]Controlling for maternal age.
[2]Infants were divided equally among an experimental paradigm involving exposure to a control vehicle, GnRH antagonist (antide), or 'antide+androgen' every other week from birth to four months of age.

Table 1.6 Maternal Rank as a Gradient of Psychosocial Stress Influences on Offspring Growth and Body Composition: Females

Habitat and Species	Age	N	Maternal Rank Definition	Result	Citation
Infant Outcome: Weight					
Captive *M. mulatta*	24-36 months	27[1]	High/Middle/Low, by tertiles	+ weight at 24 months for daughters of middle ranked dams - weight at 30 months for daughters of low ranked dams NSD for weight at 36 months by maternal rank	(Zehr et al. 2005)
Captive *P. h. anubis*	Birth-2 years	10	Upper quartile = High, IQR = Middle, Lowest quartile = Low	- weight-for-age at end of dam's postpartum amenorrhea for daughters of high ranked dams	(Garcia et al. 2009)
Semi Free-Ranging *M. sphinx*	1-7 years	87[2]	Upper quartile = High, IQR = Middle, Lowest quartile = Low	NSD for female weight-for-age by maternal rank[3]	(Setchell et al. 2001)
Free-Ranging *P. h. ursinus*	15 weeks-5.5 years	21	High/Low	+ weight-for-age for daughters of high ranked animals	(Johnson 2003)

Habitat and Species	Age	N	Maternal Rank Definition	Result	Citation
Free-Ranging *P. h. cynocephalus*	~16 months - 6 years	38	High/Low	+ weight-for-age for daughters of high ranked dams	(Altmann and Alberts 2005)
Free-Ranging *P. h. cynocephalus*	~16 months - 6 years	14[4]	High/Low	NSD for weight-for-age	(Altmann and Alberts 2005)
Infant Outcome: Height					
Captive *M. mulatta*	24-36 months	27[1]	High/Middle/Low, by tertiles	+ CRL at 24 months for daughters of middle ranked dams NSD for CRL at ages 30 or 36 months by maternal rank NSD for CHL at 24, 30, or 36 months by maternal rank	(Zehr et al. 2005)
Semi Free-Ranging *M. sphinx*	1-7 years	86[2]	Upper quartile = High, IQR = Middle, Lowest quartile = Low	NSD for CRL-for-age by maternal rank[3]	(Setchell et al. 2001)

[1]Maternal social rank was balanced across experimental treatment groups receiving prenatal exposure to testosterone enanthate, flutamide, or control vehicle daily either during early (D35-70) or late (D110-145) gestation.
[2]Total study sample was provided, with no discernable breakdown between males and females.
[3]Controlling for maternal age.
[4]While free-ranging, these animals were habituated to interactions with humans and resided in a "food-enhanced" environment with access to supplemental nutrition.

Methodological Considerations Comparing Previous Work on Maternal Social Rank Influences on Offspring Weight, Height, and Body Composition

Eleven of the 24 analyses of offspring weight reported in eight studies indicated no significant differences based on maternal rank (Altmann and Alberts 1987; Altmann and Alberts 2005; Dixson and Nevison 1997; Hinde et al. 2009; Johnson 2003; Mann et al. 1998; Mori and Watanabe 2003; Sanna et al. 2015; Setchell et al. 2001). Four of the

ten null findings resulted from investigations of the same wild population of yellow baboons from Amboseli National Park in Kenya. Four of the studies combined male and female infants in analyses, half focused on male offspring, and seven followed subjects from the peri-pubertal period to late adolescence.

Thirteen of the 24 analyses reported in the same publications observed maternal rank-based influences on offspring weight (Altmann and Alberts 2005; Bercovitch et al. 2000; Bowman and Lee 1995; Garcia et al. 2009; Johnson 2003; Setchell and Dixson 2002; Setchell et al. 2006; Setchell et al. 2001; Zehr et al. 2005), with all but two (Garcia et al. 2009; Zehr et al. 2005) documenting increased weight among offspring born to high ranked dams. Study design differences may have contributed to these contrasting relationships. For example, both Zehr et al. (2005) and Garcia et al. (2009) examined offspring weight differences at specific ages despite having longitudinal data. Further, the females involved in the Zehr et al. (2005) study were prenatally exposed to androgens as part of the larger research protocol, which in itself could explain the size variations between animals (Smith et al. 2010). As four of ten findings of increased weight among offspring born to high-ranked dams evaluated subjects from the same population of semi free-ranging mandrills from CIMRCF in Gabon, such observations are likely not independent. Eight of the findings where high maternal rank predicted increased offspring weight were reported among male cohorts, two were among female cohorts, and two emerged from studies of infants where both sexes were combined for analytic purposes.

In total, six analyses across four studies examined maternal rank effects on offspring CRL or CHL (Setchell and Dixson 2002; Setchell et al. 2006; Setchell et al.

2001; Zehr et al. 2005), with maternal influences observed in two cases (Setchell et al. 2006; Zehr et al. 2005). Four of the six analyses documenting no rank-related effects were conducted among cohorts of mandrills (Setchell and Dixson 2002; Setchell et al. 2001). In both cases where maternal rank effects were seen, the approach was a sex-specific investigation during adolescence (Setchell et al. 2006; Zehr et al. 2005). Overall, these results suggest that maternal rank has a limited influence on offspring skeletal growth during early development, but there are several study limitations to consider. First, the mandrill CRL reports are all based on animals at CIMRCF in Gabon, and study subjects overlap between reports which removes the independence of these observations rather than offering replication. In a similar vein, these reports represent observations based on mixed longitudinal/cross-sectional data, rather than examining individual patterns of growth in relation to maternal rank. This is understandable given that these reports comprise examinations of a wild population of mandrills, and an attempt to minimization human intervention, particularly given the necessity of anesthesia to perform length measurements. The report by Zehr et al. (2005) on female Rhesus macaque lengths is strengthened by its longitudinal, repeated measures design which offered the opportunity to examine CRL and CRH growth trajectories. Unfortunately, the results were instead only presented in a cross-sectional fashion using time-point specific comparisons of size by maternal rank. Additionally, these females were prenatally exposed to either testosterone enanthate, flutamide, or a vehicle control to assess the impact of androgens on pubertal timing, removing the ability to stand as unconfounded results. While maternal rank was distributed across the experimental groups, the fetal

androgen exposure itself could be masking any rank-related influences on adolescent growth (Smith et al. 2010).

Only one publication was identified that examined offspring body composition in relation to maternal social rank, and it contained conflicting results for captive versus free-ranging male Rhesus macaques (Bercovitch et al. 2000). This could reflect differences in the analytic approach and environmental conditions of each study groups. For example, the members of the captive group were more well-known to observers allowing for mothers to be assigned to tertiles of social rank, whereas a dichotomous approach for rank assignment was utilized among the free-ranging group. This in itself could alter results. Further, the supplemental nutrition provided to the colony-dwelling Rhesus males may be obscuring any difference in body size stemming from maternal social rank, as BMI and abdominal skinfold thickness were elevated among the high ranked free-ranging males, indicating that food security may contribute to these morphological differences between ranks.

Irrespective of the outcome, several key limitations of the investigations of maternal rank influences on offspring body weight are apparent. The significant variation in study design and analytic approach makes between-population comparisons difficult to interpret. For example, the reports stemming from the semi free-ranging and wild populations are mixed longitudinal/cross-sectional samples with weight information collected opportunistically when focal subjects presented at a scale. This strategy preserves the colonies habitats and minimizes the animals' exposure to humans, while limiting our ability to draw inferences on the longitudinal effects of maternal rank on offspring body size. Additionally, nearly half of the individual analyses (ten of 24)

examined the relationship between maternal rank and offspring morphology over a period spanning four or more years, and it may be that the effects on body size may be more or less pronounced depending on the stage of development. Finally, six of the analyses combined male and female subjects in their analytics under the assumption that males and females grow at similar rates during early development, which may be unfounded (Lampl et al. 2010; Veldhuis et al. 2005).

'Western' Dietary Intervention Effects on Offspring Size and Growth Trajectories

Seven publications describing dietary intervention influences on offspring size and growth trajectories were located, representing two species of macaques [*M. mulatta,* (Schwartz et al. 1988; Terasawa et al. 2012), *M. fuscata* (Fan et al. 2013; Grant et al. 2011; McCurdy et al. 2009; Rivera et al. 2015)] and one species of baboons [*P. h. cynocephalus,* (Lewis et al. 1986)] (Tables 1.7, 1.8, and 1.9). Across these studies, two approaches were utilized to examine the effects of high calorie exposure on infant development. Dietary manipulation of adult females and offspring after weaning was typically accomplished by exposing a control group to a colony standard diet with approximately 12-15% of calories from fat and an experimental group to chow comprised of 30-45% of calories from fat (Fan et al. 2013; Grant et al. 2011; McCurdy et al. 2009; Rivera et al. 2015; Schwartz et al. 1988; Terasawa et al. 2012). In contrast, Lewis et al. (1986) exposed infants immediately after birth by offering both calorically reduced and enhanced versions of formula in nursery-reared infants. The influence of perinatal dietary interventions on offspring weight and height are described below, separated by sex when permitted by the analytic strategy.

<u>Offspring Weight</u>

Males and Females Combined

Three studies reported on weight outcomes of Japanese macaque offspring born to mothers with between four to seven years of prior high fat diet exposure that was maintained through the current pregnancy and lactation period (Fan et al. 2013; McCurdy et al. 2009; Rivera et al. 2015) (Table 1.7). In these studies, high fat diet exposure was not associated with significant differences in weight at ages one, three, or six months of age (McCurdy et al. 2009), and similarly no differences in weight were observed at age 13 months between infants who were exposed post-weaning to either low- or high-fat chow (Fan et al. 2013). While the *offspring of obese (>15.8% body fat) mothers consuming the standard (control) diet* weighed more than those born to non-obese dams, this trend was not present among offspring born to obese versus non-obese consumers of the high fat diet (Rivera et al. 2015). Finally, Grant et al. (2011) reported no differences in offspring weight at one or three months of age in response to maternal consumption of a high calorie diet from ~30 days gestation (early first trimester) through lactation.

Males Only

A single study specifically examined the effects of early high calorie exposure on male weight outcomes (Lewis et al. 1986) (Table 1.8). In an experimental design with infants randomized at birth to formula with low (40.5 kcal/100g), normal (67.5 kcal/100g) or high (94.5kcal/100g) calorie densities followed by postweaning exposure to chow with 40% of calories derived from fat, lower weight was observed among the *'underfed' males* at 16 weeks of age. No other observable differences were noted in weight growth rate or absolute size at five years of age by dietary group (Lewis et al. 1986).

Females Only

Three studies reported weight-related outcomes after exposure to a high calorie diet among females ranging in age from birth to adolescence (Lewis et al. 1986; Schwartz et al. 1988; Terasawa et al. 2012) (Table 1.9). In comparison to controls observed prospectively from birth to 16 weeks of age, female baboons exposed to a low calorie density formula (67.5 kcal/100g) exhibited decreased weight gain, while *females consuming the high calorie density formula* (94.5 kcal/100g) exhibited increased weight gain (Lewis et al. 1986). Beginning at two years of age, *'overfed' females* exhibited increased weight growth velocity and by age five were statistically significantly heavier than their 'underfed' and 'normal fed' peers (Lewis et al. 1986).

Weight outcomes were reported in two separate cohorts of Rhesus macaque females with high fat diet exposure beginning in the juvenile and pre-pubescent period. Terasawa et al. (2012) documented increased weight among those *exposed to a high-fat diet* when measured monthly from ages 13 to 18 months, an effect that was detectable beginning 30 days after the onset of the high-fat diet exposure. Similarly, Schwartz et al. (1988) observed increased weight among *females after just one month of peripubertal exposure to a high-fat diet*, though in subsequent months these females weighed less than their normal chow peers.

Offspring Crown-Rump Length and Crown-Heel Length

No studies reporting on CRL or CHL outcomes in relation to a perinatal high calorie diet among a mixed-sex cohort or male only cohort were identified, while two studies reported effects among a sample of female Rhesus macaques with adolescent dietary manipulation (Schwartz et al. 1988; Terasawa et al. 2012) (Table 1.9), with

conflicting results.

When *exposed to a high fat diet* beginning at age 12 months, female Rhesus macaques exhibited increased CRL and CHL growth rate compared to their control diet peers, and their absolute CRL was longer at age 18 months and absolute CHL was longer from 15 months to 18 months when measured monthly (Terasawa et al. 2012). In contrast, Schwartz et al. (1988) did not observe statistically significant differences in CRL after peripubertal exposure to high-fat chow.

Offspring Body Composition

Males and Females Combined

Gestational and lactational exposure to a high fat diet was not associated with differences in offspring bone mineral content (BMC) through the first year of life (Grant et al. 2011) (Table 1.7). Increased percent body fat at three (Grant et al. 2011) and six months of age (McCurdy et al. 2009) has been reported, compared to control group peers, but neither study found an effect at one month of age. In contrast, at 13 months of age offspring born to mothers with up to five years of pre-conception high fat diet exposure, including exposure during the current pregnancy and lactation period, did not have different percentage body fat than their control counterparts (Fan et al. 2013).

Males Only

No studies reporting on male body composition outcomes in relation to early life high calorie diet exposure were identified (Table 1.8).

Females Only

After one month of high-fat diet exposure, female Rhesus macaques exhibited increased abdominal skinfold thickness, though by 22 months *the high-fat exposure*

group consistently exhibited decreased abdominal skinfold thickness compared to their low-fat counterparts and no differences were observed for BMI (Schwartz et al. 1988) (Table 1.9). In contrast, female Rhesus macaques with earlier exposure to a high fat diet (beginning at 12 months of age as compared to 16) exhibited increased BMI, fat mass, lean mass, and BMC through age 18 months in comparison to low-calorie controls, though no differences were noted in BMD (Terasawa et al. 2012).

Table 1.7 'Western Diet' Intervention Influences on Offspring Growth and Body Composition: Both Sexes Combined

Habitat and Species	Age	N (F)	Dietary Intervention Description	Result	Citation
Infant Outcome: Weight					
Captive *M. fuscata*	13 months	52	*High Fat Exposure* Dams placed on dietary intervention for up to 5 years prior to current pregnancy, with offspring randomized at weaning to either control or high fat diet. Control Group: Ad libitum consumption of chow composed of 14% calories from fat plus fruit and vegetable supplements. Experimental Group: Ad libitum consumption of chow composed of 36% calories from fat plus calorically-dense supplements.	NSD offspring weight in any diet group (C/E, E/E, E/C, C/E)	(Fan et al. 2013)
Captive *M. fuscata*	1 month	8 (4)	*High Fat Exposure* Dams placed on dietary intervention for up to 4 years prior to current pregnancy and maintained through lactation.	NSD offspring weight at age 1 month by diet group	(McCurdy et al. 2009)

Habitat and Species	Age	N (F)	Dietary Intervention Description	Result	Citation
			Control Group (n=4): Ad libitum consumption of chow composed of 15% calories from fat. Experimental Group (n=4): Ad libitum consumption of chow composed of 32% calories from fat.		
Captive *M. fuscata*	1-24 months	11	*High Fat Exposure* Dams placed on dietary intervention for up to 4 years prior to current pregnancy and maintained through lactation. Control Group (n=4): Ad libitum consumption of chow composed of 15% calories from fat. Experimental Group (n=7): Ad libitum consumption of chow composed of 32% calories from fat.	NSD offspring weight at age 1, 3, or 6 months by diet group	(McCurdy et al. 2009)
Captive *M. fuscata*	1-3 months	22	*High Fat Exposure* Dams placed on dietary intervention from ~30 days gestation and maintained through lactation. Control Group (n=6): Ad libitum consumption of chow composed of 15% calories from fat. Experimental Group (n=16): Ad libitum consumption of chow composed of 32% calories from fat.	NSD offspring weight at age 1 or 3 months by diet group	(Grant et al. 2011)
Captive *M. fuscata*	7.5 months	32 (16)	*High Fat Exposure* Dams placed on dietary intervention for between 2 to 7	+ weight among offspring of obese (>15.8% body fat) control dams compared	(Rivera et al. 2015)

Habitat and Species	Age	N (F)	Dietary Intervention Description	Result	Citation
			years prior to current pregnancy and maintained through lactation. Control Group (n=14, 9 dams considered obese pre-gravid): Ad libitum consumption of chow composed of 15% calories from fat. Experimental Group (n=18, 13 dams considered obese pre-gravid): Ad libitum consumption of chow composed of 37% calories from fat.	to non-obese control dams NSD weight among offspring of obese or non-obese dams that consumed the high fat diet	
Infant Outcome: Body Composition					
Captive *M. fuscata*	1-24 months	11	*High Fat Exposure* Dams placed on dietary intervention for up to 4 years prior to current pregnancy and maintained through lactation. Control Group (n=4): Ad libitum consumption of chow composed of 15% calories from fat. Experimental Group (n=7): Ad libitum consumption of chow composed of 32% calories from fat.	+ percent body fat at 3 and 6 months but not at 1 month among offspring with high fat diet exposure	(McCurdy et al. 2009)
Captive *M. fuscata*	1-3 months	22	*High Fat Exposure* Dams placed on dietary intervention from ~30 days gestation and maintained through lactation. Control Group (n=6): Ad libitum consumption of chow composed of 15% calories from fat. Experimental Group	+ body fat mass at 3 months but not 1 month among offspring with high fat diet exposure NSD offspring BMC at 1 or 3 months by diet group - lean mass at 3 months but not at 1 month among offspring with high fat diet exposure	(Grant et al. 2011)

Habitat and Species	Age	N (F)	Dietary Intervention Description	Result	Citation
			(n=16): Ad libitum consumption of chow composed of 32% calories from fat.		
Captive *M. fuscata*	13 months	52	*High Fat Exposure* Dams placed on dietary intervention for up to 5 years prior to current pregnancy, with offspring randomized at weaning to either control or high fat diet. Control Group: Ad libitum consumption of chow composed of 14% calories from fat plus fruit and vegetable supplements. Experimental Group: Ad libitum consumption of chow composed of 36% calories from fat plus calorically-dense supplements.	NSD offspring percent body fat in any diet group (C/E, E/E, E/C, C/E)	(Fan et al. 2013)

Table 1.8 'Western Diet' Intervention Influences on Offspring Growth and Body Composition: Males

Habitat and Species	Age	N	Dietary Intervention Description	Result	Citation
Infant Outcome: Weight					
Captive *P. h. cynocephalus*)	Birth-5 years	17	*Calorie Restriction and Overfeeding* Infants placed on dietary intervention from birth to age 16 weeks, during which they were bottle fed. After weaning, all infants provided ad libitum access to chow	- weight gain from birth to 16 weeks among underfed males compared to the control group NSD weight gain from birth to 16 weeks among overfed males compared to the control group	(Lewis et al. 1986)

			with 40% of calories from fat. "Underfed" Group: 40.5 kcal/100g of formula. Control Group: 67.5 kcal/100g of formula. "Overfed" Group: 94.5 kcal/100g of formula.	NSD weight growth rate to 5 years among males by diet group NSD weight at 5 years among males by diet group	

Table 1.9 'Western Diet' Intervention Influences on Offspring Growth and Body Composition: Females

Habitat and Species	Age	N	Dietary Intervention Description	Result	Citation
Infant Outcome: Weight					
Captive *P. h. cynocephalus*	Birth-5 years	15	*Calorie Restriction and Overfeeding* Infants placed on dietary intervention from birth to age 16 weeks, during which they were bottle fed. After weaning, all infants provided ad libitum access to chow with 40% of calories from fat. "Underfed" Group: 40.5 kcal/100g of formula. Control Group: 67.5 kcal/100g of formula. "Overfed" Group: 94.5 kcal/100g of formula.	- weight gain from birth to 16 weeks among underfed females compared to the control group + weight gain from birth to 16 weeks among overfed females compared to the control group NSD weight growth rate prior to 48 weeks among females by diet group + weight growth rate beginning at 48 weeks among females exposed to overfeeding as infants compared to the underfed and control groups + weight at 5 years among females exposed to overfeeding as infants compared to the underfed and control groups	(Lewis et al. 1986)

Habitat and Species	Age	N	Dietary Intervention Description	Result	Citation
Captive *M. mulatta*	12-18 months	8	*High Fat Exposure* Age- and weight-matched juvenile females placed on dietary intervention beginning at 1 year of age. Control Group (n=4): Ad libitum consumption of chow composed of 14% calories from fat. Experimental Group (n=4): Ad libitum consumption of chow composed of 42% calories from fat.	+ weight when measured monthly, from 13 to 18 months, among females exposed to high fat diet + weight growth rate from 12 to 18 months among females exposed to high fat diet	(Terasawa et al. 2012)
Captive *M. mulatta*	16-32 months	15	*High Fat Exposure* Young females placed on dietary intervention from 16 to 32 months of age. Control Group (n=10): Ad libitum consumption of chow composed of 12% calories from fat. Experimental Group (n=5): Ad libitum consumption of chow composed of 31% calories from fat.	+ body weight at age 17 months among females exposed to high fat diet - body weight at ages 19, 21, and 27-32 months among females exposed to high fat diet	(Schwartz et al. 1988)
Infant Outcome: Height					
Captive *M. mulatta*	12-18 months	8	*High Fat Exposure* Age- and weight-matched juvenile females placed on dietary intervention beginning at 1 year of age. Control Group (n=4): Ad libitum consumption of chow composed of 14% calories from fat. Experimental Group (n=4): Ad libitum consumption of chow composed of 42% calories from fat.	+ CHL growth rate from 12 to 18 months among females exposed to high fat diet + CHL when measured monthly, from 15 to 18 months, among females exposed to high fat diet + CRL growth rate from 12 to 18 months among females exposed to high fat diet + CRL at 18 months, among females exposed to high fat diet	(Terasawa et al. 2012)

Habitat and Species	Age	N	Dietary Intervention Description	Result	Citation
Infant Outcome: Body Composition					
Captive *M. mulatta*	16-32 months	15	*High Fat Exposure* Young females placed on dietary intervention from 16 to 32 months of age. Control Group (n=10): Ad libitum consumption of chow composed of 12% calories from fat. Experimental Group (n=5): Ad libitum consumption of chow composed of 31% calories from fat.	NSD BMI among females by diet group + Abdominal skinfold thickness at age 17 months among females exposed to high fat diet - Abdominal skinfold thickness from age 22 to 32 months among females exposed to high fat diet	(Schwartz et al. 1988)

[1]Study subjects were pair-housed

Summary and Discussion of Perinatal Dietary Influences on Offspring Morphology

Six of the seven weight outcomes that were described by mixed-sex analyses reported no differences in weight after perinatal exposure via manipulation of the maternal diet (Fan et al. 2013; Grant et al. 2011; McCurdy et al. 2009). These reports were primarily focused on the immediate postnatal period (e.g., before six months of age), and all animals were housed at the Oregon National Primate Research Center, suggesting the possibility of a lack of independence between reports or a reflection of colony-specific morphology. This same research group authored all of the mixed-sex reports describing body composition outcomes, where increased percentage body fat was observed in infants under six months (Grant et al. 2011; McCurdy et al. 2009) but not at 13 months of age after gestational and lactational exposure to a high calorie diet (Fan et al. 2013).

Our knowledge regarding the effects of perinatal high calorie exposure among males is limited to a single study conducted among male baboons (Lewis et al. 1986),

where accelerated weight gain and absolute body size was apparent by age five but not during the early postnatal period. Using the same study design, females exhibited accelerated weight gain trajectories by two years of age after perinatal exposure to high calorie formula, and these females were significantly heavier than their 'underfed' and 'control' peers at five years of age. A key limitation of this study is that the subjects were nursery-reared via formula; while this may actually be a highly translational approach given the prevalence of formula feeding in humans, it may have other consequences for development.

Aside from the study by Lewis et al. (1986), only Terasawa et al. (2012) and Schwartz et al. (1988) have reported on morphological outcomes in young females after exposure to a high calorie diet. In both cases, exposure began in the pre-pubertal period and the findings are conflicting. While Terasawa et al. (2012) observed consistently increased gains in weight, CRL, CHL, and indicators of body composition among those exposed to a high calorie diet, Schwartz et al. (1988) only observed an initial increase in weight and abdominal skinfold thickness in the month immediately following dietary exposure. This inconsistency could reflect the slightly earlier onset of the dietary intervention for the cohort examined by Terasawa et al. (2012), whereby plasticity in developmental trajectories may be more malleable at one year of age compared to 16 months of age or differences in the palatability of the experimental diets.

Conclusions and Future Directions

This overview describes the current state of evidence for postnatal growth outcomes among Old World nonhuman primates in response to three exposures: 1) maternal body size and composition; 2) maternal experiences of chronic psychosocial

stress through the proxy of social subordination; and 3) a high calorie diet. In total, ten, fifteen, and seven publications were identified in each area, respectively. The evidence to date supports that each of these exposures has some influence on offspring growth and development. Key gaps in the literature were highlighted, including a focus on skeletal growth and development, attention to sexual dimorphic effects and care with regard to potential confounders. Areas for methodological considerations in terms of both comparative consideration of present data sets, and design of future studies, emerged. These include a more thorough consideration for the central role played by habitat when considering translational applications of nonhuman primate research and the need for truly longitudinal data collection and analysis.

Overwhelmingly the primary outcome measure to date has been infant weight and little attention has been paid to potentially sexually dimorphic distinctions or age-specific effects. For example, no reports describing crown-heel length or body composition for males in relation to diet were found, and only one publication examined offspring body composition in response to maternal psychosocial stress, and this exclusively described effects on males (Bercovitch et al. 2000). The published literature has largely reported on outcomes among mixed-sex cohorts and these from age ranges that include disparate stages of development. For example, Sanna et al. (2015) and Altmann and Alberts (1987) reported on weight outcomes in mixed-sex cohorts of Tonkean macaques and yellow baboons, respectively, ranging in age from approximately birth to 36 months of age. In both cases, the researchers consistently did not identify differences in offspring weight-for-age in relation to maternal social rank. These are short-comings as it cannot be ruled

out that influences of maternal rank unfold at discrete points in time or have sex-specific effects.

Further, conflicting outcomes may reflect how exposures are defined. Maternal social rank, for example, has employed varying definitions, ranging from a simple dichotomous split of a large group into 'low' and 'high' (Sanna et al. 2015) to assigning a single animal as the 'alpha' in a small group and classifying the rest of animals as 'low' and 'middle' ranking (Bowman and Lee 1995). Within these paradigms, the experience of low and high rank may be very different. For example, in smaller group compound settings social subordination is exacerbated, while in larger social groups the effects of chronic stress may be alleviated by familial social support and the presence of males that reduce aggression (Ha et al. 1999).

The use of mixed-sex cohorts and mixed-cross sectional/longitudinal data sources in studies of nonhuman primate growth in response to maternal morphology and social subordination have occurred in colony, semi free-ranging, and free-ranging settings. Results likely reflect a combination of how well characterized the study population is (e.g., how well the social hierarchy is known), the accuracy of sex identification among young infants and the degree to which we as researchers disrupt animal's habitat for data collection. Approaches to increase data collection without disrupting animal interactions are in place when possible, such as the use of baited or non-baited scales (e.g., Johnson and Kapsalis 1995), though their use also contributes to the predominance of weight as compared to height or body composition outcomes.

Studies examining the effects of high calorie diets have been constrained to colony settings where nutrition can be regulated through an experimental design. The

results of these studies are inconsistent regarding whether exposure to a high calorie diet is associated with morphological differences across the early and late developmental periods, though this may be tied directly to the outcome under study. For example, gestational exposure and postnatal exposure through lactational means has been associated with differences in percent body fat but not body weight across several studies of Japanese macaques (Grant et al. 2011; McCurdy et al. 2009), suggesting that innate physiological differences are not fully captured by the simple measurement of body mass.

Finally, using nonhuman primates as a translational model for examining issues related to infant growth requires careful attention to developmental trajectories and species-typical behavior. For example, while human females typically reach menarche between ages ten and 13, macaques reach menarche between ages three and five (Walker et al. 1983). In light of their accelerated developmental trajectories, it is critical to clearly describe sampling time points in growth and development research, as a measurement taken at six months of age on a nonhuman primate does not equate to a developmental outcome for a six month old human. For example, the first six months of life for a Rhesus macaque infant is approximately equivalent to the first two years of life in human infant, while adolescence begins at approximately 16 months for a Rhesus macaque compared to 11 to 13 years for humans. In this vein, nonhuman primates breast feed on-demand for a comparatively longer portion of infancy than humans; research among humans documents health advantages for those with longer exclusive breast feeding (Duijts et al. 2010), and this difference in feeding strategy may interfere with some of the translational aspects of the nonhuman primate model. These factors must be taken into consideration as we move forward with research utilizing nonhuman primates as a model for

understanding the developmental origins of health and disease, particularly to identify mechanisms underlying epidemiological associations between pre- and postnatal growth and lifespan health (Barker et al. 2013).

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CHAPTER 2 PRIMARY AIMS, HYPOTHESES, AND METHODS

Primary Aims and Hypotheses

Aim 1: To Identify Associations Between Maternal Rank, Maternal Body Composition, and Fetal Growth and Birth Weight Outcomes

Based on previous research conducted among adult female Rhesus macaques at the Yerkes National Primate Research Center (Michopoulos et al. 2012a), it was expected that maternal rank would be related to maternal size. It was anticipated that low ranked dams would be lighter and shorter but characterized by increased percentage body fat compared to high ranked dams, and that their fetuses would reflect these differences such that birth weight outcomes would follow from distinct fetal growth trajectories during the third trimester, with offspring of higher rank exhibiting accelerated growth rates to achieve greater size.

Aim 2: To Identify Associations Between Maternal Rank, Maternal Body Composition, Postnatal Diet, Birth Weight and Infant Growth Trajectories During The First 6 Postnatal Months

Following the expectations noted in Aim 1, it was hypothesized that shorter and lighter low ranked mothers would produce infants who themselves were shorter and lighter, with reduced skeletal integrity across the first 6 postnatal months, compared to those born to high ranked mothers. It was further hypothesized that greater postnatal growth rates would occur among infants with ad libitum access to both low- and high-calorie chow – a ‘choice’ diet mimicking the human condition – and that this effect would be most prominent among infants born to low ranked mothers. This assumption was based on previous work among adult Rhesus macaque females offered a similar

choice diet (Arce et al. 2010; Michopoulos et al. 2012b; Moore et al. 2013) and is a pattern analogous to catch-up growth in humans (Dulloo et al. 2006). Finally, a cross-over design was employed to isolate effects from exposure to pre- versus postnatal stress. It was hypothesized that infants born to low ranked mothers but raised by high ranked mothers would have a distinct postnatal growth trajectory of increased body size relative to their counterparts both delivered to and raised by low ranking dams.

Methods

Study Design

This was a prospective longitudinal study of Rhesus macaque (*Macaca mulatta*) mother-infant pairs conducted at the Yerkes National Primate Research Center Field Center in Lawrenceville, Georgia. To achieve the research aims, a chronic stress exposure model followed by two interventions was designed. Adult female subjects of contrasting social rank provided the context for studying the effects of chronic stress exposure. Ultrasonography, anthropometry, and dual energy X-ray absorptiometry (DXA) assessments provided the data for assessing these effects on fetal and infant growth and body composition from gestational day 100 to six postnatal months of age.

The study comprised two data collection phases: 1) prenatal assessments to characterize maternal body composition and fetal growth, and 2) postnatal assessments of dam-infant pairs to examine offspring growth and body composition as outcomes.
No experimental manipulation of any subjects occurred during the prenatal observation period (Phase 1). During the postnatal period (Phase 2), dams and their female offspring were assessed within the context of two experimental paradigms, dietary intervention and cross-fostering, commencing at parturition and in place through the sixth postnatal month

(Figure 2.1 and Table 2.1). The study was restricted to female infants in line with the broader goals of the ongoing parent project, which is specifically examining the neurobiological effects of chronic psychosocial stress exposure and high calorie diets on female neurobehavioral development.

Figure 2.1 Graphical Depiction of the Pre- and Postnatal Assessment Schedule

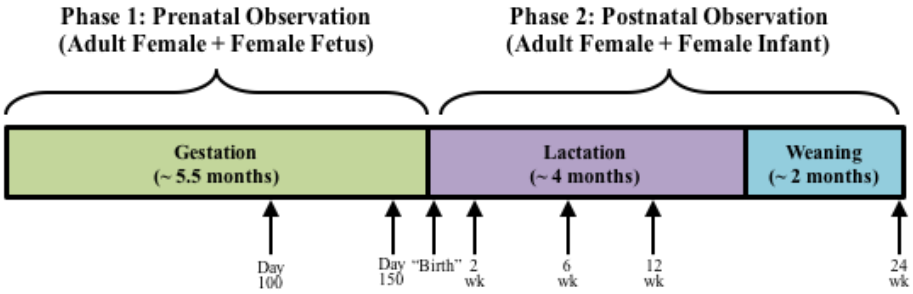


Table 2.1 Distribution of Dam-Infant Pairs, by Dietary Intervention and Cross-Fostering

Phase 1: Prenatal			Phase 2: Postnatal					
Diet	Dam Rank (N)		Diet	Cross-Foster Assignment & Rank				Total
				Cross-Foster		Biological		
				Low	High	Low	High	
LCD	Low	22	LCD	3	4	4	--	**11**
			CDD	3	4	4	--	**11**
	High	13	LCD	1	0	--	5	**6**
			CDD	3*	1	--	3	**7**
			Total	**10**	**9**	**8**	**8**	**35**

*Note: One dam-infant pair was examined at "birth" and subsequently dropped because of chronic maternal illness.

Study Subjects

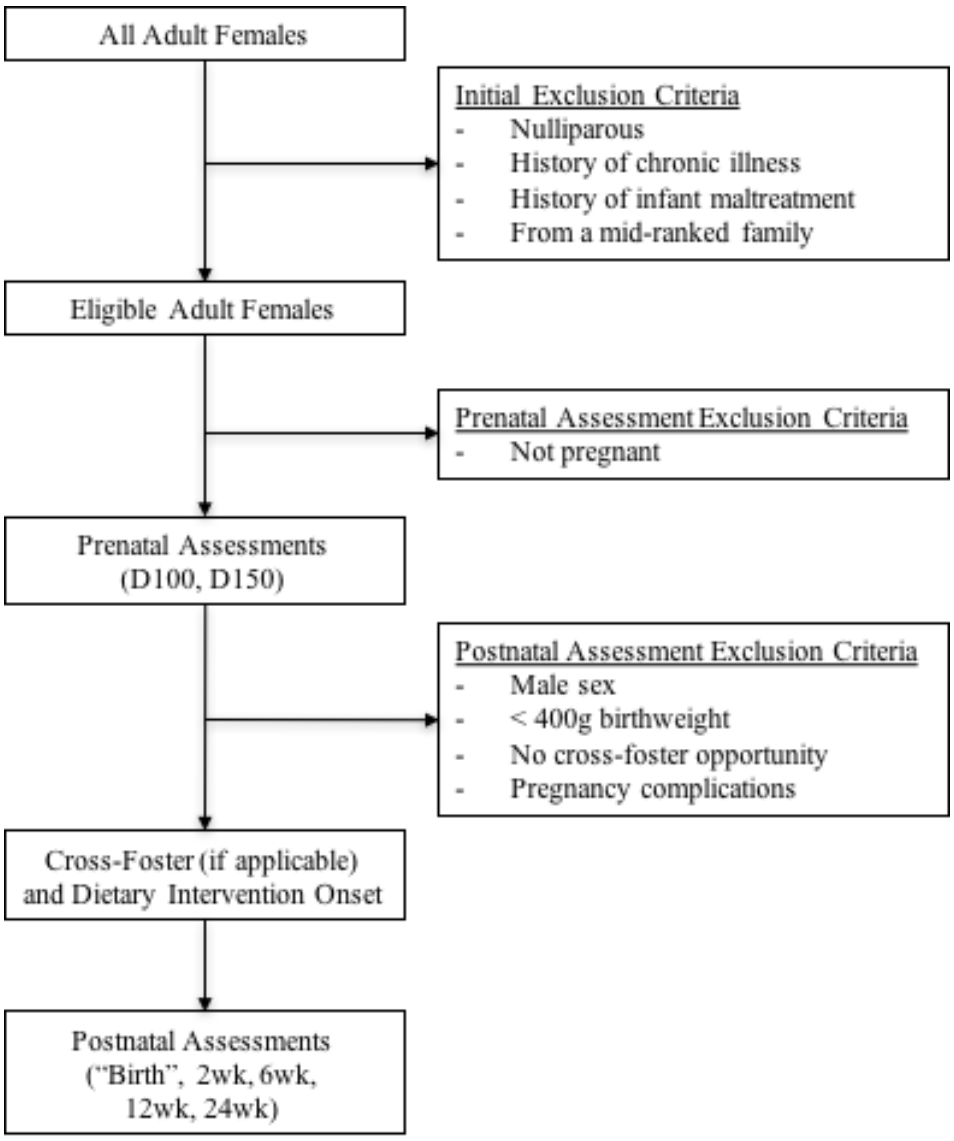
The focal infants were chosen from sequential births among animals who delivered live born infants between March 2014 and July 2015. These infants represent a convenience sample of females born during the first two years (2014 and 2015) of an ongoing multi-year study that will continue to monitor dam-infant pairs until reaching the planned target of 56 subjects, based on power calculations for the larger study's

neurobiological outcomes. The focal dams were members of three multigenerational groups consisting of 20 to 50 adult females with their immature offspring and 3 to 4 unrelated adult males. Each group lived in large outdoor compounds (38 m^2) with attached heated and cooled indoor areas at Emory University's Yerkes National Primate Research Center Field Station in Lawrenceville, Georgia. The Rhesus macaques involved in the study are from the specific pathogen-free (SPF) colony and were all born at this location, with infant subjects arising from mating activities that occurred as part of normal colony breeding procedures in the fall of 2014 and 2015. All procedures were approved by the Institutional Animal Care and Use Committee (IACUC) of Emory University in accordance with the Animal Welfare Act and the National Institutes of Health /Department of Health and Human Services "Guide for the Care and Use of Laboratory Animals."

To achieve the study goal of assessing chronic stress effects as defined by social rank, all subjects were members of either the highest or lowest one-third of families within the established linear dominance hierarchy of each outdoor compound. Dominance rank was determined by the outcome of dyadic agnostic interactions, with a subordinate animal defined as one who exhibits unequivocal submissive behavior towards another (Bernstein and Sharpe 1964; Bernstein 1970; Bernstein 1976). Familial dominance rank was continually monitored across the study by weekly systematic observations of each group whereby all occurrences of submissive behaviors, namely withdraws and grimaces, were recorded following recognized best practices (Altmann 1974; Altmann 1962; Bernstein 1976).

Adult female Rhesus macaques were initially eligible if they had at least one previous live birth, an absence of chronic clinical conditions, and no history of infant maltreatment, according to colony management records (Figure 2.2). Current pregnancy was the final inclusion requirement. For those meeting the inclusion criteria, each subject's own birth dates and full parity information were then recorded from colony management records.

Figure 2.2 Diagram of Subject Eligibility



Study Procedures

Adult female subjects and, after parturition, infants were habituated to access procedures. This included training to individually move from their outdoor enclosure into the caged area of the attached indoor area, where they were moved to a small transfer container so that they could be relocated to a nearby procedure room for anthropometry, ultrasound, or DXA. Training was performed using positive reinforcement and following guidelines and protocols approved by the Emory University IACUC. Previous work has shown that infants who experienced similar procedures exhibited no alterations in normal development (Wilson et al. 1986).

Phase 1

Ultrasounds were performed using a GE LOGIQ *e* (GE LOGIQE94WX4 software in Pediatric mode) equipped with an 8C-RS trans-abdominal probe to determine if adult females meeting the inclusion criteria were pregnant by a board-certified DVM/PhD researcher (K. Ethun). Pregnancy screening ultrasounds were performed after the female was anesthetized with Ketamine delivered intramuscularly (IM; 8-10 mg/kg). Fetal gestational age was estimated based on species-specific age-graded bi-parietal diameter and femur length references (Nyland et al. 1984). If fetal age was estimated to be less than 21 days, the subject was re-examined approximately 30 days later when the fetal head and femur had matured to the minimum recommended size for predicting gestational age.

Pregnant adult females were further assessed twice, during their “second” and “third” trimesters, with target assessment dates of gestational days 100 and 150. Assessments were scheduled based upon the fetal gestational age estimated during the

initial pregnancy screening. Dams were fasted beginning at midnight prior to each assessment, and sedated intramuscularly with Telazol (3-5 mg/kg) and supplemented with Ketamine (20-40 mg, intermuscularly) as needed to complete all planned research procedures, as described below in detail and summarized in Table 2.2.

Table 2.2 Summary of Prenatal Research Procedures on Adult Female Rhesus macaques and their Fetuses

Data Type	Units	Prenatal Period: Phase 1	
		D100	D150
Anthropometry (Maternal)			
Head circumference	Nearest 0.01 cm	✔	
Crown-rump length	Nearest 0.01 cm	✔	
Crown-heel length	Nearest 0.01 cm	✔	
Body weight	Nearest 0.01 kg	✔	✔
Body Composition (Maternal)			
BMD	Nearest 0.0001 g/cm^2	✔	✔
BMC	Nearest 0.0001 g	✔	✔
Fat mass (%)	Nearest 0.0001 g	✔	✔
BMI	Nearest 0.01 kg/m^2	✔	✔
Ultrasound (Fetal)			
Bi-parietal diameter	Nearest 0.001 cm	✔	✔
Head circumference	Nearest 0.001 cm	✔	✔
Abdominal circumference	Nearest 0.001 cm	✔	✔
Femur length	Nearest 0.001 cm	✔	✔

Repeated Measures Ultrasound and Fetal Anthropometry

Research ultrasounds were performed by the same, board-certified PHD/DVM (K. Ethun) using the GE LOGIQ *e* ultrasound machine, with an 8C-RS trans-abdominal probe with software in Pediatric mode utilized to take still images in the standardized ultrasound planes for assessing head circumference and bi-parietal diameter, abdominal circumference, and femur length. Briefly, abdominal images were taken in the axial plane at the level of the umbilical vein ductus venosus complex (Hadlock et al. 1982a); femur images were taken with the longest axis of the femur in view, avoiding tangential

sections that would shorten the femur and ensuring that the ilium, ischium, and femoral epiphyses are out of view to avoid artificially lengthening the femur (Hadlock et al. 1982b); and the head images were taken such that the anterior third of the bodies of the lateral ventricles, the third ventricle, the thalamic nuclei, and the quadrigeminal cistern complex were visible and the calavarial walls were symmetric (Shepard and Filly 1982). Each image was saved and assessed for quality by a second, single observer based upon its angle relative to the standardized plane of interest as previously described. Fetal size was then measured to the nearest 0.001 cm on the image that best conformed to the standardized planes of interest for head, abdomen, and femur. Fetal size measurements were independently performed twice for each image using the software program Image J, an open source image processing program developed and distributed by the NIH (http://imagej.nih.gov/ij/). Fetal size measurements were carried out according to established methods (Tarantal and Hendrickx 1988):

- Femur length by extending the cursor between the two ossified ends of the femur
- Abdominal circumference by tracing around the margin of the fetal abdomen with the cursor on the abdominal images
- Head circumference by tracing the outer limits of the skull with the cursor
- Bi-parietal diameter by measuring the distance between the outer margin of the skull nearest the transducer to the inner margin of the skull line farthest from the transducer.

Body Composition

Maternal body composition during pregnancy was measured at D100 and D150.Bone mineral density (BMD; g/cm^2), bone mineral content (BMC; g), lean mass

(g), and fat mass (g) were measured with the dam in the supine position using DXA (Eclipse XR scanner, Illuminatus DXA software version 4.2.3 in Research mode, Norland, Fort Atkinson, WI). Body mass index (BMI) was calculated at every pre- and postnatal time point by dividing current dam weight (kg) by crown-heel length squared (m^2).

Pregnancy Diet

Prior to parturition all adult females consumed the colony standard diet (Purina, LabDiet® #5038) in a pelleted form (Purina, LabDiet® #503A). This low calorie diet ("LCD") contains 3.46 kcal/g and is comprised of 13.5% fat, 18.1% protein, and 68.4% carbohydrate. Additionally, all subjects had access to water and seasonal fruit and vegetable supplementation per normal colony management procedures.

Phase 2

Each dam-infant pair was assessed at five time points after parturition: within zero-to-four days of birth ("birth"), 2 weeks of age (2wk), 6 weeks of age (6wk), 12 weeks of age (12wk), and 24 weeks of age (24wk). The dam and infant were fasted prior to each assessment, and all postnatal accesses occurred within 10 minutes of sunrise to meet the parent project goal of assessing diurnal cortisol rhythms during early development. At the "birth" and 2wk accesses, dams were anesthetized with Ketamine (IM, 7-10 mg/kg) for anthropometry. Infants were not anesthetized at the "birth" or 2wk access times. For all subsequent assessments, dams were anesthetized with Telazol (IM, 3-4 mg/kg) and supplemented with Ketamine (IM, 20-30 mg), while infants were sedated with Ketamine (IM, 5 mg) and supplemented with Ketamine (IM, 2 mg), as needed to

complete all planned research procedures, as described below in detail and summarized for the dam and infant in Tables 2.3 and 2.4, respectively.

Table 2.3 Summary of Postnatal Research Procedures on Adult Female Rhesus Macaques

Data Type	Units	Postnatal Period: Phase 2				
		"Birth"	2wk	6wk	12wk	24wk
Anthropometry						
Head circumference	Nearest 0.01 cm	✔	✔	✔	✔	✔
Crown-rump length	Nearest 0.01 cm	✔	✔	✔	✔	✔
Crown-heel length	Nearest 0.01 cm	✔	✔	✔	✔	✔
Body weight	Nearest 0.01 kg	✔	✔	✔	✔	✔
Body Composition						
BMD	Nearest 0.0001 g/cm^2			✔	✔	✔
BMC	Nearest 0.0001 g			✔	✔	✔
Fat mass (%)	Nearest 0.0001 g			✔	✔	✔
BMI	Nearest 0.01 kg/m^2	✔	✔	✔	✔	✔

Table 2.4 Summary of Postnatal Research Procedures on Female Infant Subjects

Data Type	Units	Postnatal Assessment Time Points				
		"Birth"	2wk	6wk	12wk	24wk
Anthropometry						
Head circumference	Nearest 0.01 cm	✔	✔	✔	✔	✔
Crown-rump length	Nearest 0.01 cm	✔	✔	✔	✔	✔
Crown-heel length	Nearest 0.01 cm	✔	✔	✔	✔	✔
Body weight	Nearest 1 g	✔	✔	✔	✔	✔
Body Composition						
BMD	Nearest 0.0001 g/cm^2			✔	✔	✔
BMC	Nearest 0.0001 g			✔	✔	✔
Fat mass (%)	Nearest 0.0001 g			✔	✔	✔
Weight/Crown-heel length	Nearest 1 g/cm	✔	✔	✔	✔	✔
Weight/Crown-rump length	Nearest 1 g/cm	✔	✔	✔	✔	✔

Anthropometry

Adult subjects. Head circumference, crown-rump and crown-heel lengths were each measured to the nearest 0.1 cm by two independent observers at D100, using

standard procedures (Cameron 2012). Head circumference was measured with a tape measure, while crown-heel and crown-rump lengths were measured with the female fully recumbent (Lampl et al. 2001) in a supine position using a pediatric stadiometer equipped with a fixed headboard and a mobile footboard. Abdominal circumference was measured at all time points with a tape measure by two independent observers, also to the nearest 0.1 cm. Body weight was measured using a portable tared scale (A&D Weighing, San Jose, CA) at all assessments, recorded to the nearest 0.01 kg.

Infant subjects. Infant anthropometry was repeated at each of the five postnatal assessments. Abdominal circumference and head circumference were measured with a tape measure to the nearest 0.1 cm by two independent observers, following standard procedures (Cameron 2012). Infant crown-rump and crown-heel lengths were measured by two independent observers using calipers at the "birth", 2wk, 6wk, and 12wk assessments and with a pediatric stadiometer equipped with a stationary headboard and mobile footboard at the 24wk assessment, with the infant fully recumbent (Lampl et al. 2001) in the supine position. Lengths recorded to the nearest 0.1 cm. A portable tared scale (A&D Weighing, San Jose, CA) was used to assess body weight and recorded to the nearest 1 g. Derived measures, weight for crown-heel length and weight for crown-rump length were calculated at each time point by dividing current weight (g) by current crown-heel length (cm) or crown-rump length (cm), respectively.

Body Composition

Adult subjects. Body composition was measured at three time points postnatally: 6, 12 and 24 weeks. Bone mineral density (BMD; g/cm^2), bone mineral content (BMC; g), lean mass (g), and fat mass (g) were measured with the dam in the supine position

using DXA (Eclipse XR scanner, Illuminatus DXA software version 4.2.3 in Research mode, Norland, Fort Atkinson, WI). Body mass index (BMI) was calculated at every pre- and postnatal time point by dividing current dam weight (kg) by crown-heel length squared (m^2).

Infant subjects. DXA (Eclipse XR scanner, Illuminatus DXA software version 4.2.3 in Small Subjects mode, Norland, Fort Atkinson, WI) was used to quantify infant body composition at three time points: 6wk, 12wk, and 24 wk. This included measures of BMD, (g/cm^2), BMC (g), and lean mass (g) with the subject in the supine position.

Dietary Intervention

Postnatally, a subset of the adult females and their corresponding infants were randomly assigned to choice access to both the LCD and a calorically-dense diet (CDD; #D07091204) that contains 4.25 kcal/g and comprised of 30% fat, 20% protein, and 50% carbohydrate (Research Diets, Inc. #D14051502B). The LCD and CDD have similar amounts of vitamins and minerals, but the CDD has significantly more sugar and cholesterol. The dietary intervention was imposed through the use of automated feeders (BioDAQ; http://www.researchdiets.com/biodaq/biodaq-nhp) within each compound, where unique RfID chips (DATAMARS; http://www.datamars.com) implanted in the wrist restricts CDD access to specific subjects, while maintaining *ad libitum* access to the LCD chow for all animals in the compound. Automated feeders have been validated in previous dietary interventions at the Yerkes National Primate Research Center, with no evidence of food competition (i.e., stealing or guarding) or food waste (i.e., pellets discarded rather than consumed) (Wilson et al. 2008). Dam-infant pairs were randomly assigned to the choice (CDD + LCD) or prudent (LCD) postnatal diet (Table 1) for the

duration of the 24-week postnatal observation period, with access to water and seasonal fruit and vegetable supplementation provided following normal colony management procedures.

Cross-Fostering

To specifically address the pre- versus postnatal effects of chronic social subordination, a portion of the female infants were cross-fostered to dams of either the same or opposite rank of their biological dams, using procedures in place at the Yerkes National Primate Research Center (Maestripieri 2005; Maestripieri et al. 2006; Maestripieri et al. 2000). Cross-fostering occurred at random, based upon the chance occurrence of births within different compounds in a 96-hour period where each infant weighed at least 400 g. These weights were recorded and used as the infant birth weight, when available. If a cross-foster was not possible within the 96-hour period, female infants were raised by their biological mother and followed postnatally.

Statistical Procedures

Stata/IC version 14.1 for Mac (Stata Corporation, College Station, TX; StataCorp LC) statistical software was used for all statistical analyses. The distributions of variables were tested by the Shapiro-Wilk test, with descriptive statistics reported as the mean and range (minimum to maximum) unless stated otherwise. Repeated-measures mixed models were used to assess the independent effects of maternal rank, morphology, age, and parity on fetal and infant size and growth, as well as dietary exposure and cross-fostering on postnatal infant size and growth trajectories; significant effects on growth rates were specifically investigated as an interaction term with age in a linear model followed by the post-estimation *margins pwcompare(effects)* command. Models investigating the effects

of maternal morphological change during the third trimester on fetal or infant growth velocity included maternal size at the end of the second trimester as a covariate to control for the potential effect of prior size. In all repeated-measures mixed models, subjects were nested within biological maternal rank per the study protocol and the focal infant was included as a random effect to control for within-subject correlation and individual-specific unmeasured effects. Age at measurement was included as a covariate in all analyses.

Birth weight and and weight for crown-heel length at birth were individually investigated as potential mediators of how maternal morphology moderated postnatal growth trajectories following the procedures outlined in Baron and Kenny (1986) and Judd and Kenny (1981).

Statistical significance was defined at alpha=0.05; the text and tables additionally denote when statistical significance was achieved at below the Bonferonni-adjusted level (specific to each analytic). Measurement reliability was assessed by calculating the standard deviation, coefficient of variation, and technical error of measurement (TEM) between observers for all measures and within-observer for the fetal measurements (Table 2.5).

TEM was calculated using the following formula:

$$\sqrt{\left(\sum_{i=1}^{N}(M_{\square 1}-M_{i2})^2/2N\right)}$$

where M_{i1} and M_{i2} are measures taken by two different observers on the same infant for all maternal morphological measures and infant postnatal measurements, and are

duplicate measures taken by a single observer for fetal measurements on the ultrasound image stills.

Table 2.5 Intra- and Inter-Observer Error: Standard Deviation and Technical Error of Measurement

	N	SD (cm)	TEM
Intra-Observer Error: Fetal			
Abdominal Circumference	62	<0.0001	0.0015
Head Circumference	61	<0.0001	0.0031
Bi-parietal diameter	61	<0.0001	0.0029
Femur Length	61	<0.0001	0.0029
Inter-Observer Error: Maternal Measures			
Abdominal Circumference	65	<0.0001	0.0054
Head Circumference	35	0.0001	0.0095
Crown-Heel Length	35	<0.0001	0.0032
Crown-Rump Length	35	0.0034	0.0587
Inter-Observer Error: Postnatal Infant Measures			
Abdominal Circumference	171	0.0003	0.0151
Head Circumference	171	0.0001	0.0099
Crown-Heel Length	171	<0.0001	0.0034
Crown-Rump Length	171	<0.0001	0.0046

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CHAPTER 3 RESULTS

Study Subjects

Thirty-five female infant Rhesus macaques distributed approximately evenly across low and high rank met the criteria for study inclusion (see Chapter 2). There were no statistically significant differences between low and high ranked dams in terms of maternal age (p=0.41) at delivery of the study infants or parity (p=0.67) (Table 3.1). Anthropometry was performed for 29 of the 35 dams at the end of the second trimester (gestational day 100, D100) and for 34 of 35 dams at the end of third trimester (gestational day 150, D150), with measures of the change in morphology between D100 and D150 available for 28 dams. Anthropometric data were collected at two prenatal study time points for 28 of the mother/infant pairs, and at five postnatal study time points for 34 of 35 infants. The female infant with incomplete postnatal data was only assessed at the 'birth' time point and was subsequently dropped from the study because her mother fell ill before the next planned postnatal assessment. Of the 34 infants, ten low ranked and six high ranked infants were assigned to the colony standard 'prudent' diet, while 11 low ranked and seven high ranked infants were assigned to the 'choice' diet.

Table 3.1 Maternal Demographics and Body Size from Gestation to Parturition

	D100 (n=29)	D150 (n=34)	Third Trimester Change (n=28)	Parturition (n=35)
Maternal Demographics (n=35)[1]				
Age (yrs)	7.71 (4-17)	--	--	--
Parity	3.11 (1-10)	--	--	--
Rank (% Low)	62.9%	--	--	--
Maternal Body Size[1]				
Weight (kg)	8.42 (6.15-15.35)	8.86 (5.84-16.80)	0.46 (-0.31-1.45)	8.36 (5.21-16.49)
Abdominal Circumference (cm)	41.97 (36.55-59.65)	45.06 (38.70-63.70)	3.09 (-1.70-7.60)	42.07 (32.65-63.50)

	D100 (n=29)	D150 (n=34)	Third Trimester Change (n=28)	Parturition (n=35)
Crown-Heel (cm)	79.58 (75.65-89.30)	--	--	--
BMI	13.19 (10.29-19.25)	13.88 (10.20-21.07)	.70 (-.54-1.82)	13.01 (10.01-20.68)
Body Fat (%)	11.91 (0-50.99)	7.80 (0-43.12)	-3.85 (-50.99- 2.47)	--
BMD (g/cm^2)	0.69 (0.58-0.92)	0.70 (0.58-0.90)	0.01 (-0.22-0.14)	--
BMC (g)	253.41 (170.10-470.70)	243.50 (125.20-420.80)	-8.45 (-70.1-19.2)	--

[1]Mean (range)

Study Protocol

Aim 1: To identify associations between maternal rank, maternal body composition, and fetal growth and birth weight outcomes.

Maternal Size and Body Composition During Pregnancy

End of the Second Trimester, Gestational Day 100 (D100)

All maternal attributes and measures of body size were normally distributed according to the Shapiro-Wilk test. Dams were on average 7.71 years old (range, 4-7) with 3 previous live births (range, 1-10) (Table 3.1). Nearly two-thirds (63%) of the maternal sample were socially subordinate (low ranked). On average, dams weighed 8.42 kg (range, 6.25-15.35) with 11.9% body fat (range, 0 to 60%). Morphologically their phenotype reflected an average: abdominal circumference of 41.97 cm (range, 36.55-59.65); crown-heel length of 79.58 cm (range, 75.65-89.30); BMI of 13.2 (range, 10.39-19.35); bone mineral content (BMC) of 253.41 g (range, 170.10-470.70); and bone mineral density (BMD) of 0.69 g/cm^2 (range, 0.58-0.92), at the end of the second trimester.

End of the Third Trimester, Gestational Day 150 (D150)

At the end of the third trimester, dams averaged 8.86 kg (range, 5.84-16.80) in weight with 7.80% body fat (range, 0-43.12), and means of 13.9 g/m^2 for BMI (range, 10.20-21.07), 45.1 cm (range, 38.70-63.70) in abdominal circumference, BMD and BMC of 243.50 g (range, 125.20-420.80) and 0.70 g/cm^2, (range, 0.58-0.90) (Table 3.1), respectively.

Maternal Changes Across the Third Trimester (Gestational Days 100-150)

Maternal body size increased during the third trimester such that dams gained, on average, 0.46 kg (range, -0.31-1.45) in weight and 3.09 cm (range, -1.70-7.60) in abdominal circumference (Table 3.1). While the mean BMI increased by a modest 0.70 g/m^2 (range, -0.54-1.82), percentage fat mass decreased by an average of 3.85% (range, -50.99- 2.47). At an increase of 0.01 g/cm^2 (range, -0.22-0.14), BMD was essentially unchanged across the third trimester, while a small average decrease of 8.45 g (range, -70.1-19.2) in BMC was observed. At parturition, the average dam weight was 8.36 kg (range, 5.21-16.49), with an abdominal circumference of 42.07 cm (range, 32.65-63.50) and BMI of 13.01 kg/m^2 (range, 10.01-20.68).

Immediately after parturition, dams averaged 8.36 kg (range, 5.21-16.49) in weight, 42.07 cm (range, 32.65-63.50) in abdominal circumference, and had an average BMI of 13.01kg/m^2 (range, 10.01-20.68) (Table 3.1). Overall, these measurements reflected a return to the body size as it had been at D100. Percentage body fat, BMD, and BMC were not assessed at parturition.

Maternal Rank Comparisons

No statistically significant differences in measured physical attributes distinguished low from high ranked mothers at the end of either the second (D100) or

third (D150) trimester, or in how maternal body size changed during the third trimester (Table 3.2). At parturition, there were no statistically significant differences in maternal weight (p=0.52), abdominal circumference (p=0.20), or BMI (p=0.29) by social rank. Body fat, BMD, and BMC were not assessed at partition.

Table 3.2 Maternal Demographics and Body Size from Gestation to Parturition, by Social Rank

	Maternal Rank		*P*-value[2]	
	Low (N=21)	High (N=14)		
Maternal Demographics (n=35)[1]				
Age (yrs)	8 (5-17)	7.23 (4-11)	0.4092	
Parity	3.23 (1-10)	2.92 (1-7)	0.6698	
Maternal Body Size at D100 (n=29)[1]				
Weight (kg)	8.28 (6.15-11.42)	8.70 (6.27-15.35)	0.5741	
Abdominal Circumference (cm)	41.745 (36.55-54.1)	42.42 (36.6-59.65)	0.7475	
Crown-Heel (cm)	79.24 (75.65-84.65)	80.15 (75.75-89.30)	0.3844	
BMI	13.14 (10.55-16.86)	13.28 (10.29-19.25)	0.8744	
Body Fat (%)	12.50 (0-50.99)	10.73 (0-42.51)	0.7187	
BMD	0.70 (0.58-0.92)	0.67 (0.60-0.84)	0.2885	
BMC	254.11 (170.10-316.10)	252.01 (170.60-470.70)	0.9297	
Maternal Body Size at D150 (n=34)[1]				
Weight (kg)	8.78 (5.84-11.93)	9.00 (6.88-16.80)	0.7495	
Abdominal Circumference (cm)	44.73 (38.7 -53.7)	45.61 (39.50-63.70)	0.6036	
BMI	13.92 (10.20-17.65)	13.82 (11.29-21.07)	0.8924	
Body Fat (%)	6.45 (0-24.45)	9.98 (0-43.12)	0.2593	
BMD	0.71 (0.58-0.82)	0.68 (0.59-0.90)	0.2812	
BMC	241.81 (125.20-306.20)	246.22 (182.70-420.80)	0.8127	
Changes During the Third Trimester (n=28)[1]				
Weight (kg)	.44 (-.31-1.11)	0.48 (-0.27-1.45	0.7549	
Abdominal Circumference (cm)	2.74 (-1.70-5.60)	3.81 (0-7.60)	0.2168	
BMI	.68 (-0.54-1.62)	0.73 (-0.41-1.82)	0.8095	
Body Fat (%)	-5.91 (-50.9-0.39)	0.05 (-5.73-2.47)	0.1184	
BMD	0.01 (-0.22-0.14)	0.01(-0.02-0.07)	0.7321	
BMC	-11.28 (-70.10-19.20)	-3.06 (-49.9-15.2)	0.3464	
Maternal Body Size at Parturition (n=35)[1]				
Weight (kg)	8.57 (6.38-11.74)	8.13 (5.21-16.49)	0.5156	
Abdominal Circumference (cm)	43.45 (32.65-32.65)	40.69 (33.55-63.50)	0.2000	
BMI	13.41 (10.59-17.33)	12.58 (10.01-20.68)	0.2914	

[1]Mean (range)

[2]ANOVA

Fetal Size and Growth

Gestational Age

Gestational age was not uniform at day of data collection during the study, with the D100 measurement actualized across a span of 11 days (ranging between 94 and 105 gestational days of age) and the D150 measurement occurring across a range of eight days (data collected between 144 and 152 gestational days of age). As gestational age at day of measurement predicted fetal size in a regression model ($p<0.05$ for each measurement parameter: femur, abdominal circumference, head circumference, and bi-parietal diameter), gestational day of measurement was included as a covariate in all fetal analyses.

Fetal Size and Maternal Influences

All measures of fetal size were normally distributed according to the Shapiro-Wilk test ($p<0.05$). Averages for the sample at D100 and D150 are shown in Table 3.3, adjusted for gestational age.

Table 3.3 Fetal Anthropometry at D100 and D150

Measurement[1]	**D100 (n=29)**	**D150 (n=34)**
Femur Length (cm)	2.65 (2.51-2.79)	4.20 (4.14-4.27)
Abdominal Circumference (cm)	11.87 (11.41-12.34)	16.33 (16.03-16.64)
Head Circumference (cm)	14.05 (13.65-14.46)	18.58 (18.40-18.75)
Bi-parietal diameter (cm)	3.55 (3.45-3.66)	4.76 (4.71-4.81)

[1]Estimated mean (confidence interval) from a mixed-effects linear regression adjusting for gestational age

Maternal age did not predict fetal size parameters at either time point. Increasing *maternal parity* was associated with increasing head circumference at the end of the third trimester (D150, $b=0.099$, $p=0.028$). *Maternal rank* had no statistically significant

influence on any measure of fetal size at the end of either the second or third trimesters (e.g., D100 or D150) (Table 3.4).

Table 3.4 Fetal Size at D100 and D150, by Maternal Rank

Measurement	Overall Model *P-value*[2]	Maternal Rank		*P*-value[2]
		Low	High	
D100 (n=28)[1]				
Femur Length (cm)	0.298	2.7075 (2.5810-2.8250)	2.6174 (2.4485- 2.7863)	0.391
Abdominal Circumference (cm)	0.572	12.1131 (11.6841-12.5420)	11.6306 (11.0141-12.2470)	0.208
Head Circumference (cm)	0.976	14.17078 (13.8263-14.5153)	14.0115 (13.5325-14.4904)	0.597
Bi-parietal diameter (cm)	0.468	3.5983 (3.5086-3.6879)	3.5184 (3.3937-3.6431)	0.308
D150 (n=34)[1]				
Femur Length (cm)	0.298	4.2254 (4.1038-4.3471)	4.2909 (4.1257-4.4560)	0.532
Abdominal Circumference (cm)	0.572	16.5389 (16.0948-16.9830)	16.3598 (15.7853-16.9344)	0.629
Head Circumference (cm)	0.976	18.7859 (18.4407-19.1311)	18.6140 (18.1676-19.0605)	0.551
Bi-parietal diameter (cm)	0.468	4.7993 (4.7095-4.8892)	4.7988 (4.6826-4.9150)	0.995

[1]Estimated mean (95% confidence interval) from a mixed-effects linear regression adjusting for gestational age
[2]Pairwise comparison of means, using the *margins* Stata command with the *pwcompare(effects)* option

Fetal Growth Rate and Maternal Influences

Maternal rank was not a statistically significant independent predictor of fetal femur, abdominal circumference, head circumference, or bi-parietal diameter growth rate during the third trimester.

Maternal size as measured at both days 100 and 150 had no statistically significant influence on the rate of fetal growth across the third trimester. *Maternal morphological changes occurring between 100 and 150* gestational days of age also had

no statistically significant effects on the rate of fetal femur, abdominal circumference, or head circumference growth, but did suggest a relationship with fetal bi-parietal growth, such that an accretion of less than one millimeter per day (b=0.09 mm, p=0.049) was predicted for each 1 cm increase in maternal abdominal circumference (Figure 3.1).

Figure 3.1 Increasing Third Trimester Abdominal Circumference is Associated with an Accelerated Bi-Parietal Diameter Growth Rate during the Third Trimester (n=28)

Maternal rank did not statistically significantly interact with any measure of maternal size during the prenatal period to influence femur, abdominal circumference, or head circumference growth rates. There was a trend for the acceleration of the rate of bi-parietal diameter to have been isolated among only high ranked fetuses (b=-0.02 mm, p=0.06).

Neonatal Size and Maternal Effects

As gestational age was estimated from an initial fetal ultrasound that occurred at convenience during the first trimester, birth outcomes were not adjusted for gestational age.The descriptive statistics for birth size are shown in Table 3.5, and were adjusted for postnatal day of measurement (mean age=1.26 days; range 0-4). *Maternal age* was not a significant independent predictor of neonatal birth weight (p=0.82), head circumference (p=0.25), or abdominal circumference (p=0.56) and *maternal parity* did not significantly predict neonatal head circumference (p=0.96), abdominal circumference (p=0.88), or birth weight (p=0.10). In contrast, birth length showed significant maternal relationships such that for each additional year of maternal age female offspring were 0.17 cm longer in crown-heel length (p=0.03), and for each additional previous live birth neonates were 0.30 cm longer ($p<0.001$).

Table 3.5 Infant Anthropometry at Birth (n=35)

Anthropometry Outcome[1]	**Sample Characteristics**
Birth Weight (g)	484.4 (473.2-498.1)
Head Circumference (cm)	19.3 (19.1-19.4)
Abdominal Circumference (cm)	12.2 (11.8-12.6)
Crown-Rump Length (cm)	20.6 (20.4-20.9)
Crown-Heel Length (cm)	30.9 (30.7-31.1)
Weight/Crown-Rump Length (cm)	23.5 (23.2-23.7)
Weight/Crown-Heel Length (cm)	15.7 (15.4-16.0)

[1]Mean (range) estimated from linear regression adjusting for observation age

Maternal rank did not significantly differentiate birth weight (Figure 3.2), head circumference (p=0.11), abdominal circumference (p=0.86), or crown-heel length (p=0.80) (Table 3.6).

Figure 3.2 Infant Birth Weight by Dam Rank (n=35)

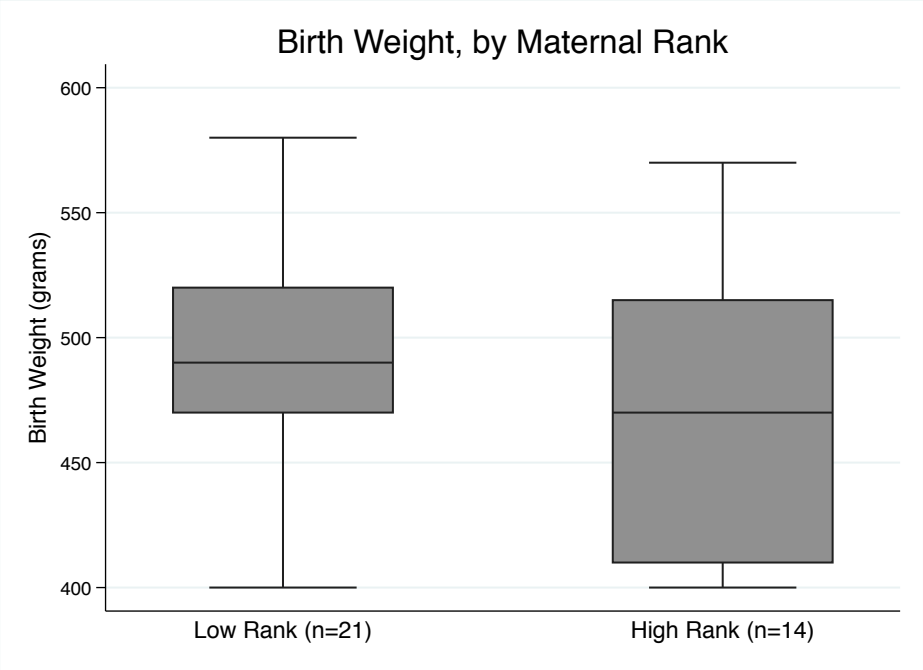


Table 3.6 Infant Anthropometry at Birth, by Biological Maternal Rank (n=35)

Anthropometry Outcome	Maternal Rank		*P-value*	
	Low	High		
Birth Weight (g)[1]	0.488 (0.400-0.580)	0.474 (0.400-0.570)	0.331	
Head Circumference (cm)[2]	19.66 (18.65-20.8)	18.71 (10.05-20.75)	0.110	
Abdominal Circumference (cm)[2]	12.098 (11.00-13.85)	12.22 (10.15-19.10)	0.860	
Crown-Heel Length (cm)[2]	30.91 (29.40-33.40)	30.81 (29.10-33.45)	0.797	

[1]Mixed effects linear regression adjusting for day of birth weight measurement (mean=1.26 days, range=0-4 days)
[2]Mixed effects linear regression adjusting for day of length and circumference measurements (mean=2.65 days, range=1-4 days)

Predictors of Infant Birth Weight

Fetal growth. Rates of fetal femur, abdominal circumference, head circumference, or bi-parietal diameter growth during the third trimester were not statistically significant not predictors of birth weight.

Maternal size. Several measures of maternal body size at the *end of the second trimester* (Day 100) were statistically significant independent predictors of birth weight among the study females. Birth weight was increased by 6.27 g for each 0.5 kg increase in maternal weight (p=0.002), 4.17 g for each 1 cm increase in maternal abdominal circumference (p=0.006), 9.4 g for each 1 cm increase in maternal crown-heel length ($p<0.001$), 7.85 g for each 5% increase in body fat (p=0.02), and 3.29 g for each 10-g increase in maternal BMC (p=0.02) at the end of the second trimester. After considering the Bonferroni correction ($a>0.002$), maternal abdominal circumference and maternal weight at D100 were the only statistically significant predictors of birth weight.

Similarly, several measures of maternal body size at the *end of the third trimester* (Day 150) were statistically significant independent predictors of birth weight among the study females. Birth weight was increased by 7.38 g for each 0.5 kg increase in maternal weight ($p<0.001$), 6.83 g for each 1 cm increase in maternal abdominal circumference ($p<0.001$), 11.83 g for each 1-point increase in BMI (p=0.001), 14.35 g for each five percent increase in fat mass (p=0.002), 4.14 g for each 10-g increase in bone mineral content (p=0.01), and a 28.5 grams increase for each 0.1 point increase in BMD (p=0.02). After considering the Bonferroni correction ($a>0.002$), maternal weight, abdominal circumference, BMI, and percentage body fat at D150 remained statistically significant predictors of birth weight.

Maternal changes across the third trimester in weight, abdominal circumference, and BMI were significant independent predictors of birth weight among the study infants. Birth weight was increased by 22.87 g for each 0.5 kg increase in dam weight across the

third trimester (p=0.02) and 35.33 g for each 1-point increase in BMI (p=0.01). These were not statistically significant after considering the Bonferroni correction (a>0.002).

Effects from Maternal Rank Interactions with Maternal Size on Birth Weight

With respect to offspring birth weight, there were no statistically significant interactions between maternal social rank and her body size at either the end of the second or third trimesters, or with changes across the third trimester.

Predictors of Crown-Heel Length at Birth

Fetal Growth Rates

Rates of fetal femur, abdominal circumference, head circumference, or bi-parietal diameter growth during the third trimester did not statistically significantly predict crown-heel length at birth.

Maternal Size at Day 100

Several measures of maternal body size at the end of the second trimester (D100) were statistically significant independent predictors of crown-heel length. Neonatal crown-heel length increased by 0.20 cm for each 1 cm increase in maternal crown-heel length (p=0.003), and 0.20 cm for each 1 cm increase in maternal crown-rump length (p=0.04). An additional 0.09 cm in crown-heel length at birth was predicted by each 10 g of maternal BMC at the end of the second trimester (p=0.02), while each five percent increase in maternal percentage body fat was associated with an increase of 0.23 centimeters in neonatal crown-heel length (p=0.005). These were insignificant when applying the Bonferroni correction (a>0.002).

Maternal Size at Day 150

Maternal size at the end of the third trimester (D150) was significantly associated with infant crown-heel length at birth. Crown-heel length was increased by 0.27 cm for each additional 1 kg of maternal weight (p=0.006), 0.09 cm for each additional 1 cm of abdominal circumference (p=0.03), 0.19 cm for each additional 1-point of BMI (p=0.04), and 0.32 cm for each additional five percent of maternal body fat (p=0.003). Each 10-g increase in maternal BMC at the end of the third trimester predicted an additional 0.09 cm (p=0.02) of crown-heel length at birth and each additional 1 g/cm^2 of maternal BMD was associated with 6.80 cm (p=0.01) of neonatal crown-heel length. These were insignificant when applying the Bonferroni correction (a>0.002).

Maternal Size Change Across the Third Trimester

Neonatal crown-heel length was not statistically significantly associated with any measured changes in maternal morphology during the third trimester.

Interactions Between Maternal Rank and Size on Neonatal Crown-Heel Length

Maternal Size at 100 and 150 Gestational Days. Maternal social rank interacted with maternal crown-rump length to influence offspring crown-heel length at birth (b=0.40, p=0.035). Postestimation commands revealed that among females born to high ranked mothers, neonatal crown-heel length was increased by 0.46 cm for each 1 cm increase in maternal crown-rump length (p=0.002). A concomitant increase for infants born to low ranked dams was not observed (p=0.63). Maternal social rank did not interact with any measures of maternal body size at the end of the third trimester to predict neonatal crown-heel length.

Change in Maternal Size Across the Third Trimester

Increasing maternal BMD during the third trimester interacted with maternal rank to influence infant crown-heel length at birth (b=40.76, p=0.004). While the predicted effect was strong and favored crown-heel length increases specifically among high ranked infants, further investigation of the finding indicated that it was influenced strongly by one maternal-infant pair. No other measures of maternal morphological change across the third trimester interacted with maternal rank in predicting infant crown-heel length at birth.

Predictors of Weight/Crown-Heel Length at Birth

Fetal Growth Rate

No statistically significant effects on neonatal weight for crown-heel length were found from growth of fetal femur, abdominal circumference, head circumference, or bi-parietal diameter.

Maternal Size at Gestational Day 100.

Maternal crown-heel length was measured only at the D100 assessment and predicted neonatal weight/crown-heel length at birth. In addition, maternal weight, abdominal circumference, and BMC at the end of the second trimester predicted neonatal weight/crown-heel length at birth. Weight/crown-heel length was increased by 0.14 g/cm for each 0.5 kg increase in maternal weight (p=0.02) and by 0.10 cm for each 1 cm increase in maternal abdominal circumference (p=0.02) at the end of the second trimester. Additionally, a 1 cm increase in maternal crown-heel length predicted 0.20 cm in infant weight/crown-heel length (p=0.006). These were insignificant when applying the Bonferroni correction (a>0.002). No other measures of maternal body size at the end of the second trimester predicted infant weight/crown-heel length at birth.

Maternal Size at Gestational Day 150

Maternal morphology at the end of the third trimester was a strong predictor of weight/crown-heel length at birth. Weight/crown-heel length was increased by 0.05 g/cm for each 0.5 kg increase in maternal weight (p=0.002), 0.16 g/cm for each 1 cm increase in maternal abdominal circumference ($p<0.001$), 0.28 g/cm for each 1-point increase in BMI (p=0.004), and 0.29 g/cm for each five percent increase in maternal body fat (p=0.019) at the end of the third trimester. Additionally, each 10-g increase in maternal BMC was associated with an additional 0.09 g/cm in weight/crown-heel length (p=0.05). The influence of maternal gestational weight gain and maternal abdominal circumference remained statistically significant after applying the Bonferroni correction ($a>0.002$).

Maternal Change in Size Across the Third Trimester

Maternal BMI change during the third trimester was the only morphological attribute associated with infant weight/crown-heel length at birth. Weight/crown-heel length was increased by 0.28 g/cm for each 1-point increase in BMI (p=0.036) during the third trimester. This was insignificant when applying the Bonferroni correction ($a>0.002$).

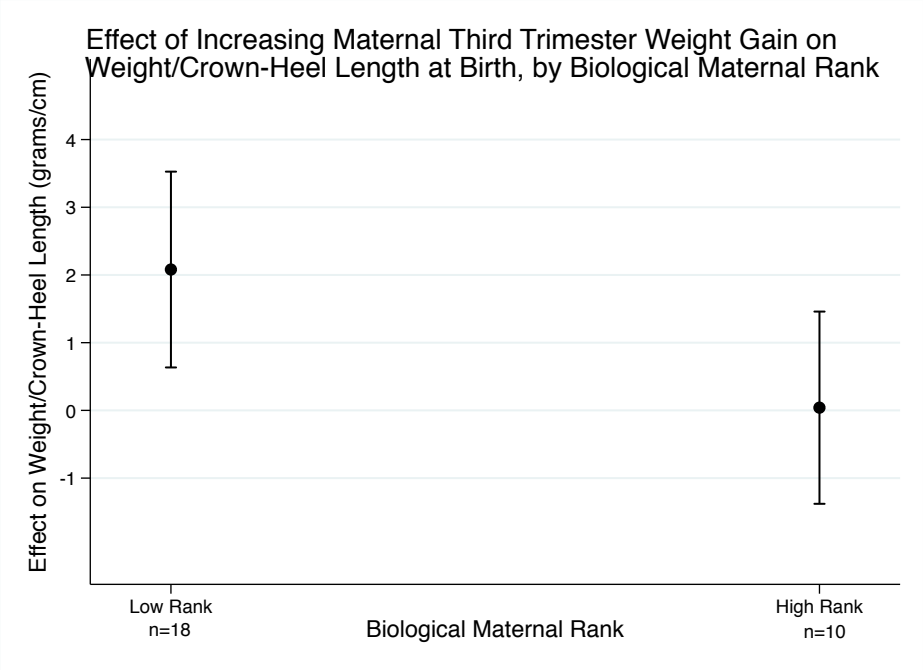
Interactions Between Rank and Maternal Size on Weight/Crown-Heel Length at Birth

No statistically significant interactions were found between maternal social rank and body size at the end of either the second or third trimesters with respect to neonatal weight/crown-heel length.

Maternal rank modified the effects of maternal weight gain during the third trimester on infant weight/crown-heel length at birth (b=-2.04, p=0.04). Postestimation commands revealed that neonatal weight/crown-heel length was increased by 1.04 g/cm

among low ranked females for each 0.05 kg of maternal weight gain (p=0.005). No such effects were observed among neonates born to high ranked dams (p=0.96) (Figure 3). No other interactions between maternal rank and measures of maternal morphological change during the third trimester were associated with infant weight/crown-heel length at birth.

Figure 3.3 Effect of Maternal Third Trimester Weight Gain on Weight/Crown-Heel Length at Birth, by Maternal Rank



Aim 2: To identify associations between maternal rank, maternal body composition, postnatal diet, birth weight and infant growth trajectories during the first 6 postnatal months

Predictors of Postnatal Size and Growth Rates

Maternal Rank Effect on Postnatal Growth Rates During the First Six Months

There were no statistically significant independent effects of maternal rank on growth rates during the first six postnatal months.

Cross-Foster Effect on Postnatal Growth Rates During the First Six Months

There were no statistically significant effects on postnatal growth rates for any studied body dimension as a result of cross-fostering an infant to a mother of opposite biological rank. Specifically, the trajectory of growth was not different for infants born to a high ranked dam, raised postnatally by a low ranked dam, in comparison to peers who were born to a low ranked dam subsequently raised postnatally by a high ranked dam.

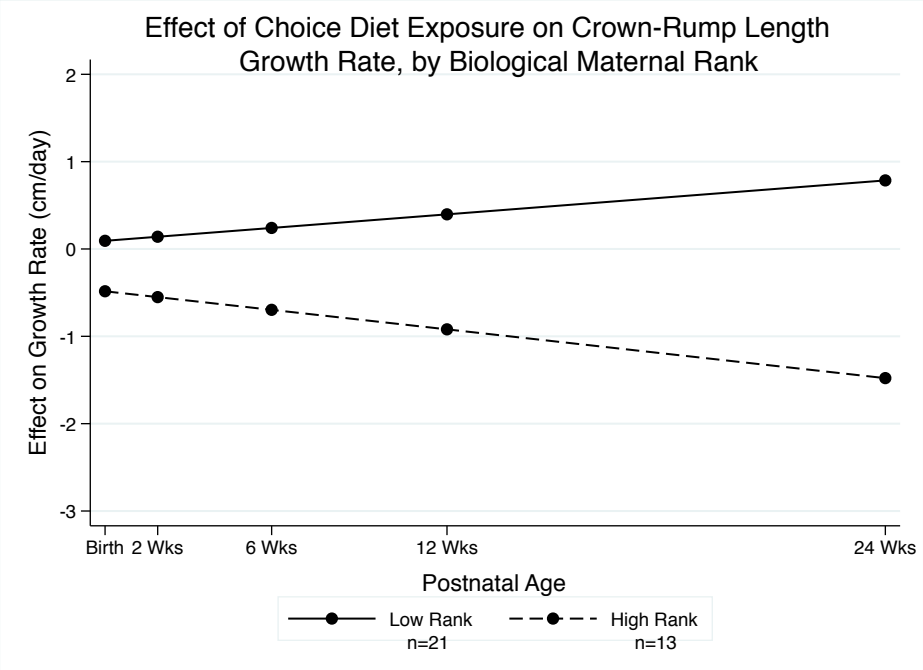
High Calorie Diet Effect on Postnatal Growth Rates During the First Six Months

The dietary exposure protocol did not independently significantly differentiate infant growth rates in the first six postnatal months. Specifically, exposure to a high-calorie diet via breast milk pre-weaning, and chow pellets after weaning did not alter postnatal growth rates in any dimension from birth to six months of age.

Interaction Effects Among Maternal Rank and Diet on Postnatal Growth Rates During the First Six Months

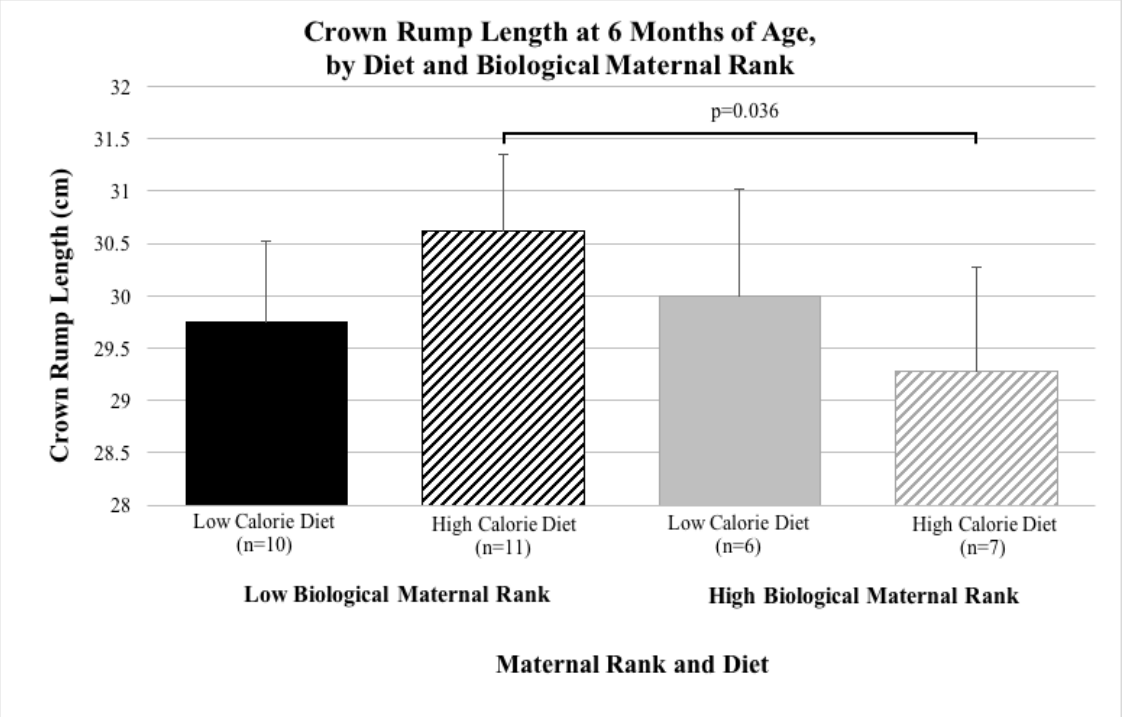
Maternal rank and diet did interact, however, to suggest a trend on crown-rump length accrual (b=-.01, p=0.069; birth weight as a covariate) such that in the presence of the choice diet, infants born of low ranked mothers experienced accelerated growth compared to their peers born of high ranked females at six and 12 weeks of age (Figure 3.4). The effects were on the order of a 0.05 cm/day ($p<0.001$) difference in the rate of crown-rump length accrual, leading to high ranked infants being smaller by 0.7 cm at six weeks of age ($p<0.001$) and 0.6 cm at twelve weeks of age ($p<0.001$). There were no statistically significant differences in body size at any other time point.

Figure 3.4 Effect of Diet and Maternal Rank on Crown-Rump Length Growth Rate



By six months of age, exposure to a choice diet offering access to high calorie chow interacted with maternal rank to suggest emerging differences in crown-rump length (b=-0.009, p=0.069): Among infants with access to the choice diet, females who were born to low ranked mothers were 1.33 cm longer in crown-rump than their peers born to high ranked mothers (p=0.036) (Figure 3.5). There were no differences in crown-rump length among high ranked dams in relation to postnatal diet (p=0.18) or between low and high ranked dams who were reared on the colony standard diet (p=0.55).

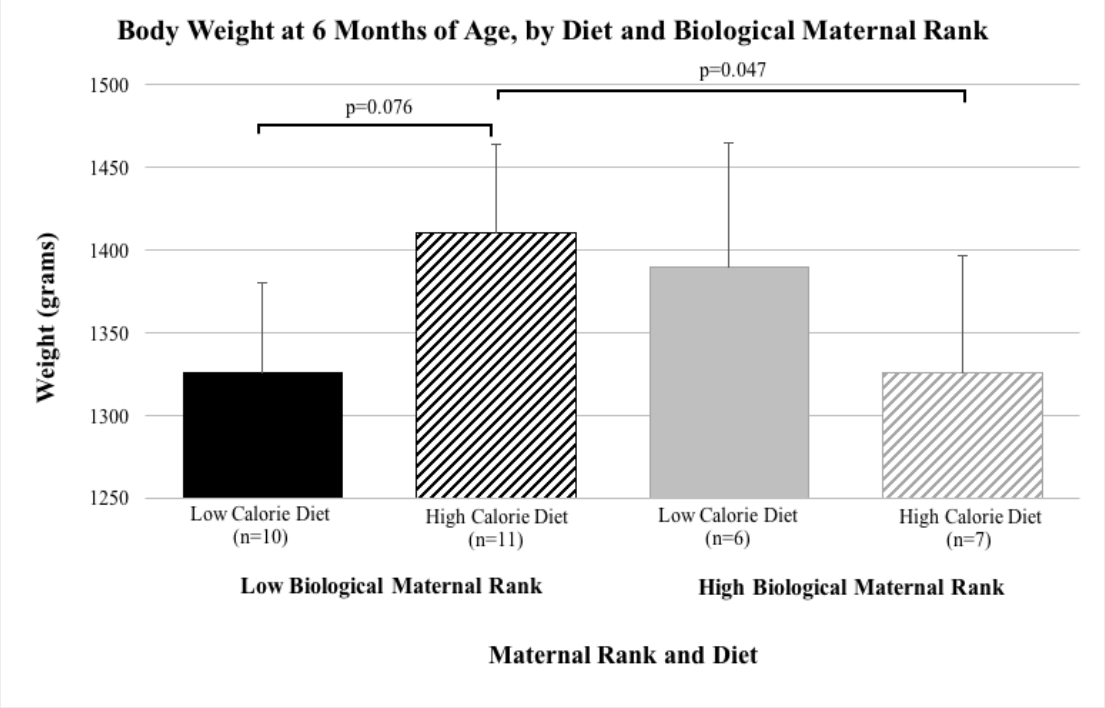
Figure 3.5 Crown-Rump Length at 6 Months of Age, by Diet and Biological Maternal Rank



Interactions between maternal rank and dietary exposure suggested trends in the rates of both BMC accrual (p=0.10) and weight gain (p=0.14) across the first six postnatal months. As published findings report that the effects of maternal rank and dietary intervention tend to emerge later in development (Lewis et al. 1986; Setchell et al. 2001), these infant parameters were assessed at the age of six months to investigate if the trends in growth rate differences would emerge as size differences across time. This was not found for BMC: by six months of age, no significant interaction between exposure to the choice diet and maternal rank was evident (b=-5.12, p=0.29). In contrast, body weight differences had emerged. By six months of age, among infants exposed to a choice diet, those born to low ranked mothers weighed an average of 89.1 g more than their peers born to high ranked mothers (p=0.05) (Figure 3.6). Additionally, among all offspring of low ranked females, those exposed to the choice diet tended to have greater

body weight relative to their peers reared on the prudent, colony standard diet (p=0.07). There were no differences in body weight among offspring born to high ranked dams in relation to postnatal diet (p=0.64), or between low and high ranked infants who were reared on the prudent, colony standard diet (p=0.94).

Figure 3.6 Body Weight at 6 Months of Age, by Diet and Biological Maternal Rank



Maternal Body Size Effects on Postnatal Growth Rates During the First Six Months

Neither maternal body size at the end of the second and third trimesters nor her changes across the third trimester statistically significantly predicted the rate of offspring growth in crown-heel length, crown-rump length, weight for crown-heel length, abdominal circumference, or head circumference during the first six postnatal months. Growth in terms of infant weight, weight for crown-rump length, bone mineral density, bone mineral content, and lean mass were influenced. Specifics are described below.

Infant BMC accrual from six weeks to six months of age was significantly influenced by maternal head circumference, body weight, percent fat and bone strength. For each 1 cm increase in maternal head circumference, infants gained on average an additional 0.02 g/day (p=0.04), and for each 1 kg increase in maternal body weight at D100 and D150, infant BMC was accrued at an additional 0.01 g/day (p=0.004) and 0.01 g/day (p=0.002), respectively. Higher maternal body fat at gestational day 100 was associated with greater rates of BMC accrual, with each five percent increase of maternal body fat associated with an additional 0.012 g/day (p=0.004). A mother's own skeletal integrity predicted her infant's rate of BMC accrual such that for each 10-g increase in maternal BMC at days 100 and 150, infants accrued 0.005 g/day ($p<0.001$) and 0.004 g/day (p=0.004), respectively. Similar increases in BMC accrual rates were seen in response to increased maternal BMD. The effects of maternal weight at D150, BMC at D100, and change in BMC across gestation remained statistically significant after adjusting for the Bonferroni correction ($a>0.002$).

Changing maternal size across the third trimester influenced the rate of infant postnatal gains in weight and bone content. The more dams gained in weight and BMI across the third trimester, the more their infants gained in both weight and weight-for-length across the first six postnatal months. Infant weight gain was greater by 0.4 g per day (p=0.03) for each 0.5 kg of maternal weight gained during pregnancy and 0.6 g per day (p=0.02) for each 1-point increase in BMI. These effects extended to proportional weight gain such that infant weight/crown-heel length was 0.01 g/cm per day (p=0.03) greater as maternal BMI increased and infant weight/crown-rump length gain was 0.015 g/cm per day (p=0.005) greater as maternal BMI increased across the third trimester.

Postnatal accrual of infant bone mineral content (b=0.05, p=0.02) was significantly influenced by maternal pregnancy weight gain. By contrast, maternal increases in percentage fat mass and BMC during the third trimester predicted *decreased* infant BMC accrual from six weeks to six months, with a reduction of 0.005 g/day for each one percent increase in maternal fat mass gained during the third trimester (p=0.04), and for each 10 g maternal BMC increase during the third trimester infants exhibited a reduction in postnatal BMC accrual of 0.018 g/per day ($p<0.001$).

No other measures of maternal body size at the end of the second or third trimester, or changes across the third trimester, statistically significantly predicted the rate of infant lean mass accrual from six weeks to six months of age.

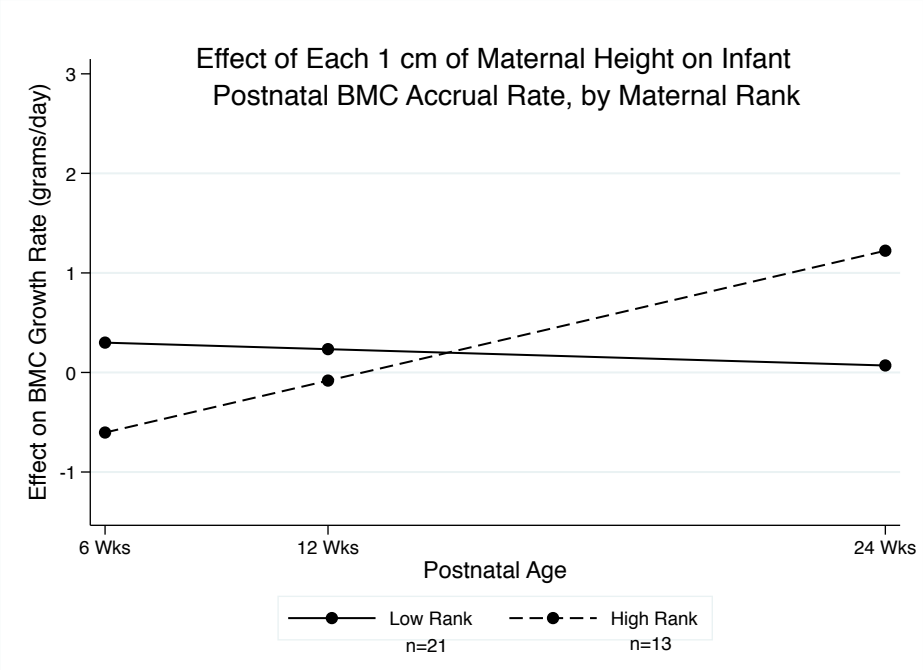
Maternal Rank Interactions with Maternal Body Size Effects on Postnatal Infant Growth Rates

Social rank did not independently moderate maternal body size effects on infant growth rates across the first six postnatal months in weight, crown-heel, or crown-rump length, weight/crown-heel or weight/crown-rump length, abdominal circumference, or head circumference at any measurement time. Social rank did interact with maternal body size to modify infant postnatal bone mineral density and content accrual, in addition to the rate of gain in lean mass. These effects are described below.

Maternal size in crown-heel length and abdominal circumference during pregnancy had effects on offspring postnatal bone growth that were modified by rank. Increasing maternal crown-heel length was associated with increasing rates of postnatal BMC accrual among infants delivered of high-ranked dams by comparison with their peers delivered of low rank dams from age six weeks to six months (b=0.01, p=0.008).

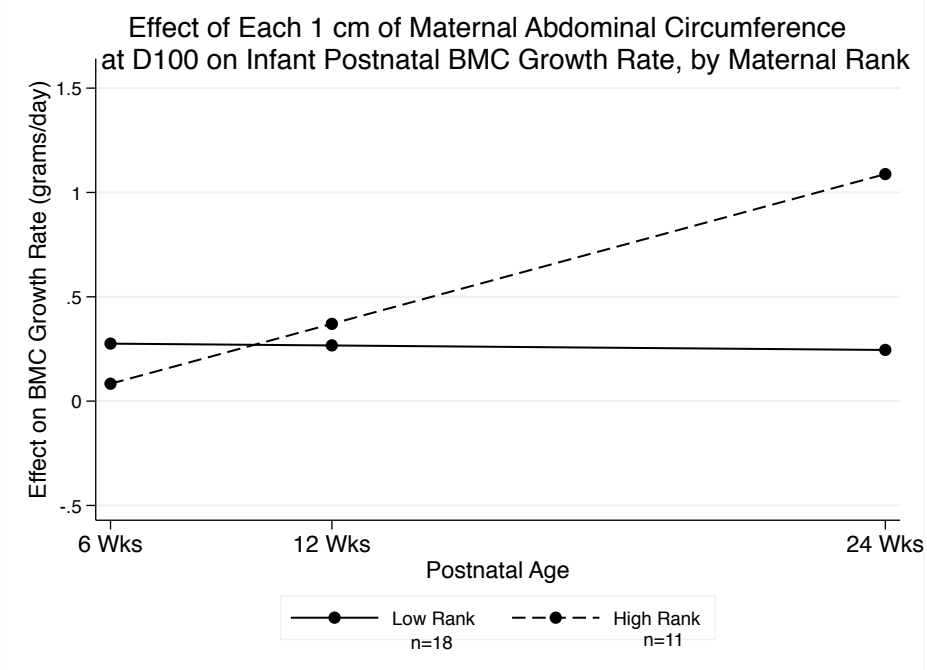
This difference was an average additional 1.223 g of BMC accrual per day for each additional 1 cm of maternal crown-heel length by six months of age among infants delivered of high ranking mothers (p=0.024) (Figure 3.7). A similar effect on BMC accrual was observed in relation to maternal crown-rump length (b=0.008, p=0.025).

Figure 3.7 Maternal Rank Influences How Maternal Height Moderates Postnatal BMC Accrual Rate



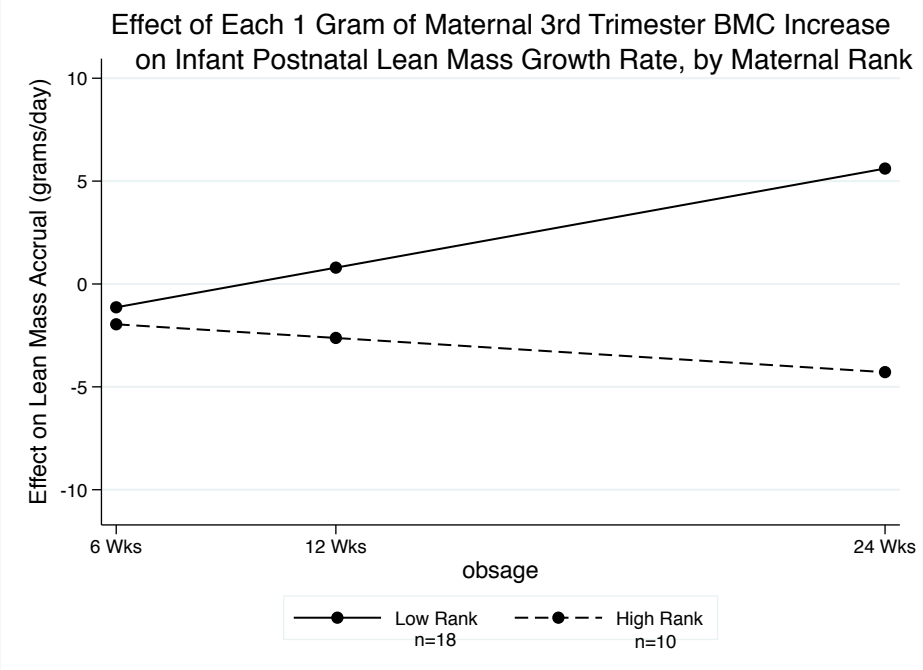
Increasing maternal abdominal circumference at the end of the second trimester was also associated with a greater rate of BMC accrual between six weeks and six months of age among infants of high-ranked as compared to low-ranked mothers (b=0.007, p=0.01). By six months of age this was an average additional 0.843 g/day of BMC for each 1 cm increase in maternal abdominal circumference at D100 (p=0.02) (Figure 3.8).

Figure 3.8 Maternal Rank Influences How D100 Maternal Moderates Postnatal BMC Outcomes



Effects of *changes in dam body parameters* across the third trimester of pregnancy on offspring bone growth were also modified by maternal rank. BMC *loss* during the third trimester was significantly moderated by rank, with infants of *low* ranked mothers exhibiting *increased* BMC deposition rates compared to their peers of higher ranked mothers (b= -0.00001, p=0.049). At 12 weeks of age the estimated daily BMC gain was 3.416 g/day faster (p=0.09) and by six months of age had increased to 9.895 g/day faster (p=0.02). Additionally, for each 1 g of BMC gained by dams during the third trimester, infants born to low ranked mothers had greater rates of postnatal lean mass accrual between the ages of six weeks and six months compared to their peers delivered of high ranking dams (b=0.029, p=0.03) (Figure 3.9).

Figure 3.9 Maternal Rank Influences How Maternal Third Trimester BMC Moderates Postnatal Lean Mass Rate



Birth Weight Effects on Postnatal Growth Rates

Infants who were larger at birth grew more rapidly postnatally in both weight and lean body mass. Each 10 g of birth weight predicted an average weight gain of 0.06 g/day (p=0.003) with an increased rate of lean mass accrual of 0.17 g/day (p=0.001) from six weeks to six months of age.

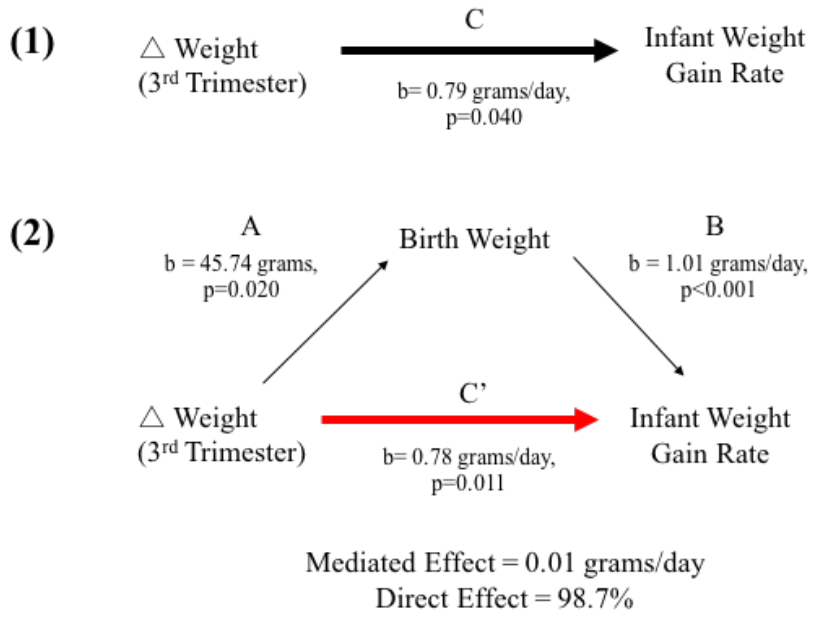
Are Birth Weight Effects on Offspring Postnatal Growth Mediating Maternal Prenatal Effects or are They Independent?

It is of interest to investigate whether birth weight is an independent predictor of postnatal growth or is merely a proxy for prenatal growth, summarizing effects from maternal size and/or pregnancy experiences. The potential effect of birth weight as a mediator of prenatal exposures was investigated (Judd and Kenny 1981). This approach requires that a mediator be independently predicted by a variable that also predicts a

common outcome. In the present study, birth weight was a potential mediator of both maternal third trimester pregnancy weight and BMI gain on the infant postnatal weight trajectory. The empirical question is whether birth weight is merely a proxy for the effects of maternal size on fetal growth, as summarized in birth weight, or has an independent predictive power for the rate of postnatal weight growth?

As an independent predictor, every 1 g of birth weight predicted an additional 0.0006 g/day of postnatal weight gain during the first six months (p=0.003). As an independent predictor, 1 kg of maternal third trimester weight gain predicted both 45.7 g of infant birth weight (p=0.02) and 0.79 g/day in infant postnatal weight gain (p=0.04) during the first six postnatal months (Figure 3.10, Panel 1). When birth weight was added to the maternal weight gain regression as a covariate, maternal weight gain accounted for 0.78 g/day (p=0.01) of infant postnatal weight gain. Hence, the indirect effect of birth weight accounted for 1.3% of the influence of maternal third trimester weight gain on the rate of infant postnatal weight gain, indicating that birth weight had a minimal effect as a partial mediator (Figure 3.10, Panel 2).

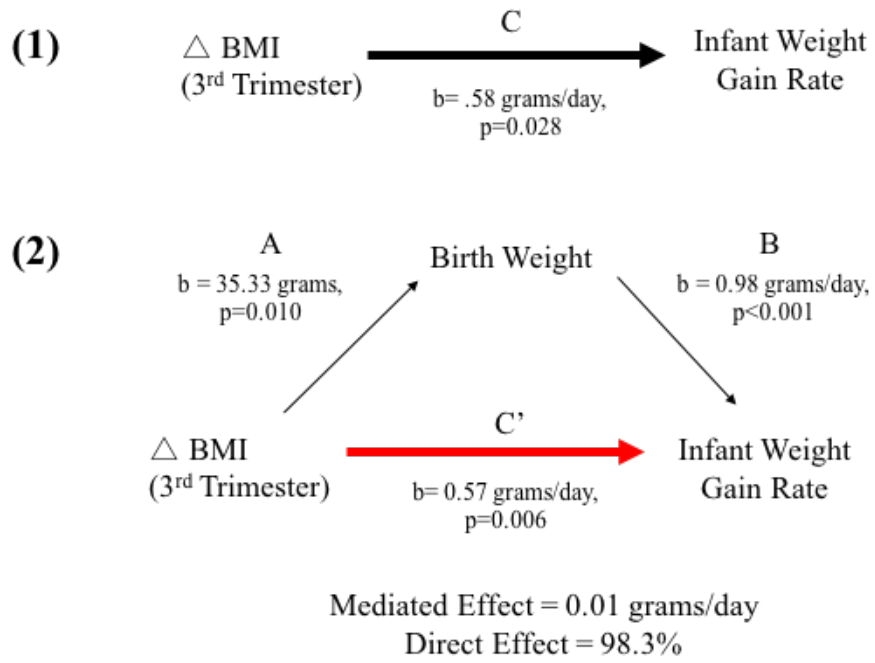
Figure 3.10 Birth Weight as a Mediator of Late Gestation Weight Change Effects on Postnatal Infant Weight Gain



Likewise, as an independent predictor, each 1-point increase in maternal BMI during the third trimester was associated with an additional 35.3 g of infant birth weight (p=0.01) and 0.58 g per day of infant postnatal weight gain during the first six postnatal months (p=0.01) (Figure 3.11, Panel 1). When birth weight was added as a covariate, maternal prenatal BMI gain accounted for 0.57 g/day (p=0.006) of infant postnatal weight gain. Hence, the indirect effect of birth weight accounted for less than two percent of the influence of maternal third trimester weight gain on the rate of infant postnatal weight gain, indicating that birth weight had a minimal effect as a partial mediator (Figure 3.11, Panel 2).

Taken together, these results identify strong direct effects of late pregnancy maternal weight and BMI increases on the subsequent postnatal infant growth trajectory in weight. By contrast, birth weight appears to have had a independent direct effect on infant lean body mass growth.

Figure 3.11 Birth Weight as a Mediator of Late Gestation Maternal BMI Changes on Postnatal Infant Weight Gain



Crown-Heel Length at Birth Effects on Postnatal Growth Rates

Crown-heel length at birth predicted only the rate of lean mass accrual from six weeks to six months of age, with each 1 cm of crown-heel length at birth associated with 0.58 g/day (p=0.01) of lean mass accrual from six weeks to six months of age. There was no basis to investigate mediation effects through birth length as no measured parameters met the criteria (Baron and Kenny 1986).

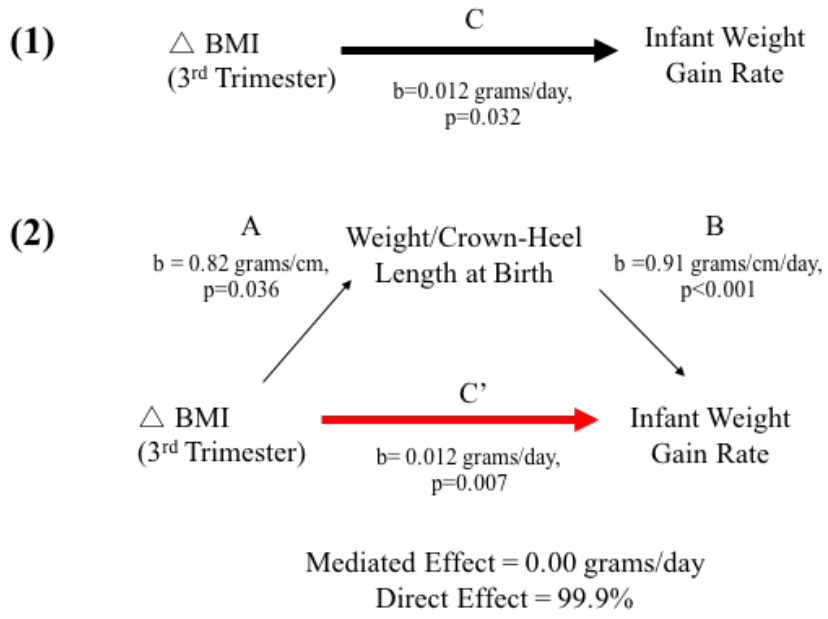
Weight/Crown-Heel Length Effects on Postnatal Growth Rates

Weight/crown-heel length at birth predicted the rate of weight gain from birth to six months, with each 1 g/cm of weight/crown-heel length at birth predicting an additional 0.23 g/day (p=0.004) in postnatal weight gain from birth to six months of age.

Does Weight/Crown-Heel Length at Birth Mediate How Maternal Body Size Moderates Female Offspring Postnatal Growth Trajectories?

Like weight, the proportional variable, weight/crown-heel length at birth, also mediates maternal pregnancy BMI and weight change effects on the rate of infant postnatal weight gain from birth to six months of age. As an independent variable, neonatal weight for crown/heel length predicted postnatal infant weight accrual of 0.23 g per day (p=0.004). Increasing maternal BMI during the third trimester independently predicted both an additional 0.82 g of infant weight/crown-heel length at birth (p=0.036) and 0.012 g per day of infant postnatal weight gain during the first six postnatal months (p=0.03) (Figure 3.12, Panel 1). When weight for crown-heel length at birth was entered into the model, it independently predicted 0.91 g/day of postnatal weight gain ($p<0.001$), but the direct effect of maternal BMI change and weight/crown-heel length at birth on the rate of postnatal weight gain was unchanged, at 0.012 g per day (p=0.007) (Figure 3.12, Panel 2). Thus, when birth weight for crown-heel length was added into the model with maternal pregnancy BMI, direct pregnancy effects were not attenuated, with weight/crown-heel length at birth mediating less than one percent of the influence of maternal third trimester BMI change on the rate of infant postnatal weight gain.

Figure 3.12 Effect of Weight/Crown-Heel Length at Birth on How Third Trimester BMI Change Moderates Postnatal Weight Gain



Chapter 3 References

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CHAPTER 4 DISCUSSION

Summary of Findings

This is the first prospective study of fetal growth among Rhesus macaques (*Macaca mulatta*) relative to maternal social rank, which has been previously validated as a translational model for examining physiological outcomes stemming from chronic psychosocial stress imposed by social subordination (Michopoulos et al. 2012a). The design is notable for its attention to offspring sex and repeated measures' assessments of maternal and infant body size and composition across the intrauterine and postnatal periods. A postnatal dietary intervention was added to assess potential latent prenatal effects from rank-related *in utero* exposure to heightened glucocorticoids (Michopoulos et al. 2012a) that might manifest in the form of differential growth responses to postnatal caloric challenge. A postnatal cross-over design permitted control for pre- versus postnatal maternal rank effects. This design addresses a number of limitations in previous studies. Total sample size in the present study (n=35), while large in comparison to many nonhuman primate studies, is more modest by comparison with studies in humans and may have limited statistical power to identify all significant effects. Overall, the pattern of results reflects how the intrauterine milieu lays the foundation for postnatal developmental trajectories. Key findings are described below and summarized in Table 4.1.

Table 4.1 Summary of Key Findings

Influence	Fetal Growth	Birth Phenotype	Postnatal Infant Growth Rate
Maternal Rank	None	None	None
Choice Diet Exposure	None	None	None
Cross-Fostering	None	None	None
Maternal Morphology at D100	None		

Influence	Fetal Growth	Birth Phenotype	Postnatal Infant Growth Rate
+ W, AC, % FM, CHL, BMC		+ BW	
+ % FM,CHL, CRL, BMC		+ CHL	
+ W, AC, CHL		+W/CHL	
+ W, AC, BMI, %FM, HC, BMC, BMD			+ BMC
Maternal Morphology at D150	None		
+ W, AC, BMI, % FM, BMC, BMD		+ BW	
+ W, AC, BMI, %FM, BMC, BMD		+ CHL	
+ W, AC, BMI, %FM, BMC		+BW/CHL	
+ W, AC, BMI, %FM, HC, BMD			+ BMC
Maternal Third Trimester Change			
+ AC	+ BPD		
+ W, BMI		+ BW	
+ BMI		+ BW/CHL	
+W, BMI			+ W
+ BMI			+ W/CHL
+ BMI			+ W/CRL
+ % FM			+ BMD
+ W, BMI			+ BMC
+ % FM, BMC			- BMC
Interaction of Social Rank and Maternal Morphology at D100	None		
High rank*CRL		+ CHL	
High rank*CHL, High rank*CRL			+ BMC
High rank*AC			+ BMC
Interaction of Social Rank and Maternal Morphology at D150	None	None	None
Interaction of Social Rank and Maternal Third Trimester Morphological Change			
Low rank*W		+ BW/CHL	
High rank*CRL		+ CHL	
High rank*AC			+ BMC
Low rank*BMC loss			+ BMC
Low rank*BMC gain			+ Lean Mass
Interaction of Social Rank and Choice Diet Exposure	None	None	
Low rank*choice diet (effects on growth rate & absolute size)			+ CRL + W

Note: Reported at $p \leq 0.05$

As assessed by fetal ultrasound, postnatal anthropometry and DXA, there were no significant independent effects of maternal rank, dietary exposure, or maternal postnatal cross-fostering on fetal growth, birth size, or postnatal growth rates across the first six

months. Maternal rank did have effects on fetal and infant growth rates in interaction with maternal size during pregnancy, and in response to the postnatal dietary intervention exposing infants to a high calorie diet alternative.

During the prenatal period, only fetal bi-parietal diameter was significantly independently influenced by maternal morphology in this sample. Increasing maternal abdominal circumference across the third trimester was associated with concurrent acceleration in bi-parietal diameter. A trend in the interaction term between age and maternal rank identified this acceleration as occurring among fetuses of lower ranked dams (p=0.06), who also exhibited modestly increased head circumference at birth (p=0.12). Whether this relationship represented a direct anatomical reflection of fetal head dimensions in maternal abdominal circumference (larger fetal heads leading to larger maternal abdominal circumferences) and/or a more subtle metabolic relationship between the mother and her fetus is not known. For example, this late term acceleration of growth may represent brain maturation just prior to parturition, and have no relationship directly with how maternal abdominal circumference is mediating the skeletal growth of the head.

Indicators of both maternal lifespan health (increased maternal crown-heel length, BMC) and her positive energy balance during pregnancy (increased weight, percentage body fat, BMI) were significantly positively associated with her neonate's size: increasing maternal size predicted increasing birth weight, crown-heel length, and weight for crown-heel length. The relationship between positive energy balance during pregnancy and neonatal size suggests that, for example, increased maternal weight gain during the third trimester is a reflection of growth in the fetus itself. For example,

maternal weight gain during the third trimester is positively correlated with infant birth weight (r=0.42). In turn, neonatal size positively predicted the infants' own rates of postnatal weight gain and lean mass accrual. This observation suggests that offspring growth rates are set *in utero* and continue postnatally. This is in line with observations from in-vitro fertilization studies in humans that document that the culture media used during the implantation process predicts birth weight and postnatal growth rates (Kleijkers et al. 2014).

These maternal/fetal morphology relationships were moderated, however, by maternal social rank, suggesting that the intrauterine environment modulated how maternal morphology was translated into size at birth for offspring born to low- as compared to high-ranked mothers. Specifically, infants born to high ranked dams had increased crown-heel length at birth in response to markers of maternal lifespan health (maternal crown-rump length, head circumference, BMD), while those born to low ranked mothers exhibited increased birth weight and birth weight for crown-heel length in response to markers of current maternal energy balance (weight, BMI).

Similarly, maternal rank moderated the postnatal effects of maternal morphology on infant growth, suggesting persistent effects from intrauterine conditions across early development. The rate of infant BMC accrual from six weeks to six months of age was accelerated among infants born of high ranked mothers relative to their peers born of low ranked mothers with increasing maternal crown-heel length and abdominal circumference at the end of the second trimester, and increasing fat mass percentage and BMD across the third trimester. These effects were not experienced by low-ranked infants; instead their postnatal growth rates were predicted by whether their mothers gained or lost BMC

during the third trimester. Postnatal BMC accrual was accelerated for low ranked infants whose mothers lost BMC during late pregnancy, suggesting that mothers leached calcium and phosphate from their own skeletal tissue to meet the fetal developmental infant needs (Kent et al. 1993) that subsequently was reflected by catch-up growth at the physiological level in the form of accelerated postnatal bone mineralization. In contrast, subordinate infants born to mothers who gained BMC during late gestation exhibited accelerated lean mass accrual. This may more generally reflect that the bones of these infants were more mineralized at birth and that subsequent catch-up growth favored weight gain in the form of energetically active skeletal muscle. Taken together, this suggests that maternal BMC during pregnancy contributes to altered postnatal growth strategies at the tissue level that were not captured using traditional anthropometry.

Finally, maternal social rank moderated postnatal growth in response to the 'choice' diet that included at-will access to a higher-calorie alternative such that accelerated postnatal crown-rump length and weight gain occurred among infants delivered of low ranked mothers by comparison with their peers delivered of high ranked mothers. After six months of postnatal high calorie diet exposure, infants born to low ranked dams had both greater crown-rump length and increased body weights compared to the offspring of high ranked dams.

In combination, the overall results suggest that higher maternal rank 'permitted' more robust expression of infant bone growth, including its genetic underpinnings, while offspring of lower maternal rank are on a trajectory that includes catch-up growth and a proclivity for resource storage at the expense of skeletal strength. These *in utero* effects are measurable at the tissue level postnatally, and exacerbated in response to caloric

exposure. One interpretation of this outcome is that low maternal rank during prenatal development acted as a chronic intrauterine exposure to glucocorticoids and other stress related signals (e.g., proinflammatory cytokines). In combination with the finding of reduced BMC accrual at this age among low-ranked infants, an underlying physiological dysregulation of tissue accumulation may have occurred. Further, this postnatal growth pattern may be analogous to 'catch-up' growth seen in human infants, often associated with obesity across the lifespan.

The study outcomes are in line with the study hypotheses regarding growth effects associated with chronic intrauterine exposure to glucocorticoids attendant to low maternal rank during prenatal development. These data are unique by comparison with previous nonhuman primate studies, in terms of both study design and analytical strategies.

Comparison of Results to Previous Studies in Old World Primates

Previous reports among contemporaneously-aged Old World nonhuman primates focused independently on the three exposures in the present study: 1) maternal social rank, 2) maternal morphology, and 3) postnatal high calorie diet exposure, without considering them as a system. Comparing the present results with these earlier studies is complicated not only by this difference in study design and analysis, but in terms of the ethological relevance of comparisons across species of nonhuman primates. There is questionable validity in simple comparisons between study samples that differ in adaptive strategies to local ecologies which include long term differences in locomotor, dietary and social structural patterns, population demography and breeding patterns. It is not entirely clear how these fundamental distinctions contribute to physiological

discontinuities. With these caveats the present results are seen to be both similar to, and distinctive from, earlier work as follows.

Social Rank

Simple independent effects of maternal rank on fetal or postnatal offspring morphology were not observed in the present study. This is in agreement with studies on weight among mixed-sex cohorts of captive baboons (Altmann and Alberts 1987), captive Rhesus macaques (Hinde 2009), and captive Tonkean macaques (Sanna et al. 2015) or crown-rump length in semi free-ranging mandrills (Setchell et al. 2001) during early infancy. In contrast, Bowman and Lee (1995) reported increased weight at birth followed by decreased rate of weight gain in the first 12 weeks of life among high ranked infants in a mixed-sex cohort of captive Rhesus macaques. Likewise, Setchell et al. (2001) documented increased weight-for-age among a mixed-sex cohort of infant baboons born to high ranked dams. These conflicting results may illustrate the importance of an unstudied interaction between rank and maternal size that could be confounding all of these earlier studies.

Maternal Morphology

The present study adds to the literature describing influences of maternal morphology on offspring body size and growth in infancy among Old World primates, and females in particular. Only six studies have reported on infant morphology in relation to maternal morphology at ages contemporaneous to our study (Bercovitch et al. 2000; Bowman and Lee 1995; Hinde et al. 2009; Price et al. 1999; Rivera et al. 2015; Setchell et al. 2001). These publications focused primarily on body weight outcomes among

captive macaques. The most detailed report, and the only previous documentation of offspring crown-rump length described semi free-ranging mandrills (Setchell et al. 2001).

Specifically, among the present sample*, dams of increasing weight, both at the end of the second and third trimesters and across the third trimester, delivered female infants of increasing birth weight who subsequently gained weight more rapidly postnatally*. Similar findings are reported regarding birth weight (Bowman and Lee 1995; Price et al. 1999) and postnatal weight gain (Bowman and Lee 1995) among mixed-sex cohorts of captive Rhesus macaques. Increasing dam pre-gravid weight, but not gestational weight gain, predicted higher infant weight at both 7.5 months of age in a mixed-sex cohort of captive Japanese macaques (Rivera et al. 2015), and at 12 months of age among captive and free-ranging Rhesus macaques (Bercovitch et al. 2000).Finally, increased maternal weight at one month postpartum predicted increased weight at one and 3.5 months of age among individuals from Hinde et al's mixed-sex cohort of Rhesus macaques (Hinde et al. 2009). In line with our findings, no association between pre-gravid dam weight and crown-rump length-for-age was found among the mandrill study of Setchell et al. (2001). As infant sex significantly modifies maternal morphology effects on fetal growth rates, direct comparisons among these studies is not possible (Lampl et al. 2010).

Increasing maternal pre-gravid BMI predicted accelerated infant postnatal weight gain in the present study sample, with no effect on postnatal crown-heel or crown-rump length gains. Similar positive relationships were reported in weight-for-age among a mixed-sex cohort of free ranging Rhesus macaques aged between one and 24 months (Johnson and Kapsalis 1995), with a parallel lack of findings for crown-rump length-for-

age from birth to eight months of age in a mixed-sex cohort of mandrills (Setchell et al. (2001)

Maternal crown-heel length predicted infant birth weight. This agrees with the observation by Bowman and Lee (1995) of a positive correlation between maternal crown-rump length and birth weight among captive female Rhesus macaques.

High Calorie Diet

No previous study design has looked specifically at effects on infant size and growth of exposure to maternal rank prenatally followed by postnatal caloric density, thus no direct comparisons are possible with our data. In our sample, *postnatal body composition was not independently predicted by postnatal exposure to the high calorie choice diet, but these results were modified when stratifying by social rank such that socially subordinate infants gained more weight and crown-rump length when challenged with a high calorie diet in comparison to their peers born to high ranked mothers*. Only one previously published study described infant morphology in response to a dietary intervention restricted to the postnatal period, in which accelerated postnatal weight gain prior to weaning was found among infant baboons fed a high calorie, high fat formula through 16 weeks of age (Lewis et al. (1986).Mixed-sex cohorts of Japanese macaques exposed to high calorie dietary interventions both pre- and postnatally were characterized by increased body fat and decreased lean mass by age three months compared to their unexposed peers (Grant et al. 2011; McCurdy et al. 2009).

Comparisons Across Studies

Differences in study design, species-typical behavior and local ecologies make meaningful comparisons across species of nonhuman primates challenging. Specific

aspects of design that make direct comparisons to our present study results difficult include infant sex, maternal and infant measurement timing and the focus on maternal rank and timing of dietary intervention. The present study focused on outcomes exclusively among females through the first six months of life, while earlier reports come largely from mixed-sex cohorts. Our maternal morphology measures were time-specific, captured at the end of the second and third trimesters which inherently capture aspects of the fetus. While several comparison studies had access to preconception measures of maternal body size, these data were not analyzed from this perspective. The dietary intervention in our study was implemented during the postnatal period with a protocol that offered subjects a choice between high and low calorie chow, while other reports involve birth outcomes among female dams with chronic (>4 years) exposure to only a high calorie diet; these scenarios are not interchangeable. Given the variance in daily caloric intake across females observed in small social groups of rhesus monkeys, simply providing an obesogenic diet does not necessarily mean females are consuming similar amount of calories and future quantification of calorie intake will be critical to assessing dietary effects in follow up studies.

Between species comparisons face inherent variation in findings across studies that likely arise from differences in habitat; this includes the stability of nutritional resources, risk from environmental conditions, and interactions between animals. For example, hurricanes, tornadoes, and less severe fluctuations in climate are associated with increased mortality and reductions in food availability among free-ranging and semi-free ranging nonhuman primates (Behie and Pavelka 2012; Pavelka et al. 2003). In contrast,

colony-dwelling nonhuman primates live in compounds that generally offer protection from extreme shifts in weather and are protected from nutritional insecurity.

Physiological factors confounding inter-species comparisons include influences from fundamental biological distinctions tied to features such as sexual dimorphism and locomotion that reflect broader trends in their own species evolution with divergence from a common ancestor occurring at least six to eight million years ago (Steiper et al. 2004), if not longer (Raaum et al. 2005). For example, the heightened sexual dimorphism in mandrills is evidence of selection of sex-specific physical growth strategies (Badyaev 2002) which suggests that their developmental trajectories may be highly different than those we might observe in less sexually dimorphic species. Similarly, the quadrupedal nature of baboons is revealed in their species-specific geometry of the femur (Hansen et al. 2009) which reflects an alternate pattern of mechanical loading than primarily arboreal Old World nonhuman primates who have less body weight. These adult features may well reflect very different growth patterns in earlier development.

Variations within species must also be considered when undertaking inter-study comparisons. Biological aspects of population isolation and adaptations to local ecologies are reflected in phenotypic variation in captive colonies derived from different founder populations. For example, the major histocompatibility complex (MHC) loci is considered to be highly maintained across species by balancing selection. An examination of the loci in five geographically isolated populations of Rhesus macaques in western Sichuan, China, however, documented substantial variation (Yao et al. 2014). The effect of founder population distinction is reflected in both the morphological phenotypes (Paterson 1996) and genotypes (Kanthaswamy and Smith 2004) of Rhesus

macaques that are part of biomedical-oriented research colonies, pointing towards the likelihood that disagreements in study outcomes are tied to underlying un-measured variability between study cohorts. For example, Chinese-derived Rhesus macaques are significantly longer in length than Indian-derived Rhesus macaques (Hamada et al. 2005), a representation of within-species adaptations to local ecologies. As our study and others (Price and Coe 2000; Price et al. 1999) documented strong relationships between maternal and infant morphology, successive generations of within-colony breeding could lead to unique colony-specific phenotypes that are reflected in research outcomes.

As the present study design was conceived as a translational analog to a specific human scenario, the lack of comparable nonhuman primate studies should not be surprising. Of greater relevance to the study goal is how the present results compare to findings among human maternal-infant pairs.

Comparison of Results to Previous Studies in Humans

Reports describing associations between *birth weight as a marker of fetal growth, and subsequent infant growth trajectories,* are abundant, but only a limited body of work has specifically examined fetal growth with objective quantitative measures (see review in Norris and Cameron 2013). Ultrasonography permits an anatomical record with which to compare postnatal size measures and thereby directly address relationships between fetal exposures for their impact on both pre- and postnatal growth. Previous reports among human infants have tended to focus independently on the three exposures in the present study: 1) maternal morphology, 2) experience of psychosocial stress, and 3) high calorie foods, with less attention to the interactions among these exposures. Comparing the present results with studies conducted among human infants is complicated not only

by heterogeneity in study design and analysis, but also in terms of the ethological relevance of cross-species comparisons even in the context of the translational relevance between humans and nonhuman primates (Phillips et al. 2014). With these caveats the present results are seen to be both similar to, and distinctive from, earlier work among human fetuses and infants. Considering their accelerated life history, the present results following Rhesus macaques to six months of age is comparable to human studies that follow infants to the age of approximately two years of age. The importance of this early developmental period – colloquially tagged as the first 1,000 days – for lifespan health, and in particular obesity risk, is increasingly recognized (Bhutta et al. 2012; Woo Baidal et al. 2016).

Direct Correlations between Fetal and Infant Growth Rates

Fetal growth rates of the femur, abdominal circumference, head circumference, and bi-parietal diameter were not independently significantly associated with neonatal size or rates of postnatal growth in any anthropometric measurement during the first six months of life. Longitudinal studies across from pre- to postnatal life are rare to date, with a recent systematic review by Norris and Cameron (2013) locating 29 studies where 24 reports represented outcomes form only five cohorts. Two studies identified in this review focused on the outcomes examined by the present research (Mook-Kanamori et al. 2011; Vik et al. 1996), and only one other known publication to-date has tackled this issue (Harvey et al. 2012). Among a sample of British infants from Southampton, a positive correlation was observed between third trimester femur growth and postnatal crown-heel length growth during the first six months of infancy that waned by one year of age (Harvey et al. (2012). These data suggest that there may have been transient

effects among the Rhesus in the present study during the first eight postnatal weeks that waned by six months of age. Such effects may not have been identified due to the study protocol, which did not include data collection at that time point. Additionally, the constant, on-demand breast feeding among the nonhuman primate subjects contrasts with dietary patterns among humans that may be associated with differences in growth patterns across (Griffiths et al. 2009). In contrast, among the Dutch infants from the Generation R cohort, the rate of femur growth during both the second and third trimesters predicted the rate of body length growth through age two years (Mook-Kanamori et al. 2011). Finally, among a prospective cohort of infants from Norway and Sweden, Vik et al. (1996) documented rapid length growth from birth to six months of age among infants characterized by reduced femur length growth during the third trimester who were born to mothers who smoked during pregnancy, relative to peers born to non-smoking mothers. These variations among the two human samples describe no simple 'human pattern' and may well reflect inter-subject individual variability evident from 'percentile' crossing described during infancy whereby the rate of growth is accelerating and decelerating in comparison to growth reference charts (Mei et al. 2004). Moreover, it cannot be excluded that taxonomic differences between primate and human skeletons may be involved, whereby the proportional differences in leg growth among bipedal, longer-legged humans follows a different trajectory than that among quadrupedal and arboreal primates.

In lieu of crown-heel length, a better comparative frame for examining skeletal growth may be based on the developmental biology of bone through measurements of BMC. Two longitudinal human cohort studies document carryover effects from fetal

femur growth rate to postnatal BMC accrual (Harvey et al. 2012; Heppe et al. 2014). In the Dutch Generation R Cohort, fetal femur growth rates in both the second and third trimesters not only predicted the rates of both postnatal weight and height gain from birth to six years of age, but did so for BMC assessed by DXA at age six years (Heppe et al. 2014). Similarly, Harvey et al. (2012) documented associations between postnatal BMC accrual assessed by DXA during the first four years of life, and both fetal femur growth and change in abdominal circumference among a mixed-sex cohort from Southampton. Here, the relationship was strongest with BMC at four years of age in comparison to previous yearly assessments. Our study cannot address these longer term relationships. Timing effects were also evident in the human study, such that fetal abdominal circumference changes early (between 11 and 19 weeks) rather than later (between 19 and 34 weeks) gestation predicted the rate of BMC accrual. As our study only measured fetal growth during the third trimester, we are unable to examine similar timing effects. Additionally, while the rate of BMC accrual in our study was not predicted by fetal growth indicators, it was strongly influenced by maternal morphology and the interaction of maternal social rank and morphology. This suggests that intrauterine growth *influences postnatal BMC accrual* although the specificity of our measurements or the timing of fetal growth assessment was not sensitive enough to capture the relationship.

Maternal Morphology, Fetal and Infant Size and Growth

Maternal weight and BMI in mid- to late-pregnancy, and their respective changes across the third trimester, predicted neonatal birth weight and the rate of postnatal infant weight gain in this cohort of female Rhesus macaques. Similar results have been reported for weight among human neonates (Abrams and Selvin 1995; Yan 2015; Yu et al. 2013),

with third trimester maternal weight gain, in particular, a strong predictor of infant birth weight (Abrams and Selvin 1995; Strauss and Dietz 1999), even among samples confined to female infants (Wander et al. 2015). The importance of infant sex may be reflected in the contradictory results observed among maternal-infant pairs in the Minneapolis-St. Paul, MN-based Diana project, in which trimester-specific effects of maternal weight gain were analyzed without stratifying the sample by infant sex (Brown et al. 2002). More limited data are available for assessing the effects of maternal morphology on postnatal infant growth rate. Among infants in the Avon Longitudinal Study of Pregnancy and Childhood (ALSPAC) cohort, the rate of postnatal weight gain during the first two years of life was not predicted by maternal pre-pregnancy BMI or weight (Ong et al. 2000). The distinction between our results and these may reflect heterogeneity in study design, where all of our measures of maternal weight and BMI reflect the effects of early fetal tissue accumulation whereas Ong et al. (2000) was privy to measures of maternal body size prior to conception. These differences may also reflect species-specific modes of maternal morphological influence on infant weight gain.

Increasing maternal BMI during the third trimester was associated with increased weight for crown-heel length at birth, in addition to continued *accelerated weight for crown-heel length growth rate* during the first six months of life. No analog is found in the human literature, but maternal pre-pregnancy BMI was positively correlated with infant percent fat mass in the Generation R Study of Dutch maternal-infant pairs (Ay et al. 2009). Weight for crown-heel length is a corollary measure of infant body composition, though whether these outcomes can be directly compared between humans and macaque infants is unclear.

Among these female Rhesus macaques, *infants with higher birth weight grew more rapidly postnatally in weight, but did not exhibit accelerated BMC accrual rates* across the first six months of life. Both low and high birth weight are associated with rapid weight gain in infancy in humans (Casey et al. 2012; Dennison et al. 2006; Sacco et al. 2013; Yu et al. 2011; Zhao et al. 2012), and in combination may underlie the J- (Parsons et al. 2001) or U-shaped (Newby et al. 2005) association between birth weight and later risk of obesity. Our finding of an association between birth weight and infant weight gain is analogous to the human literature, and suggests that these Rhesus infants may be at heighted risk for overweight and obesity. Previous studies conducted among human infants have observed a relationship between size or growth rate in infancy and skeletal integrity among older children and adults. For example, Demerath et al. (2009) documented that accelerated weight gain from birth to age two was associated with accelerated advanced skeletal maturity, which may indicate that birth size predicts accelerated skeletal fusion. Jones and Dwyer (2000) noted an association between birth weight and birth length with BMD at age eight, while Vidulich et al. (2007) observed weight and length at one year of age to predict BMC at age ten. Similarly, birth weight and weight at one year of age were associated with BMC and BMD among approximately 70 year old members of the Herfordshire cohort (Dennison et al. 2005). Outcomes addressing bone quality during infancy and early childhood in humans were not identified; this may represent a gap in the literature, or that birth size influences on skeletal integrity appear later in development.

Maternal Psychosocial Stress, Fetal and Infant Size and Growth

Maternal social rank was not an independent predictor of fetal or postnatal growth, but rather interacted with measures of maternal morphology and postnatal diet to predict postnatal growth rates in our sample. Maternal social rank was a proxy for chronic maternal stress in the present study. Assuming that chronic stress should be reflected in fetal and infant growth rates, the negative results could be interpreted to imply a lack of validity of rank as a marker of chronic stress that can be passed across the feto-placental barrier. Alternatively, the results could be seen as identifying the insufficiency of the rank-related stress to provoke a risk uniformly across pregnancies, but revealing contingent conditions that increase such risks, such as maternal body size and dietary intake. Animal studies in nonhuman primates have demonstrated reduced neonatal size after repeated agitation with acute stressors (e.g., light or noise) (Schneider et al. 1999; Schneider 1992), while similar associations have been reported in humans after events such as sudden spouse death (Witt et al. 2016) and high magnitude earthquakes (Torche and Echevarria 2011). Chronic stress from sources ranging from unemployment-related depression (Dooley and Prause 2005) to intimate partner violence is associated with small birth size outcomes. These observations have been explained by heightened exposure to glucocorticoids through unrestrained hypothalamic-pituitary-adrenal (HPA) axis reactivity that is concurrent with down-regulated placental 11ß-hydroxysteroid dehydrogenase 2 (11ß-HSD2) bioactivity stemming from chronic stress exposure (Fowden et al. 2004; Fowden et al. 2006). That the relationship between stress in pregnancy and poor neonatal outcomes is attenuated by increasing social support through counseling or strengthening social ties has been used as counterfactual evidence for the influence of stress on fetal development (Feldman et al. 2000).

The present study found increased birth weight for crown-heel length among socially subordinate infants in response to third trimester maternal weight gain. These observations suggest that size at birth required additional features of late pregnancy captured by the parameter maternal weight gain to reveal salient aspects of the rank-related fetal experience. It is actually unclear what third trimester weight gain actually represents, as it reflects weight gain shared between mother and fetus. If the weight was partitioned to mothers rather than their offspring one might expect a relatively smaller neonate for maternal size. If the weight was primarily partitioned to the fetus, one might expect relatively larger infants for maternal size. Here, maternal third trimester weight gain and neonatal birth weight reveals a moderate to strong positive correlation ($r=0.42$), suggesting that third trimester maternal weight gain is biased to measure fetal weight in this sample. From this viewpoint, it can be suggested that subordinate infants who express rapid late gestation weight gain are those who exhibit increased weight for crown-heel length at birth. Whether this is an expression of disproportionate weight gain relative to length increase is not resolvable with the present data.

Among humans, Hompes et al. (2012) evaluated stress at the end of the third trimester using both salivary cortisol and a psychological questionnaire, finding both indicators predicted increased neonatal ponderal index. These similar results suggest that the macaque social rank-based exposure in the present study was a valid stress proxy, and that similar physiologies may be operational. Further parallels to human circumstances are unclear. Low socioeconomic status (SES) is used as an indicator of increased psychosocial stress exposure in humans. Whether or not SES is actually capturing stress, or is a proxy for limited resource availability enacted by societal structural factors that

influence physiology is debatable. Nonetheless, low SES is an exclusion item for participation in the current cohort that is under observation for developing new World Health Organization-sponsored fetal growth charts (Merialdi et al. 2014) and is accepted as a causal factor influencing fetal growth and birth weight outcomes. For example, British infants born into the lowest class consistently exhibit increased odds of neonatal mortality and low birth weight in comparison to those born into the highest social class (Weightman et al. 2012). This negative effect of low SES on neonatal birth outcomes has remained unchanged over four decades when controlling for the secular increase in birth weight (Glinianaia et al. 2013).

We noted *accelerated postnatal crown-rump length and weight gain in response to the interaction of low rank and exposure to a choice diet.* Similar to our findings, among Dutch maternal-infant pairs participating in the Generation R Study, low maternal educational attainment – a marker that is strongly correlated with low SES – predicted accelerated infant length growth during the first 18 months of life (Silva et al. 2012). Rapid weight gain, irrespective of birth weight, was also associated with low SES in British infants participating in the Gemini Study (Wijilaars et al. 2011). These results may reflect the interaction between income and dietary quality during infancy, as lower rates of breast feeding and increased consumption of high calorie foods in early childhood are associated with lower parental education and SES (Emmett and Jones 2014; Oakley et al. 2013). In this vein, accelerated postnatal weight gain and weight for length growth rates were associated with early exposure to high calorie and high fat foods in an American cohort of women and their children; these outcomes were exacerbated in women reporting chronic stress (Thompson and Bentley 2013).

Comparisons Across Studies

In summary, heterogeneity in study design introduced difficulties for comparing the results of the present study with published findings of human fetal and postnatal growth in relation to maternal morphology, the experience of psychosocial stress, and postnatal nutrition. These differences include effects of locality, the choice of study question, and the complexities of measuring both stress and food intake. Most of the studies describing fetal growth longitudinally, and all of the studies with a carryover design to continue anthropometry postnatally, represent individuals from countries with universal health care systems where research is conducted in parallel with the provision of routine clinical care. Interaction effects between potential exposures have rarely been addressed. This reflects analytical decisions at the level of the research team, and possibly publication bias against null results. Further, there are inherent limitations in the breadth and depth of information that any one study can collect given the need to minimize participant burden. Particularly in these longitudinal studies, the risk of attrition must be carefully balanced with data collection to ensure the longevity of the overarching research program.

Two other intrinsic limitations exist within this field of research in general, and specifically to the interpretation of the present study results. Body size and stature are strongly influenced by genetics and are highly heritable with significant paternal influences (Silventoinen et al. 2010; Silventoinen et al. 2003). Paternity has not yet been ascertained for the current cohort and is limited to less than ten males. This limited paternal genetic variability is likely influencing the overall variability of infant morphology, and is confounded with the sensitivity and specificity of anthropometry.

Additionally, the present study is not privy to measures of maternal morphology prior to mid-pregnancy or intrauterine growth experiences during the first two-thirds of gestation. The importance of early gestation for ensuing growth trajectories cannot be ignored; for example, fetal growth during the first but not later trimesters is predictive of maternal risk of preeclampsia (Erez et al. 2008) and early accelerated growth was observed among infants who delivered pre-term (Lampl et al. 2009). Further, we cannot eliminate the possibility that misclassifications of gestational age were made in response to rapid first trimester growth that biased our timing of subsequent fetal ultrasonography. Studies of human infants are subject to analogous limitations due to reliance on similar gestational age growth reference curves, though their predictive value can be enhanced through maternal report of last menstrual date and sexual activity. Similarly, in nonhuman primates this can be improved by timed mating.

Proposed Mechanism: Social Subordination Induces Dysregulated Skeletal Metabolism *In Utero* with Consequences for Postnatal BMC Accrual and Weight Gain

This project utilized a translational nonhuman primate model to investigate if exposure to chronic maternal stress has intergenerational health effects by altering growth in early development in a way that poses subsequent health risks for offspring in the context of nutritional abundance in the modern world. Chronic stress in humans, which is deeply rooted within social interactions and enforced by structural inequalities, may modify the maternal/fetal physiological milieu during pregnancy and alter growth in a manner that predisposes offspring to later health compromise, particularly when confronted with the caloric abundance of modern lifestyles. This study exploited the well

documented stress associated with chronic social subordination in Rhesus macaques as the test condition proxy for chronic stress exposure and, in combination with maternal anthropometry, aimed to evaluate effects on fetal and postnatal growth and body composition as outcome variables. The postnatal intervention, exposing a sub-sample of infants to a high calorie diet from parturition onwards, investigated whether prenatal exposure to maternal stress had underlying physiological consequences that are exacerbated by diet and reflected in postnatal growth. Based on previous studies, our working model assumed that: 1) social subordination in nonhuman primates is characterized by chronic activation of the HPA axis, with concomitant excess endogenous glucocorticoid production (Michopoulos et al. 2012a); and 2) maternal glucocorticoids cross the placenta (Seckl and Holmes 2007; Singh et al. 2012) to influence fetal physiology with subsequent effects on postnatal growth that are exacerbated by exposure to a high calorie diet.

The data document effects of fetal exposure to chronic maternal stress on postnatal growth in bone and weight gain patterns that suggest alterations at the level of metabolism. Infants born to low ranked mothers exhibited altered postnatal growth trajectories, characterized by greater crown-rump length (CRL), a measure equivalent to sitting height in humans, and weight accrual by six months of age, as compared to infants born to high ranked mothers. Postnatal exposure to a high calorie diet attenuated BMC accrual among these same infants. Taken together, these results suggest that chronic intrauterine glucocorticoid exposure predisposed exposed infants to altered postnatal metabolism, with susceptibility to weight gain and compromised skeletal integrity in the face of caloric abundance. A review of the current state of knowledge regarding the role

of the skeleton in regulating global energy metabolism suggests mechanisms by which gestational exposure to excess glucocorticoids could alter metabolism both pre- and postnatally to generate the disparate phenotypes we observed among females born to low compared to high ranked dams.

Skeletal Metabolism: Cross-Talk between Osteoblasts and Adipocytes

Historically bone has been seen predominately as a modestly static organ, a *target tissue* for hormones and a hard tissue *structural support* for organs that enables mobility. Research during the past decade is changing the paradigm. The skeleton is emerging as an endocrine organ in its own right, excreting bone-specific hormones that bind to and modulate receptors across a broad range of skeletal and non-skeletal tissues alike to coordinate global energy metabolism (Fukumoto and Martin 2009; Lee and Karsenty 2008; Lee et al. 2007). It is now clear that the skeleton regulates metabolism via local (e.g., autocrine and paracrine signaling), systemic (e.g., endocrine system), and central (e.g., sympathetic nervous system) mechanisms, which in combination simultaneously express inherent genetic functionality while remaining sensitive to current signals of energy and other hormonal constituents that modulate insulin sensitivity. These processes are believed to be broadly conserved across vertebrate species (DiGirolamo et al. 2012).

Stem Cell Differentiation by PPARγ: Balancing Osteoblast and Adipocyte Hormone Production

All cells in the body have their origins in hematopoietic stem cell (HSC) or mesenchymal stem cell (MSC) niches, where differentiation and lineage commitment is influenced across the lifespan by complex signaling pathways that reflect the combination of endogenous inflammatory, hormonal, and other influences (Bhaskar et al.

2014; Blank et al. 2008). Peroxisome proliferator-activated receptors (PPARs), a class of transcription factors that control the expression of a host of genes associated with metabolism, adipogenesis, and inflammation across tissues in the body, are also key regulators of HSC and MSC differentiation (Chute et al. 2010; Lecka-Czernik and Suva 2006). The gamma isoform, PPAR-γ, is expressed in both white and brown adipose tissue, and is activated by fatty acids (Forman et al. 1996) with consequences for bone resorption and formation, reflecting a point of interaction between bone and adipose tissue with influences on metabolic function. PPAR-γ activation up-regulates adiponectin secretion from adipocytes (Maeda et al. 2001), stimulating osteoclastogenesis from HSCs (Wan et al. 2007) and adipogenesis with concomitant decreases in osteoblast formation from MSCs (Ali et al. 2005), leading to a phenotype of decreased bone mass, accelerated fat accumulation, and metabolic syndrome in mice that can be reversed by synthetically decreasing PPAR-γ activity (Akune et al. 2004). It is this central capacity of PPAR-γ activity, through its differential action on osteoblast and adipocyte differentiation from MSCs (Lecka-Czernik and Suva 2006) and osteoclast differentiation from HSCs (Chute et al. 2010), that may be a central mechanism for regulating metabolic function across the lifespan that originates in intrauterine life.

Dysregulated MSC Differentiation: Implications for Metabolism

Lecka-Czernik and Rosen (2016) propose that osteoblasts and adipocytes utilize distinct energetic pathways as they differentiate from MSCs, whereby both cell types utilize glucose during their initial progenitor phase (Shyh-Chang and Daley 2015) after which pre-osteoblasts leverage oxidative phosphorylation and glycolysis (Esen et al. 2013; Guntur et al. 2014) and pre-adipocytes use mitochondrial respiration (Tormos et al.

2011). This separation would be indicative of an evolutionarily conserved program by which cell fates reflect availability of energy across two separate pathways that reflect cell-specific functions in the body: to store energy by producing adipocytes or to form and mineralize bone through osteoblasts (Lecka-Czernik and Rosen 2016). This is in contrast to life history theory predictions of energy trade-offs across three competing physiological domains (e.g., maintenance and repair of existing tissues, expansion of body size, and reproductive effort) (Hill and Kaplan 1999; Stearns 1992), that direct energy to one domain at the expensive of the other. Bone remodeling has been offered as an example of costly maintenance due to its continual regeneration across the lifespan (Parfitt 1980) that is compromised in the form of bone mineral content loss in favor of promoting fitness via increased reproductive output (Madimenos 2015). The emerging data suggests instead that bone has a unique intrinsic energy source that is buffered from transient changes in extrinsic energy availability that enables continued bone remodeling (Esen et al. 2013; Frey et al. 2015; Regan et al. 2014) which in turn produces and maintains the cellular components that have a functional role in global energy metabolism (DiGirolamo et al. 2012), a potential fitness enhancing advantage shared across vertebrates. For example, in an *in vivo* mouse model Regan et al. (2014) demonstrated that low-oxygen tension stabilizes the hypoxia inducible factor-1 alpha (HIF-1a) pathway that in turn stimulates glycolysis to provide a distinct energy substrate to locally fueled cancellous bone formation independent of other energetic sources. These findings illustrate how endogenous energy production offers a primary support system for the basic functions that are typically ascribed to the ‘maintenance’ domain of life history theory-based models of physiology and homeostasis.

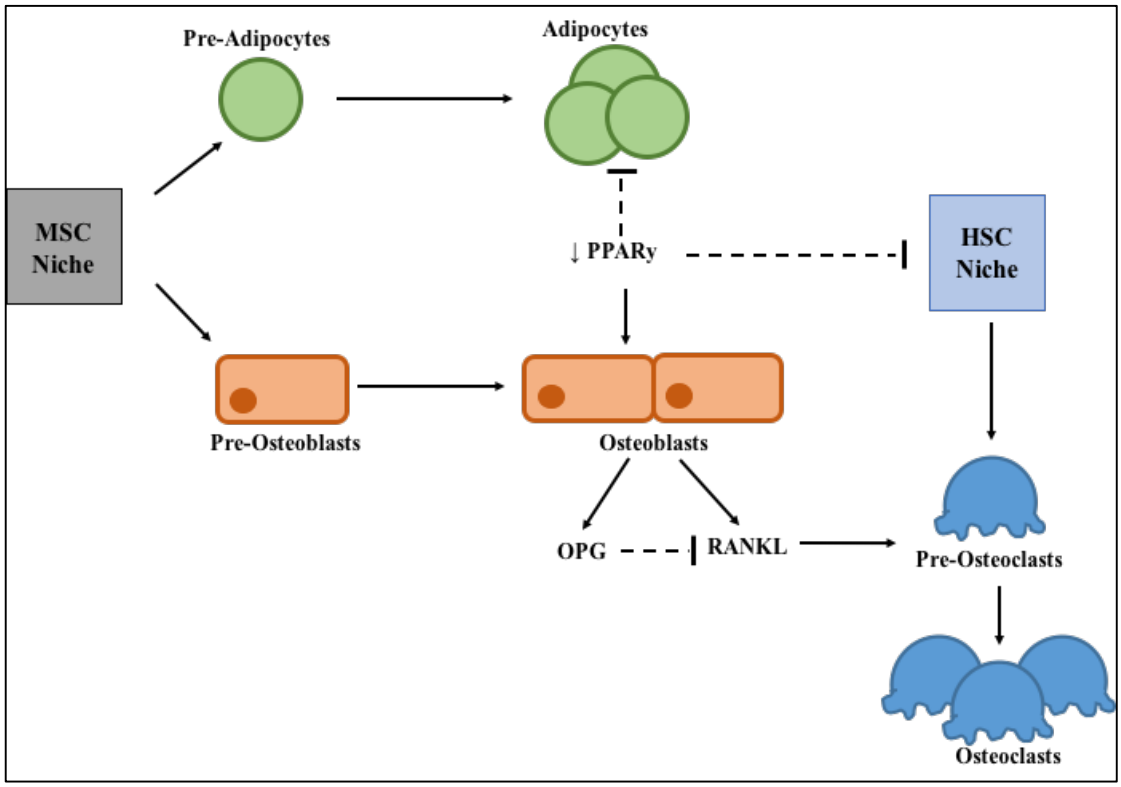
While Lecka-Czernik and Rosen (2016) propose separate energetic substrates for osteoblasts and adipocytes once MSC differentiation has been launched, the initial conditions that guide lineage commitment represent an avenue for disruption of basic skeletal metabolism that originates through disproportionate MSC progenitor differentiation and proliferation of adipocytes relative to osteoblasts. PPAR-γ activity, through its differential action on osteoblast and adipocyte differentiation, respectively, from MSCs (Lecka-Czernik and Suva 2006) represents one such mechanism that is driven by glucocorticoid exposure. At endogenous physiological concentrations, glucocorticoids stimulate Wingless-related integration site (Wnt) proteins and suppress the Wnt antagonist secreted frizzled-related protein 1 (sFRP1) to preference MSC progenitor cells to differentiate into the osteoblast lineage (Zhou et al. 2008). In response to excess glucocorticoids, PPAR-γ is activated upstream and the Wnt pathway is subsequently suppressed (Mak et al. 2009), which promotes MSCs to differentiate into adipocytes instead (Carcamo-Orive et al. 2010; Shi et al. 2000). This subtle difference may set the stage for long-term alterations to metabolism by reducing osteoblast proliferation and increasing adipocyte formation, with downstream effects on the relative production of osteocalcin from bone and adiponectin and leptin from fat.

Osteoblast Regulation of Bone Formation and Remodeling

The two primary bone cell types, osteoclasts and osteoblasts, are tightly coupled to perform the ongoing process of bone formation, mineralization, and resorption. Osteoclasts are derived from HSC niches, as are macrophages and dendritic cells, and like other immune system cells are characterized by their activity to break down apoptotic cells. In contrast, osteoblasts differentiate from MSC niches, sharing a common

origin with adipocytes and chondrocytes that later go on to become fat cells and cartilage, respectively. As a functional unit, osteoblasts regulate osteoclast activity by coupled synthesis of receptor activator of nuclear factor-κB ligand (RANKL) and osteoprotegerin (OPG). Osteoblast secretion of RANKL up-regulates the recruitment, activation, and survival of osteoclasts (Charles and Aliprantis 2014) with concurrent production of OPG, which acts as a decoy receptor for RANKL and down-regulates pro-osteoclast activity (Weitzmann 2013). These actions balance bone formation and resorption in healthy tissue (Figure 4.1).

Figure 4.1 Integrated Differentiation of Osteoblasts, Osteoclasts, and Adipocytes



Osteocalcin: Synthesis and Bio-activation from Osteoblasts

In addition to RANKL and OPG, osteoblasts also synthesize osteocalcin, important in bone's role in energy metabolism. Osteocalcin exists in two forms. The

protein takes on an alpha-helical conformation after post-translational modification via vitamin K-dependent carboxylation, whereby the conversion of three glutamate (Glu) residues to glutamic acid (Gla) residues (Hauschka et al. 1989) enables γ-osteocalcin to bind to hydroxyapatite, absorb calcium, and subsequently mineralize bone. Bio-available osteocalcin is undercarboxylated (UC-osteocalcin), synthesized endogenously in the acidic conditions present during normal bone resorption (Engelke et al. 1991). In this form, osteocalcin functions as a hormone, with the proposed role as regulator of systemic energy metabolism through its actions on insulin (Lee and Karsenty 2008; Lee et al. 2007).

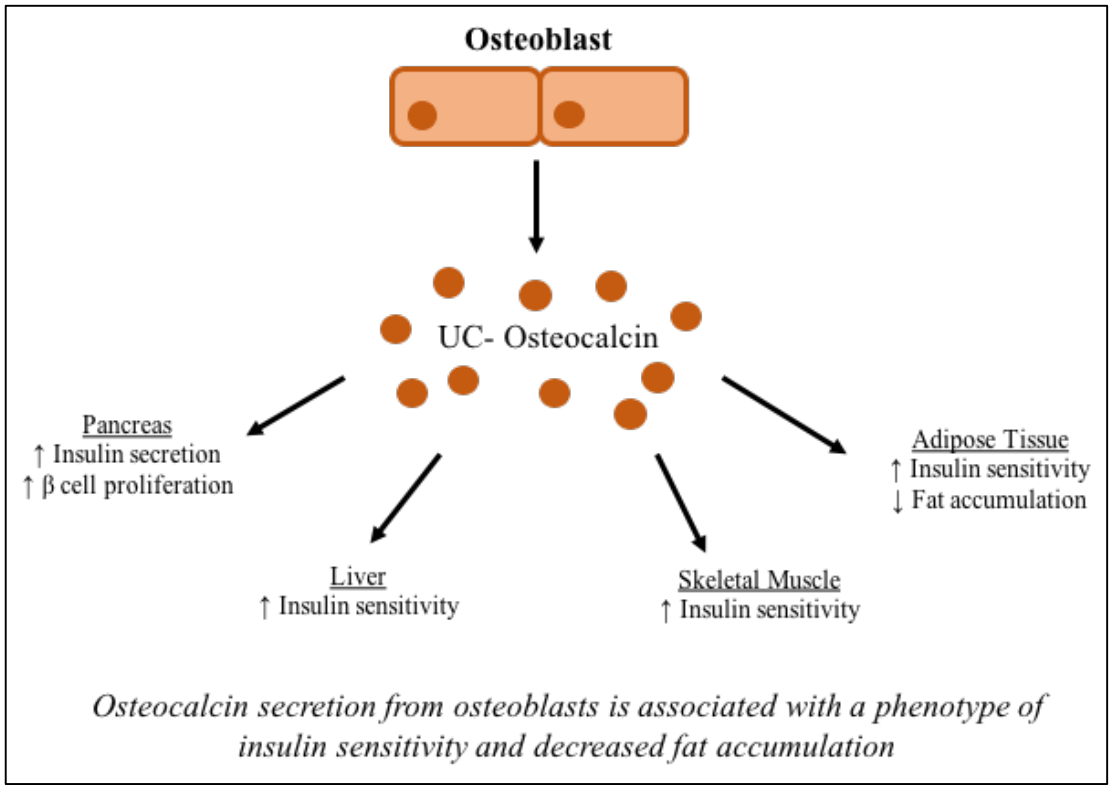
While UC-osteocalcin influences activities in the pancreas, skeletal muscle, and adipose tissue, the specific receptor or receptors mediating its activity remained elusive until very recently (Li et al. 2016). The only presently known receptor for UC-osteocalcin, GPRC6A, has confirmed expression in skeletal and adipose tissue, the brain, pancreas, heart, kidney, and testes, but not in the ovaries (Otani et al. 2015; Oury et al. 2011; Pi and Quarles 2012; Pi et al. 2011). GPRC6A is believed to be non-specific to UC-osteocalcin, as it is also activated by calcium, zinc, testosterone, and several amino acids, leading Clemmensen et al. (2014) to propose that GPRC6A is a sensor of innate protein balance and, in turn, overall energy status.

Osteocalcin: Functional Significance for Insulin Sensitivity in Rodents and Humans

Rodent studies first demonstrated the basic biochemical role of UC-osteocalcin in energy metabolism to stimulate pancreatic beta cell proliferation and the production of insulin. Specifically, osteocalcin-deficient mice are characterized by lower serum insulin levels, higher blood glucose, and excess visceral body fat accumulation in comparison to

wild type peers (Ducy et al. 1996; Lee et al. 2007). Infusion with UC-osteocalcin reverses this phenotype, whereby both fat mass and total body weight are returned to species-normal levels and insulin sensitivity is restored (Ferron et al. 2008). More recent experiments by Ferron et al. (2012) have shown that UC-osteocalcin administration not only improves glucose tolerance and insulin sensitivity in mice fed a prudent diet, by simultaneously increasing insulin secretion and beta-cell proliferation in the pancreas, but that concurrent UC-osteocalcin infusions in mice consuming a high fat diet help to normalize glucose levels, prevent insulin resistance, and protect against obesity. Ferron et al. (2012) suggest that this is an indication that UC-osteocalcin is improving glucose uptake in the liver, adipose tissue, and muscle, thus having cross-systems effects on energy metabolism (Figure 4.2).

Figure 4.2 Effects of Undercarboxylated Osteocalcin on Metabolic Function Across Organ Systems



Similar to the phenotype observed in mice, UC-osteocalcin levels are inversely related to markers of metabolic impairment in human adults (Jung et al. 2016; Kindblom et al. 2009) and children (Kim et al. 2014; Reinehr and Roth 2010; Wang et al. 2014). That this relationship was not present in a study of children exhibiting overweight without hyperglycemia (Abseyi et al. 2012) points towards the complex relationship between UC-osteocalcin and other hormones involved in metabolism, including the possibility that decreased circulating levels of UC-osteocalcin reflects chronic metabolic dysregulation. In a sample of young adult males, participation in a supervised exercise program increased total and UC-osteocalcin levels after only eight weeks, with positive correlations between the degree of weight loss, change in percentage body fat, and improvement in insulin sensitivity (Kim et al. 2015). Thus, UC-osteocalcin levels are modifiable, and are either responsive to, or reflective of, current energy availability. In combination, these findings suggest that UC-osteocalcin has a functional role in moderating glucose re-uptake and insulin production as it does in rodent species.

Skeletal Energy Metabolism: An Interface between UC-Osteocalcin, Leptin, and Adiponectin

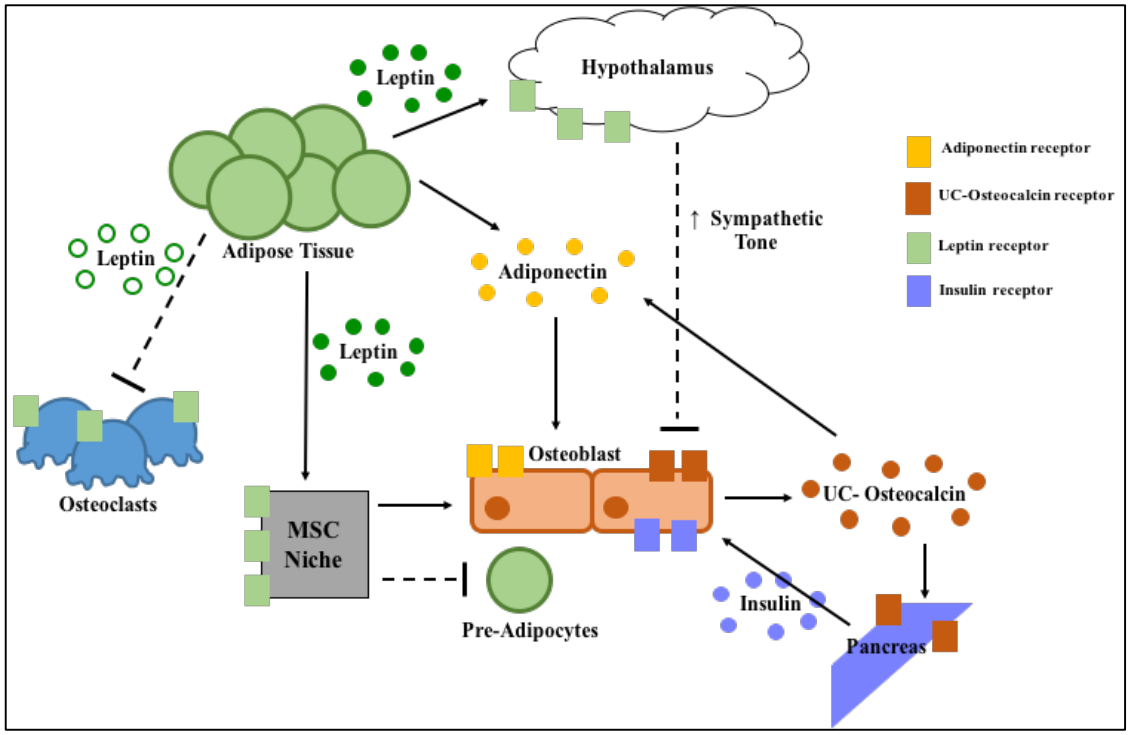
Undercarboxylated-osteocalcin's activity is believed to work in concert with adipose-derived hormones or adipokines, including leptin and adiponectin, to regulate global energy metabolism by coordinating insulin secretion and glucose re-uptake. Adipocytes in white adipose tissue expand to store fatty acids as triglycerides for later use (Skurk et al. 2007). Adipocyte hypertrophy stimulates leptin secretion, with consequent central effects on the hypothalamus that include appetite suppression, increasing sympathetic tone, and HPA axis activation (Ducy et al. 2000). In mice, the leptin-

generated increase in sympathetic tone up-regulates *Esp* gene expression within osteoblasts to reduce UC-osteocalcin synthesis, subsequently driving down insulin production in the pancreas (Hinoi et al. 2008; Pi et al. 2011). In combination with chronic adipocyte hypertrophy, as seen in experimental mice fed a high fat diet (Wang and Scherer 2014), simultaneous increases in leptin-related insulin resistance and decreases in UC-osteocalcin-related insulin sensitivity can result in metabolic dysfunction. Wang and Scherer (2014) suggest that insulin resistance ensues from chronic adipocyte hypertrophy followed by apoptosis and inflammation, whereby triglycerides accumulate systemically in the liver, skeletal muscle, and bone marrow rather than just in adipocytes.

Leptin itself has opposing central and local effects on skeletal tissue. Leptin suppresses bone formation centrally through indirect activation of the β2 receptor on osteoblasts by up-regulating sympathetic tone, targeting receptors in the ventromedial hypothalamus (Ducy et al. 2000; Elefteriou et al. 2004; Takeda et al. 2002). In contrast, leptin also promotes osteoblast differentiation and proliferation through its direct action on leptin receptors expressed on MSCs in bone marrow (Zhou et al. 2014). Leptin's synthesis and activity are intricately linked to the bioactivity of both adiponectin and UC-osteocalcin, including their joint effects on MSC differentiation and proliferation. Adiponectin is synthesized in inverse proportion to adipose tissue, broadly associated with improving insulin sensitivity and fatty acid oxidation in the liver and skeletal muscle (Brochu-Gaudreau et al. 2010) through its two primary receptors AdipoR1 and AdipoR2 (Yamauchi et al. 2003). Adiponectin acts centrally to reduce sympathetic tone and down-regulate leptin synthesis, increasing bone mass and reducing insulin resistance (Kajimura

et al. 2013), with secretion from adipocytes up-regulated by UC-osteocalcin (Lee et al. 2007) (Figure 4.3).

Figure 4.3 Hormonal Cross-Talk Across Bone and Fat Cells



Chronic Glucocorticoid Exposure: Implications for Bone Mineralization and Skeletal Metabolism

Regulation and Dysregulation of Glucocorticoid Production

Chronic glucocorticoid production has been previously documented among socially subordinate female Rhesus macaques (Michopoulos et al. 2012a). Briefly, in response to stressful stimuli the hypothalamic-pituitary-adrenal (HPA) axis is activated by corticotropin-releasing hormone (CRH) produced in the paraventricular nucleus of the hypothalamus, which in turn up-regulates pituitary production of adrenocorticotropic hormone (ACTH) with subsequent stimulation of glucocorticoid production by the adrenal cortex. This reaction is regulated via a negative feedback loop whereby

glucocorticoids from the periphery in turn stimulate central inhibition of CRH and ACTH production (Smith and Vale 2006). In acute stress situations, this reaction is quickly inhibited, but in conditions of chronic stress the negative feedback loop is disrupted as the activity of glucocorticoid receptors on the hypothalamus and pituitary gland are increasingly down-regulated, CRH and ACTH production of glucocorticoid synthesis goes unchecked, and a phenotype of increasing glucocorticoid resistance across the body emerges. In adult female Rhesus, this is associated with dysregulation across the body (Michopoulos et al. 2012a).

Critical Role of Glucocorticoids for Bone

Activation of the HPA axis is critical for normal skeletal function. For example, ACTH directly acts on bone tissue to stimulate osteoblast proliferation (Shimeld and Holland 2000) and collagen synthesis (Isales et al. 2010). A primary function endogenous concentrations is to act on MSCs to promote osteoblast differentiation and mineralization of the extracellular matrix by promoting the expression of alkaline phosphatase (ALP) (Eijken et al. 2006; Iba et al. 1995). In fact, by expressing 11ß-hydroxysteroid dehydrogenase 1 (11ß-HSD1), osteoblasts themselves can convert cortisone to cortisol locally (Cooper et al. 2000), activating ALP-driven mineralization of skeletal matrix (Eijken et al. 2005). Evidence for cell-level glucocorticoid effects comes from transgenic mice, in which disrupted glucocorticoid signaling in mature osteoblasts is associated with a phenotype of impaired bone mineralization, reduced bone volume, lower bone mass, and lower trabecular number by comparison with wild-type controls, demonstrating the importance of glucocorticoid signaling for bone remodeling and maintenance (Kalak et

al. 2009; Sher et al. 2006). Thus, glucocorticoid production is important for normal development and maintenance of the skeleton.

Glucocorticoid Excess Induces Frailty and Perturbed Metabolism

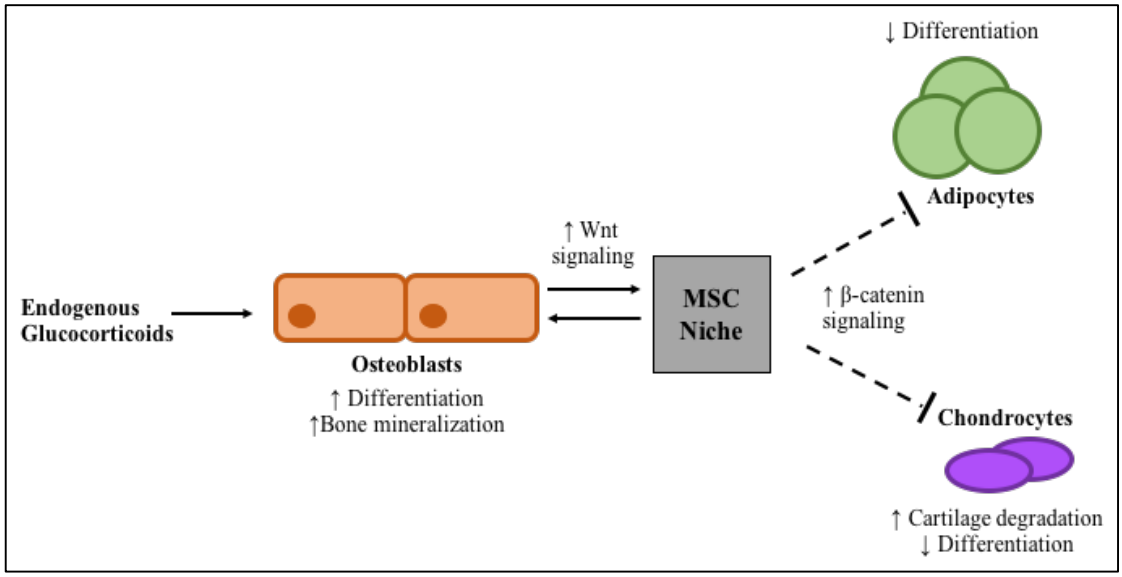
Chronic stress, however, produces excess circulating glucocorticoids, which has adverse effects on bone mineralization through several pathways. Excess glucocorticoids reduce intestinal calcium absorption and inhibit calcium reabsorption by the kidney (Ritz et al. 1984), thereby promoting a negative calcium balance (Perez et al. 2008). These effects are documented by the often reported association between pharmacological glucocorticoid treatments, used to reduce inflammation, and osteoporosis / sarcopenia (Anagnostis et al. 2009; Moghadam-Kia and Werth 2010). Chronicity of excess glucocorticoids, as results endogenously from prolonged stress and the ensuing dysregulated HPA axis, and exogenously from glucocorticoid pharmacotherapy, has substantial negative effects on metabolic function that leads to a diabetes-like phenotype. This includes impaired glucose tolerance and insulin resistance, a decreased ability for insulin to suppress endogenous glucose production, and visceral obesity (Anagnostis et al. 2009; Fernandez-Rodriquez et al. 2009; Moghadam-Kia and Werth 2010; Rafacho et al. 2014). These effects are proposed to reflect alterations in the skeleton's ability to properly serve in its role as an endocrine organ, with glucocorticoids considered to be the most powerful inhibitor of UC-osteocalcin synthesis from osteoblasts (Cooper et al. 2016). In mice, excess glucocorticoids suppress the synthesis and distribution of UC-osteocalcin by osteoblasts and a corresponding phenotype of glucose intolerance, dyslipidaemia, and obesity. Importantly, reinstating UC-osteocalcin synthesis by up-regulating BGLAP activity reinstates UC-osteocalcin production and reverses this

phenotype even with concomitant high dose glucocorticoid treatment (Brennan-Speranza et al. 2012).

Glucocorticoids in Normal Bone Formation and Growth

Under normal conditions during growth, glucocorticoids work in concert with sex steroids and growth factors to organize the joint chondrocytic, osteoblastic, and osteoclastic action that underlies bone elongation at the level of the growth plate through their actions on Wnt and β-catenin signaling *in utero* and postnatally (Lui et al. 2014). Namely, the earliest stages of limb bud development *in utero* require glucocorticoid stimulation of Wnt and β-catenin signaling cascades to recruit ALP for bone mineralization (Yang 2003). Disruption of β-catenin signaling through the up-regulation of PPAR-γ or absence of glucocorticoids (Lu and Carson 2010) in postnatal bone is associated with excess chondrogenesis at the growth plate, with unrestrained β-catenin signaling associated with cessation of activity at the growth plate (Andrade et al. 2007). Thus, Wnt and β-catenin signaling suppress chondrogenesis in favor of osteoblast differentiation and maturation, in addition to subsequent remodeling and degradation of the cartilaginous matrix (Zhou et al. 2009), setting the stage for bone growth and mineralization. (Figure 4.4, redrawn from Henneicke et al. 2014).

Figure 4.4 Glucocorticoid Effects on Osteoblastic-Mediated MSC Niche Differentiation

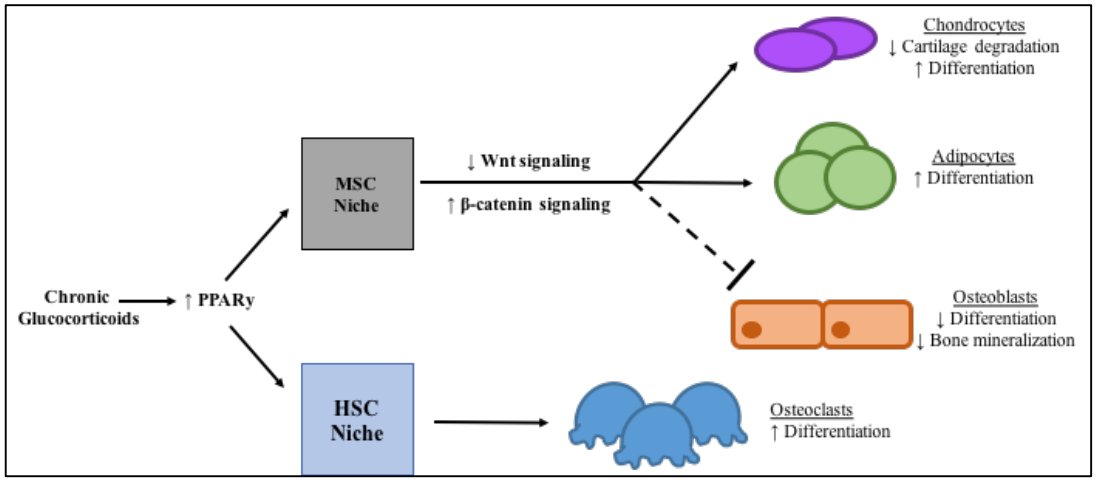


Redrawn from: Henneicke et al. 2014

Glucocorticoid Chronicity Impairs Normal Bone Formation and Growth

However, at high concentrations glucocorticoids inhibit Wnt and β-catenin signaling by up-regulating PPAR-γ, which has implications both for the differentiation potential of MSCs into osteoblasts and chondrocytic activity at the growth plate (Andrade et al. 2007; Yao et al. 2008; Zhou et al. 2008). Excess glucocorticoids stimulate the expression of PPAR-γ, increasing the rate of adipocyte differentiation from MSCs (Yao et al. 2008), while also down-regulating β-catenin and preventing growth plate matrix mineralization (Andrade et al. 2007) (Figure 4.5).

Figure 4.5 Effects of Chronic Glucocorticoid Exposure on MSC and HSC Differentiation



Potential downstream implications of this process include a dysregulation between adipocytes and osteoblasts and/or that the products of osteoblasts, including collagen and osteocalcin synthesis, are compromised (Henneicke et al. 2014; Moutsatsou et al. 2012). For several tissues, including bone, 11ß-hydroxysteroid dehydrogenase 2 (11ß-HSD2) modulates the degree to which glucocorticoids can exert their effects at a local level (O'Brien et al. 2004). With glucocorticoid chronicity, 11ß-HSD2 activity is down-regulated, enabling a pathway that is concurrent with up-regulated PPAR-γ to alter bone formation. Importantly, as 11ß-HSD2 is expressed by the placenta and in fetal bone tissue, its bioactivity represents a pathway for modulating intrauterine exposure to circulating maternal glucocorticoids.

Intrauterine Glucocorticoid Exposure: A Transgenerational Mechanism for Programming Skeletal Metabolism

Maternal-Fetal Regulation of Glucocorticoid Exposure

Glucocorticoids cross the placenta to enter fetal circulation (Seckl and Holmes 2007; Singh et al. 2012), with vital roles for fetal organ maturation and labor stimulation

(Liggins 1994). Observations that glucocorticoid levels in pregnant women are up to ten-fold higher than in fetal circulation (Montano et al. 1991) form the basis of the argument that placental 11ß-HSD2 modulates fetal exposure to maternal glucocorticoids (Benediktsson et al. 1997; Burton and Waddell 1999). The regulation of 11ß-HSD2 bioactivity remains unclear (Chapman et al. 2013), though correlations between circulating estrogen and the bioactivity of placental and kidney 11ß-HSD2 (Burton et al. 1998; Gomez-Sanchez et al.) suggest an endogenous means for controlling its expression. Placental 11ß-HSD2 activity is variable across pregnancy, and there is no consistent mammalian pattern (Burton and Waddell 1999): activity is elevated in baboons from mid to late gestation (Pepe and Albrecht 1990), decreased during mid to late gestation in sheep (Yang 1997), and low during later gestation in rats (Burton and Waddell 1994). In humans, placental 11ß-HSD2 activity rises steadily across gestation (McTernan et al. 2001) until a rapid decline commences at approximately week 38 of gestation (Murphy and Clifton 2003). The rise in 11ß-HSD2 activity is concurrent with observed changes in endogenous maternal glucocorticoid production across pregnancy. In humans, maternal cortisol levels successively rise from conception onwards, and peak at approximately three times the basal non-pregnant levels during the third trimester (Jung et al. 2011). This is driven at least in part by placental secretion of corticotrophin releasing hormone (CRH) that stimulates maternal adrenal production of cortisol, setting off a feed-forward reaction chain that leads to continually heightened circulating cortisol (Campbell et al. 1987; Goland et al. 1995; Goland et al. 1992). The increase in maternal circulating cortisol and parallel rise of placental 11ß-HSD2 activity is thus proposed as a feto-placental mechanism to attenuate fetal exposure to glucocorticoids (Reynolds 2013).

11ß-HSD2 Expression and Fetal Physiology

The importance of 11ß-HSD2 is reflected in offspring morphology in the near term and physiological performance in the long term. The inhibition of maternal 11ß-HSD2 activity during gestation is associated with a phenotype of hypertension, hyperglycemia, and HPA axis hyperactivity in offspring across several placental mammalian species, including rodents, guinea pigs, sheep, and nonhuman primates (see review in Chapman et al. 2013). For example, in rats inhibition of 11ß-HSD2 activity by exogenous injection of carbenoxolone and chronic infusion of glucocorticoids through the duration of pregnancy produces a phenotype of low birth weight and subsequent hyperglycemia and hypertension in adulthood (Lindsay et al. 1996a; Lindsay et al. 1996b). Further, in murine placentas that are null for 11ß-HSD2, placental growth cessation precedes fetal growth restriction and the placenta exhibits reduced expression of PPAR-γ (Wyrwoll et al. 2009). Similarly, reduced placental levels of 11β-HSD2 are associated with intrauterine growth restriction in humans (Dy et al. 2008; Shams et al. 1998; Wächteret al. 2009). The assumption is that this leads to hypercortisolemia as a mechanism for fetal growth restriction.

Additionally, fetal tissues, including bone, liver, kidney and brain, express 11ß-HSD2 from at least mid-gestation onwards (Benediktsson et al. 1997; Burton and Waddell 1999) and 11ß-HSD2 is expressed in essentially all postnatal tissues (see review in Chapman et al. 2013). Thus, 11ß-HSD2 bioactivity in the fetus may serve as a secondary modulator of glucocorticoid effects across the duration of gestation and into the postnatal period. This is a mechanism by which central pathways can be influenced by prenatal experiences and exposures. For example, in experimental models of both

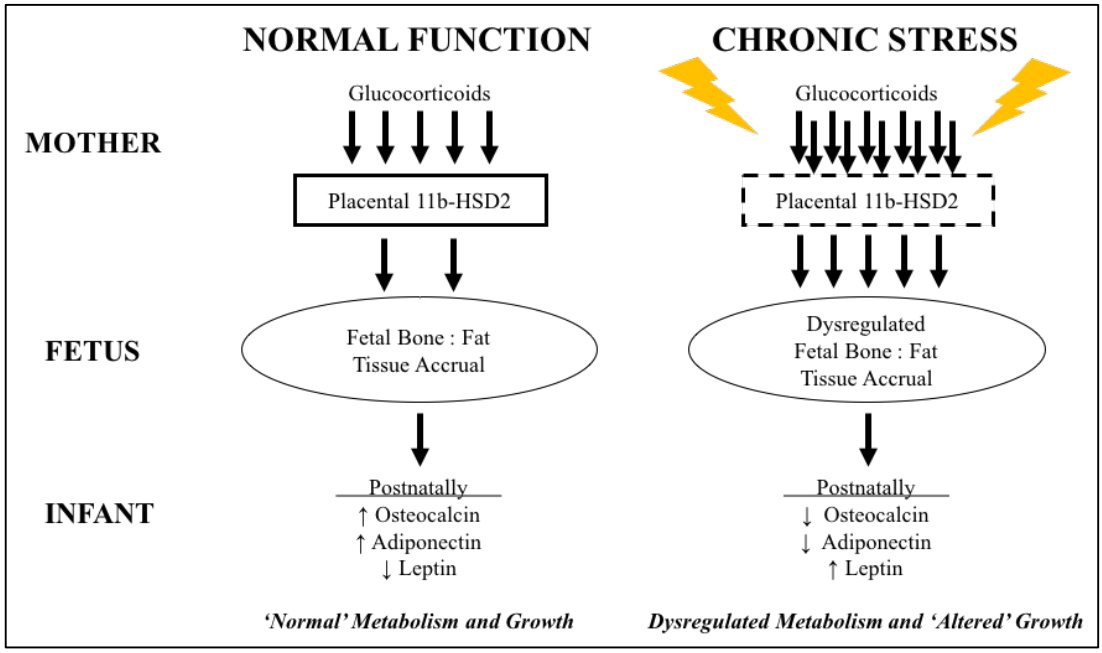
early- and mid-gestational caloric restriction and gestational diabetes, fetal kidney 11ß-HSD2 activity is down-regulated *in utero* among animals who exhibit hypertension as adults (Fujisawa et al. 2004; Whorwood et al. 2001). These data identify prenatal glucocorticoid exposure via altered 11ß-HSD2 activity as a central pathway by which *in utero* environments can lay the foundations for health in later life (Reynolds 2013; Seckl and Holmes 2007).

Suppressed 11ß-HSD2 due to Chronic Social Subordination as a Mechanism for Health Risks

In response to chronic HPA activation, the combination of up-regulated glucocorticoid production and down-regulated 11ß-HSD2 transcription and bioavailability has been documented in animal models and humans alike (Glover et al. 2009; O'Donnell et al. 2012; Sarkar et al. 2001; Welberg et al. 2005). We propose that this represents a distinct pathway for altering MSC and HSC differentiation pathways that influences body composition, and in turn global energy metabolism that may mechanistically explain the study observations of distinctive growth trajectories among monkeys born to socially subordinate mothers compared to their peers delivered of high ranked mothers. Maternal lifetime exposure to chronic stress sets up a physiological environment characterized by a tendency to suppress 11ß-HSD2 activity, which in turn translates to increased gestational exposure to glucocorticoids. This physiological environment augments risks for modifications to fetal skeletal and adipose tissue development, which in turn increases risks for altered postnatal metabolism and body composition. This sequence may underlie our observation that low ranked infants

exhibited attenuated BMC accrual and higher infant weight gain by six months of age, effects exacerbated subsequent to high calorie postnatal dietary exposure (Figure 4.6).

Figure 4.6 Proposed Mechanism: Altered Growth Trajectories in Subordinate Females from Excess Fetal Glucocorticoid Exposure and Dysregulated Metabolism Originates in the Skeleton



Evidence to support this view comes from documentation of up-regulated glucocorticoid synthesis among both pregnant (Crockford et al. 2008) and non-pregnant (Shively et al. 1997) (Michopoulos et al. 2012a; Michopoulos et al. 2012b; Shively 1998) female nonhuman primates that increases as the degree of exposure to aggression and social subordination increase. The combination of down-regulated 11ß-HSD2 in placental and fetal skeletal tissue that is concurrent with glucocorticoid excess (Benediktsson et al. 1997; Burton and Waddell 1999; Sarkar et al. 2001) could directly impact osteoblast differentiation from MSCs (Carcamo-Orive et al. 2010; Cheng et al. 1994; Shi et al. 2000; Yao et al. 2008), in addition to impairing the function of already formed osteoblasts (Toth and Grossman 2013) *in utero*.

Implications of a Glucocorticoid-based Pathway as a Mechanism for the Study Results and Other Observations among Nonhuman Primates

The potential for glucocorticoids as a mechanistic pathway underlying the present study's observations is supported by previously described associations between pre- and postnatal growth patterns among nonhuman primates. The specific proposed pathway is supported at the cellular level by the documentation that excess glucocorticoids inhibit Wnt and β-catenin signaling while up-regulating PPARγ expression, which together reduce osteoblast differentiation and increase the rate of adipocyte and chondrocyte differentiation from MSCs (Yao et al. 2008). This activity disrupts remodeling, bone elongation, and mineralization at the level of the endochondral growth plate (Andrade et al. 2007; Zhou et al. 2008), and could explain our observation of attenuated BMC accrual among fetuses of low ranked infants. A recent report on infant morphological outcomes among African vervets (*Chlorocebus aethiops*) after mid- and late- gestational exposure to a synthetic glucocorticoid (de Vries et al. 2007) offers additional insight. de Vries et al. (2007) documented dose-dependent reductions in fetal femur length in late gestation, with shortened postnatal crown-heel length, femur length, and forearm length observed beginning between six and eight months of age. This may be analogous to our finding that infants born to high ranked dams of greater crown-heel lengths, whose fetuses had presumably less intrauterine exposure to glucocorticoids, were growing longer in crown-heel length and accruing more BMC relative to their low ranked counterparts. Further, similar to our results of no social rank-based differences in neonatal weight, crown-heel length, or birth weight for crown-heel length, de Vries et al. (2007) observed no

differences across any measure of anthropometry at birth between controls and those with exogenous glucocorticoid exposure.

The present study data further documented accelerated weight gain and concomitant attenuation of BMC accrual postnatally among low ranked infants. These observations are compatible with glucocorticoid-compromised UC-osteocalcin synthesis and its consequences thereafter. First, as noted above, glucocorticoids can reduce the total volume of osteoblasts thereby decreased the cellular sources available to secrete UC-osteocalcin, while increasing adipocytes and adipokine byproducts (Carcamo-Orive et al. 2010; Cheng et al. 1994; Shi et al. 2000; Yao et al. 2008). Additionally, glucocorticoid levels influence the ability for mature osteoblasts to produce UC-osteocalcin (Cooper et al. 2016; Toth and Grossman 2013) and may prevent conversion into the bioactive undercarboxylated form, as this occurs in hepatocytes (Wallin and Hutson 1991) and epithelial cells in lung tissue (Gilbert and Rannels 2003). A glucocorticoid path to dysregulated osteocalcin production would simultaneously have downstream implications for adiponectin and leptin synthesis from adipocytes, favoring insulin resistance. This pathway may be operational among the vervets followed by de Vries et al. (2007) who exhibited higher fasting plasma insulin levels, reduced glucose uptake in response to an oral glucose tolerance test, and significantly elevated circulating levels of cortisol at eight months of age. These infants exhibited a phenotype analogous to pre-metabolic syndrome in response to the mid- and late-term exposure to heighted glucocorticoids. Posthumous examination at one year of age revealed a substantial reduction in both the size and total volume of pancreatic beta cells (de Vries et al. 2007).

Finally, the present study documented accelerated weight gain among infants delivered of low ranked mothers after postnatal exposure to a high calorie diet. Both accelerated weight gain and body fat accrual are predicted outcomes of reduced UC-osteoclacin based on laboratory studies noting glucose intolerance in mice who lack osteocalcin (Lee et al. 2007). Favoring leptin over adiponectin production can drive adipocyte accumulation, while additionally favoring chronic insulin resistance favoring weight gain. Further, the intrauterine exposure to glucocorticoids in addition to alterations in leptin secretion may have also contributed to developmental changes to satiety signaling and overeating. Previous studies have documented that socially subordinate adult female Rhesus macaques consume more total calories when offered a high calorie diet, and that daily consumption remains elevated even after returning to a prudent diet (Arce et al. 2010; Michopoulos et al. 2012c; Moore et al. 2013). The observation of increased weight gain among socially subordinate female infants raises the testable hypothesis that similar disordered eating, in combination with altered metabolism due to osteocalcin deficiency, is occurring.

Exogenous glucocorticoid administration and reports of perceived chronic stress are both associated with obesity from childhood through adulthood (Berthon et al. 2014; Gunderson et al. 2011; Liu and Umberson 2015; Spencer and Tilbrook 2011). Further comparisons with human studies to date provides additional support for the hypothesized mechanism for the present findings.

Implications of a Glucocorticoid-based Pathway as a Mechanism for Observations among Human Infants

Evidence for altered fetal osteocalcin production in the face of overly abundant maternal glucocorticoids comes from a number of perspectives in human studies, and together with evidence of osteocalcin-deficiency related bone frailty and pre-diabetes symptoms further support the present hypothesis. Support for glucocorticoid-related osteocalcin suppression comes from reports of inverse correlation between osteocalcin levels in umbilical cord blood and glucocorticoid levels simultaneously collected from both umbilical cord and maternal circulation (Benediktsson et al. 1995; Delmas et al. 1987). Observations not previously attributed to osteocalcin mechanisms, but compatible with the present pathway include reports that among children treated with exogenous glucocorticoids for nephrotic syndrome (Panczyk-Tomaszewska et al. 2015) and asthma (Wolthers and Heuck 1998), and cystic fibrosis, conditions specifically associated with impaired vitamin K-dependent carboxylation processes (Fewtrell et al. 2008), all exhibit a phenotype of reduced UC-osteocalcin and low bone mineral content. Outcomes of osteocalcin dysregulation may further encompass observations of metabolic syndrome-related bone compromise among children. For example, Pollock et al. (2010) documented lower total body BMC among overweight 7-11 year olds with pre-diabetes relative to their peers. A negative association between inulin resistance and BMC and BMD was noted among a cohort of obese Brazilian juveniles aged 13 to 18 (do Prado et al. 2009) and overweight Hispanic children aged 9 to 13 (Afghani et al. 2005).

Study Limitations

Reflections on Primary Aims

Aim 1: To identify associations between maternal rank, maternal body composition, and fetal growth and birth weight outcomes

At the project onset, it was assumed that low ranked dams would be of smaller body size with greater fat percentage than those of high rank. It was hypothesized that fetal growth patterns and size at birth would follow, such that fetuses of low ranked mothers would exhibit a phenotype of smaller body size *in utero*, and in turn exhibit reduced birth weight with a tendency to increased sensitivity to fat. These predictions were based on findings among Rhesus macaques of lower weight among subordinate adolescents raised in large social groups (Wilson et al. 2012; Zehr et al. 2005) and adult females maintained in smaller, experimentally formed social groups (Michopoulos et al. 2012a), and a trend towards increased weight among wild female baboon infants, juveniles, and adolescents who were born to dominant mothers (Altmann and Alberts 2005; Johnson 2003). The present study results identify that the underlying assumption aligning social rank with specific maternal morphological phenotypes was incorrect. There were no significant differences in maternal body size during either the prenatal period or at parturition, and low ranked female adults did not exhibit increased percentage body fat compared to their high ranked peers. The distinct rank-based phenotypes documented by Michopoulos et al. (2012a) among adult female Rhesus macaques may not be a singular pattern, but may reflect an exacerbation of social subordination resulting from differences in the ecological setting between the two groups. The sample studied by Michopoulos et al. (2012a) were maintained in experimentally formed small social groups, experienced a smaller housing area, and an absence of familial social support. By contrast, the present cohort was housed in larger, multi-generational family units. This may have attenuated the intensity of stress experienced by animals confined to smaller living areas under more socially isolated circumstances.

The study results identified no significant influences on third trimester fetal growth trajectories from maternal rank, body size or body composition.Neither the rate of fetal growth across the four dimensions measured (femur length, abdominal circumference, head circumference, and bi-parietal diameter) nor their interaction with maternal rank predicted birth size. A modest deceleration in the rate of bi-parietal diameter growth during the third trimester (p=0.08) with increasing maternal body fat percentage among fetuses of low ranked dams compared to high ranked dams corresponds to the prediction that fetuses of low ranked dams might be increasingly sensitive to maternal body fat.

The present results do not rule out biological effects on fetal growth from maternal rank, size and body composition that occurred during the first two-thirds of gestation, or effects that may be more nuanced than can be resolved by infrequent anatomical ultrasound measures of four body parts.

The outcomes bring to light several considerations regarding study design. First, the assumption of maternal phenotypic matching to social rank was not unreasonable based on data at hand, but turned out to be quite incorrect. An alternative strategy would have been to clarify that the study animals were indeed described by rank-specific characteristics prior to onset. Second, there was a lack of specificity in the study hypotheses that becomes evident after data acquisition and brings attention to the importance of sensitivity and specificity of outcome measures. As similar longitudinal research had not been previously conducted, this may be more of a conclusion than a limitation. It may, however, be valuable in the future to pre-specify an approach to more specifically characterize “fetal growth.” One approach would be to develop and test an

equation for estimating fetal weight in line with those used in human clinical settings, such as Shepard's equation based on bi-parietal diameter and abdominal circumference (Shepard et al. 1982) or Hadlock's equation based on femur length, head and abdominal circumferences (Hadlock et al. 1984).

Aim 2: To identify associations between maternal rank, maternal body composition, postnatal diet, birth weight and infant growth trajectories during the first 6 postnatal months

There were no simple effects of maternal rank or body composition on birth weight or growth trajectories in the first six postnatal months. The prediction that body size would be largest among low ranked infants exposed to a choice diet with ad libitum access to high-calorie chow was at least partially supported, with an interaction between rank and diet emerging at six months of age when the focal infants were themselves directly consuming the high calorie chow alternative.

It was predicted that the cross-fostering design would illuminate distinct postnatal growth trajectories whereby being raised by a high ranked dam would 'buffer' an infant from the any long-term effects of gestational exposure to low rank. This hypothesis was refuted, as no differences in growth rate were observed in response to cross-fostering. Instead, all predictors of postnatal growth rate and size outcomes were related to initial size at birth, biological maternal phenotype, and the interaction between biological maternal phenotype and rank. Overall, a key weakness of this approach was that the pre-specified predictions of how maternal size and rank would translate into growth outcomes were non-specific, which later limited the analytic strategy.

Reflections on Project Design

Overall, the research and analytic procedures were carried out as pre-specified, with limited deviations from the original study plan. Key weaknesses are described below.

Estimation of Gestational Age

The focal offspring in this study were not time-mated; that is, they were conceived in a compound where males and females copulated at will. This limited estimation of gestational age via ultrasound during the first trimester using measures of femur length, abdominal circumference, head circumference, and bi-parietal diameter to comparison against a published medical reference. Using this method, fetuses who initially grew at a faster rate would have been assigned an older predicted gestational age and fetuses who initially grew at a slower rate would have been assigned a younger predicted gestational age. Further, the fetal growth reference did not differentiate between male and female fetuses which may be an inappropriate assumption given the differing trajectories of fetal growth for male and female human infants (Lampl and Jeanty 2003).

Model Assumptions

Previous studies of macaque females at the Yerkes National Primate Research Center, specifically, and other colonies have identified a distinct HPA axis phenotype of glucocorticoid dysregulation in socially subordinate animals (Michopoulos et al. 2012a; Michopoulos et al. 2012b; Shively and Clarkson 2009; Shively and Wallace 2001). An underlying assumption of the present study is that these adult female dams exhibit a similar hormonal profile in response to low rank, with the inclusion of only the lowest one-third and highest one-third of adult females from each compound leveraged as a means to exacerbate the underlying rank-based physiological phenotype. At the present

time we have not yet determined whether the actual HPA axis reactivity of the adult females in this study were differentiated by rank; thus, we cannot confirm that the underlying assumption is valid.

Sample Size

The data presented here represent a subsample of female infants that are part of a larger, ongoing project co-funded by National Institutes of Health grants awarded to Drs. Mark Wilson and Mar Sanchez. The sample size (n=35) may be underpowered, but the study is strengthened by the repeated measures approach.

Timing of Maternal, Fetal, and Postnatal Anthropometry

The first systematic research measures of fetal and maternal morphology were obtained at approximately day 100 of gestation, or the end of the second trimester. Thus, measures of maternal morphology are biased to include any effects the fetus had on her current physical state, and measures of maternal morphological change during the third trimester also reflect fetal tissue and how maternal size accommodates fetal growth. Overall, the anthropometry proceeded approximately according to the planned schedule, with measurements occurring at two prenatal time points (D100 and D150) and five postnatal time points ('birth', two weeks, six weeks, 12 weeks, and 24 weeks). Table 4.2 depicts the planned versus actual schedule of accesses by day of age; the variation between planned and actual anthropometry was greatest at the six month time point.

Table 4.2 Planned versus Actual Age at Each Measurement

Timing	Planned Access Age	Mean Access Age (days)	Minimum Access Age (days)	Maximum Access Age (days)
Prenatal	Gestational day 100	99.07	94	105
	Gestational day 150	148.41	144	152
Postnatal	Birth (weight only)	1.26	0	4

	Birth (weight and other anthropometry)	2.65	1	4
	2 Weeks (14 days)	13.28	8	17
	6 Weeks (42 days)	42.53	39	46
	12 Weeks (84 days)	83.76	79	89
	24 Weeks (168 days)	176.61	169	184

Specificity of Anthropometry, Study Team, and Researcher Participation

The specificity of anthropometry is a limitation of the project. Weight was recorded to the nearest 0.005 kg and height, abdominal circumference, and head circumference to the nearest 0.05 cm, but the general issues of anthropometry, namely subject compliance (Lampl et al. 2001) remained. This was minimized during postnatal measures beginning at six weeks of age by anesthetizing the infants, but all anthropometry at 'birth' and two weeks of age was performed on awake infants. While the internal validity of the body composition estimates is high as indicated by daily quality assurance scans of a phantom, the DXA scanner has not been externally validated, which may be a limitation when comparing these results to comparable research conducted at other facilities.

Given the overall nature of the parent project, the study team that performed the anthropometry contributed to this specific study is large and varied over time. All team members were trained and tested for their skills in performing the measurements, but the possibility of measurement errors cannot be ruled out. A single, trained DVM/PhD researcher (K. Ethun) performed all of the ultrasounds and saved the ultrasound still images. The author (A. Mummert Anixter) performed all fetal ultrasound measurements on the still images, and participated in greater than 70% of all accesses where anthropometry was performed over the two-year research period. Within observer

consistency is one of the greatest assets a longitudinal study can have; due to the overarching magnitude of the parent study, this attribute was limited.

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CHAPTER 5 CONCLUSIONS

Overview

The dramatic rise in obesity prevalence among both children and adults in the United States (Ogden et al. 2014) and globally (Ng et al. 2014) over the last quarter century has no single origin, and reflects the intersection of our evolved human biology with the contemporary world. Using a translational animal model, we have demonstrated that postnatal growth trajectories as observed at the phenotypic level with implications for underlying physiology are a reflection of the intrauterine growth experience that is not captured by measures of birth size alone. Situating the emergence of obesity within this perspective suggests that interventions take an intergenerational approach, and that the effectiveness of such programs may only be seen if measured at longer timescales.

Theoretical Considerations and Implications

The multi-disciplinary theoretical debates concerning the origins of the modern obesity and chronic disease epidemic have converged largely within the domain of evolutionary theory, broadly emphasizing the concept of a *mismatch* (Gluckman and Hanson 2006) between evolved physiology and the modern environment (Trevathan 2010; Trevathan et al. 2008). Explanations have included *thrifty genes* (Neel 1962) that preference energy storage, *thrifty phenotypes* (Hales and Barker 1992) that are set *in utero* and conflict with the postnatal environment, and *predictive adaptive responses (PARs)* that alter growth trajectories to reduce mortality risk in risky environments (Gluckman et al. 2005). Incorporating these views with prior documentation of the influence of maternal and environmental conditions on body size and physical growth (e.g., McKewon and Record 1954; Ounstead 1965) and their relationship to later disease

risk (e.g., Forsdahl 1977; Gennser et al. 1988), the *developmental origins of health and disease* (DOHaD) framework (Barker 2004; Barker 2012) provides a context for investigating how *in utero* experiences translate into health across the lifespan.

The DOHaD framework was formulated primarily from epidemiological associations between *birth size as a marker of fetal growth* and *adult health outcomes* (Barker et al. 1989a; Barker and Osmond 1986; Barker et al. 1989b). Birth size, and most commonly birth weight, has been utilized in this area of research because its easy accessibility within health records and is thought to generally capture maternal, placental, and broader environmental influences on fetal development. However, birth weight fails to capture actual fetal growth patterns which would contribute to the identification of critical periods linking intrauterine experiences to later life health. Recent prospective work is documenting the experience of growing in conjunction with physiological processes and ensuing chronic diseases, in particular taking advantage of longstanding, intergenerational cohort studies that from across the globe (e.g., Richter et al. 2012). This approach moves the field forward beyond *associations* and towards the evaluation of *causal processes* linking early development and lifespan health. The present study contributes to this area by demonstrating that birth weight alone does not capture the intrauterine experience. In addition, the findings draw attention to methodological issues involving the limitations of traditional anthropometry to capture *in utero* alterations to physiological processes that have systemic effects for subsequent growth. Finally, the data lead to a hypothesized mechanism which calls attention to the weakness of a simplistic use of concepts like ‘energy availability’ in relation to skeletal growth as presently used in the large-scale sense, and redirects attention to cellular level processes

driving bone elongation and mineralization by reading both global and local energy sources (Lecka-Czernik and Rosen 2016).

Birth Weight is Not the Causal Mechanism

Key critiques of the developmental origins framework have included an overuse of inductive reasoning (Paneth 1994; Paneth and Susser 1995), inconsistent findings when independent studies are combined in meta-analyses and systematic reviews (Tu et al. 2005; Weinberg 2005), and a failure to fully address cumulative lifespan exposures (Elford et al. 1992; Elford et al. 1991). Additional questions are raised when considering what the static indicator 'birth weight' truly captures in terms of the intrauterine experience, as many fetal growth pathways can give rise to the same phenotypic size outcome (Bloomfield et al. 2006; Lampl et al. 2009; Lampl et al. 2012). This may be a fundamental contribution to the disparate outcomes that have been reported when assessing the predictive capacity of birth weight for later adult health outcomes (Lampl and Mummert 2014; Lampl et al. 2015).

The present study draws attention to inherent limitations of relying on birth weight as a summary indicator of the intrauterine experience and in turn a predictor of potentially 'risky' growth. While birth weight was a statistically significant independent predictor of postnatal weight gain in this cohort, it did not mediate the effects of maternal body size on infant growth rates. That is, birth weight alone did not capture the broader contributions of maternal morphology to the rate of infant growth in this sample of female Rhesus macaques. This finding offers a plausible explanation for variations in the relationship between birth weight and adult health outcomes that others have critiqued (Elford et al. 1991), as most studies have considered primarily independent rather than

synergistic effects of maternal phenotypes on birth weight outcomes. In addition, disparate outcomes may inherently arise due to underlying between- and within-population variation in body morphology that reflects adaptations to local environments such as seen in high-altitude groups (Beall 2013; Frisancho 2013). While it is clear from the 'U' shaped relationship between birth weight and chronic disease risk (Whitaker 2004) that neonatal characteristics do have some predictive capacity, the results herein suggest that its use as a clinical indicator for early intervention to prevent childhood obesity must be contextualized within individual family health history data.

Predictive Power of Fetal Anthropometry and Stabilizing Selection for Bone Form and Function

This study represents the first data derived from a carryover design of pre- to postnatal life to assess fetal and postnatal growth trajectories among nonhuman primates, with the ability to assess these outcomes in response to maternal morphology, psychosocial stress, and a postnatal high calorie diet challenge. Only increasing abdominal circumference and fetal bi-parietal diameter growth rate during the third trimester were significantly independently associated, with no further significant relationships detected between the predictors of interest and fetal growth. Subsequent size at birth and postnatal growth trajectories, however, were influenced by the intrauterine experience when maternal morphology, social rank, and postnatal diet were considered. Exposures incurred *in utero* (e.g., effects of maternal morphology and social stress) were most strongly associated with alterations to postnatal infant bone mineral content. How early in development these alterations began is not known, as our approach of fetal ultrasonography beginning at the end of the second trimester could not have detected

such physiological changes during gestation. The results raise interesting points for consideration. Given the highly conserved nature of the skeleton across vertebrates, including the strong genetic and heritable aspects guiding its form and function (Silventoinen et al. 2010; Silventoinen et al. 2003), it is important to consider that perturbations in development as measurable using anthropometry are likely to be limited except in the extremes, particularly during the final weeks of gestation.

The recent evidence for the skeletons role in whole body energy metabolism (Fukumoto and Martin 2009; Lee and Karsenty 2008; Lee et al. 2007) substantiates the need for strong stabilizing selection on bone to conserve its innate physiological function for metabolism (Campbell et al. 2004; Flatt 2005). This is reflected by the powerful conservation of basic biochemical properties across vertebrates (Donoghue et al. 2006). For humans specifically, the prolonged nature of skeletal development and growth may represent an opportunity to lengthen the period for achieving peak bone mass (Weaver et al. 2016). This may, in turn, have fitness advantages in the form of metabolic function and transference of BMC across the lifespan. The allometric relationship between BMC and body size is strong (Heymsfield et al. 2011), and selection for 'good' bone tissue, particularly in women, has reproductive fitness advantages given its role as a calcium/phosphate depot for promoting fetal and infant growth (Kovacs 2003; Kovacs 2005).

We demonstrated in our data that a reduction of maternal BMC across gestation was associated with accelerated postnatal BMC accrual for infants born to low ranked females. Selection would be strong in promoting early and high peak BMC if the contemporary observation of pregnancy- and lactation-related bone mineral density loss

(Salari and Abodollahi 2014) and inverse relationship between parity and bone mineral density (Gur et al. 2003) was commonplace across evolutionary time scales (White and Armelagos 1997). In the present data, we observed that females born to high ranked mothers benefited more in terms of BMC from maternal phenotypes of tallness and BMC. From the perspective of the importance of BMC, this could be an intergenerational mechanism for health and reproductive fitness. While the relationship between attained height and reproductive fitness has often been explained in terms of an outcome of sexual selection for larger body size (Stulp and Barrett 2016), this may be more directly related to the intergenerational nature of how skeletal health is transmitted: Taller bodies are indicative of a female's own early growth environment and, therefore, represents an inherent physiological advantage.

Osteoporosis represents a disease of the expansion of longevity and a breakdown of near- and long-term metabolic processes. Osteoporosis is fundamentally an imbalance between resorption and bone formation that disproportionally affects women at younger ages than men (Drake et al. 2015). Its emergence is often accompanied by increased fat accumulation in premenopausal women (Toth et al. 2000), an association that may reflect the onset of dysregulated of skeletal metabolism. The earlier occurrence of osteoporosis among women reflects: 1) initially a lower peak BMC resulting from cumulative effects of smaller body size and reduced testosterone, 2) the metabolic rigors of pregnancy on the skeleton itself, and 3) the the reduction of estrogen production at the onset of menopause. Because the negative ills associated with bone loss occur past prime reproductive ages, antagonistic pleiotropy would have limited selective influence (Trevathan 2007; Tung and Iqbal 2007).

The data presented here documented early postnatal differences in bone mineral content accrual and weight gain that may reflect underlying variation in metabolic function, but do not specifically provide insight into the full causal process. Similar difficulties are embedded within the associations in humans between childhood diabetes/obesity and reduced BMC content (Kim et al. 2014; Reinehr and Roth 2010; Wang et al. 2014), where the origination point of the causal chain linking insulin resistance and decreased BMC cannot be inferred within the study design. In combination, however, these findings generate a testable hypothesis that such outcomes are set in place through pathways of MSC differentiation (Lecka-Czernik and Rosen 2016) that are set *in utero.*

Energy Sources for Bone Growth

The ongoing reformation process in bone represents a form of plasticity at the level of cellular division potential that may reflect an underlying adaptation favoring increasing body size even during nutritional scarcity, which has become dysregulated in our current environment of nutritional excess. Lecka-Czernik and Rosen (2016) propose that osteoblasts and adipocytes utilize distinct energetic pathways as they differentiate from MSCs, whereby both cell types utilize glucose during their initial progenitor phase (Shyh-Chang and Daley 2015) after which pre-osteoblasts leverage both oxidative phosphorylation and glycolysis (Esen et al. 2013; Guntur et al. 2014) and pre-adipocytes use mitochondrial respiration (Tormos et al. 2011). This separation would be indicative of an evolutionarily conserved program by which cell fates reflect availability of energy across two separate pathways that reflect cell-specific functions in the body: to store energy by producing adipocytes or to form and mineralize bone through osteoblasts

(Lecka-Czernik and Rosen 2016). This novel proposal contrasts with long-held views that frame energetic processes in a closed allocation-based system as put forth by life history theory. Here, predictions of energy trade-offs across three competing physiological domains (e.g., maintenance and repair of existing tissues, expansion of body size, and reproductive effort) (Hill and Kaplan 1999; Stearns 1992) are proposed as foundational, that direct energy to one domain at the expensive of the other. Bone remodeling has been offered as an example of costly maintenance due to its continual regeneration across the lifespan (Parfitt 1980) that is compromised in the form of bone mineral content loss in favor of promoting fitness via increased reproductive output (Madimenos 2015).

In contrast, these emerging data suggest instead that bone has a unique intrinsic energy source buffered from transient changes in extrinsic energy availability, enabling continued bone remodeling (Esen et al. 2013; Frey et al. 2015; Regan et al. 2014), which in turn produces and maintains the cellular components that have a functional role in global energy metabolism (DiGirolamo et al. 2012). This has a potential fitness enhancing advantage shared across vertebrates. For example, in an *in vivo* mouse model Regan et al. (2014) demonstrated that low-oxygen tension stabilizes the hypoxia inducible factor-1 alpha (HIF-1a) pathway, that in turn stimulates glycolysis to provide a distinct energy substrate to locally fuel cancellous bone formation independent of other energetic sources. These findings illustrate how endogenous energy production can support basic functions that are typically ascribed to the 'maintenance' domain of life history theory-based models of physiology and homeostasis. Others have criticized life history theory for not being inclusive of factors such as sociality for their effect on energy balance, specifically, and health outcomes and reproductive fitness, generally (Worthman

2003). These new data on the skeleton minimally should make us reconsider how we apply life history theory to understanding growth and development, and suggest we may benefit from more nuanced approaches to the concept of 'energy'.

Translational Implications for Human Health

We observed variation in the postnatal growth strategies for infants born to mothers of low and high social rank, with the former favoring accelerated accumulation of soft tissue in the form of total body weight and lean mass at the expense of bone mineral content. In contrast, infants born to high ranked mothers exhibited accelerated accumulation of bone mineral content without concurrent effects on soft tissue morphology. We propose that these distinct pathways of growth extend from differences in intrauterine exposure to glucocorticoids that subsequently altered fetal bone, hand in hand with alterations to metabolic function. While our model leveraged maternal social subordination as a proxy for glucocorticoid exposure, other exposures similarly up-regulate the production of glucocorticoids, including both over- and undernutrition (Cottrell et al. 2012) and nicotine use (Mendelson et al. 2006). Further, in our study increased positive maternal energy balance (early increased weight and higher gestational weight gain) was associated with accelerated postnatal weight gain and weight to crown-heel length gains. Maternal obesity itself is an exposure that evokes a glucocorticoid storm (Leddy et al. 2008). Thus, the mechanism proposed here is of translational significance far beyond just the experience of chronic stress. Instead, it represents a common pathway by which multiple life exposures contribute to a similar outcomes of accelerated weight gain, which in turn increase the risk for chronic disease. Based on this hypothesis, key individual-level targets for intervention include focusing efforts to

improve early childhood skeletal health and community-level targets that include support for programs that seek to reduce behaviors that are associated with elevating glucocorticoids, particularly among girls and women of childbearing age.

Opportunities for Intervention

The results of the present study call attention to the underlying variability in postnatal BMC acquisition, an understudied area, and identification of intrauterine factors that contribute to these outcomes. This has been suggested previously by epidemiological observations linking early infant outcomes to the risk of osteoporosis in late adulthood (Cooper et al. 2009; Cooper et al. 2006) and the efforts to conduct prospective evidence documenting how pre- and postntatal factors also influence BMC composition during childhood by the same research group (Harvey et al. 2012; Heppe et al. 2014). The results of the present study joins others to suggest that interventions aiming to increase peak bone mineral content, particularly in females, will have two-fold results: 1) reducing the risk of osteoporosis in an individual's current lifetime, and 2) stimulating intergenerational transfer of bone mineral content to improve health for subsequent generations. Benefits from such interventions go beyond individuals' well-being and have implications for health policy. Improvements in this area could reduce osteoporosis-related spending due to both direct health care costs and indirect effects stemming from disability (Fox et al. 2015). Efforts in this area are already underway (Weaver et al. 2016), sponsored both by the government and private organizations, who are testing the effectiveness of different approaches through research with key benefits noted for outcomes attributable to physical activity and calcium supplementation (Beck and Snow 2003; Karlsson et al. 2008).

This study utilized social subordination as a proxy for the human experience of chronic psychosocial stress, which has previously been associated with hypercortisolism and dysregulated HPA axis functioning in nonhuman primates and humans alike (Marmot and Sapolsky 2014; Meyer and Hamel 2014; Nater et al. 2013). In addition to psychosocial stress, glucocorticoid chronicity is exhibited in response to behaviors like cigarette smoking (Mendelson et al. 2006) and chronic conditions like obesity and diabetes (Park and Ahima 2015; Steffensen et al. 2015). Community- and individual-level interventions that both increase social support and target behaviors that underlie hypercortisolism can be effective at improving health in the broadest sense. For example, by increasing social support individuals may be less likely to engage in negative coping behaviors like smoking, with simultaneous benefits for underlying physiology. Programs incorporating techniques such as meditation and self-affirmation coaching have demonstrated reductions in the symptoms of psychological stress, including levels of circulating glucocorticoids (Cohen and Sherman 2014; Goyal et al. 2014). To maximize the benefit for intergenerational population-level health, programs should specifically address coping and self-care strategies among adolescent and young women of childbearing age. Key outcomes of this approach could include an attenuation of the negative maternal influences on neonatal health that are associated with concurrent reports of psychosocial stress (Hompes et al. 2012), such as the acceleration of postnatal weight gain observed among socially subordinate infants in the present cohort.

Balancing Risks and Benefits: Failures When 'Normal' Growth is Expected

The importance of early development for health has gained increasing attention given the substantial body of work documenting their association with lifespan health

(Barker 2012). Several proposals have been put forward to identify those most at risk, for example by using routine clinical monitoring of weight-for-length percentile crossing (Taveras et al. 2011), or developing prognostic risk algorithms that can be integrated with a medical record (Robson et al. 2016) or used by parents as a mobile phone application (Santorelli et al. 2013). The former approach has been criticized (Frongillo and Lampl 2011), as it ignores that percentile crossing is a typical feature of early infant postnatal growth (Mei et al. 2004) and that population-level growth charts misrepresent the fundamental nature of skeletal grow (Lampl 2012; Lampl and Thompson 2007). Further, increased weight alone does not yield insight into the underlying physiological system; excess fat mass not lean mass is the true health concern.

The results from this study show that the latter approach, developing risk algorithms, needs to cast a wide net in terms of what 'predictors' are used when constructing such tools, including how factors interact or synergize. The present study documented that maternal phenotypes differentially translated into health benefits depending on maternal social rank, while social rank alone was not predictive of fetal or postnatal growth trajectories. The translational application of our indicator of chronic psychosocial stress must be carefully considered for its application to human maternal stress. Demographic characteristics such as socioeconomic status are commonly used for population-level research as indicators of stress exposure, and have been shown to be associated with health outcomes of children and adults alike in global settings (Marmot 2005). However, these indicators can be transient and thus not predictive of past or future risk. Maternal or paternal educational attainment are suggested as alternative more stable proxies, as education cannot be taken away, though the recent United States economic

recession has shown that education is not always protective from income insecurity (Western et al. 2012).

When determining how to incorporate more nuanced individual-level indicators of potential in utero stress exposure, we must carefully balance the ethical implications of asking such questions without providing due support to families. For example, while there are several surveys that can be employed to assess maternal experience of stress during pregnancy (Harville et al. 2009), clinicians may not be equipped with the tools or experience needed to provide emotional support or counseling based on the survey outcomes (Halpern 2003). Thus, while our findings point towards the importance of considering how maternal stress affects infant physiology, the translational applications for predicting obesity risk among infants and children must be carefully considered in consideration of the potential unknown and unintended consequences. In this vein, risk profile tools are useful only in environments where such information can empower change rather than induce feelings of stigma (Puhl and Heuer 2010), which interferes with efforts to alleviate symptoms associated with the outcome of interest.

The possibility of pharmacological interventions for reducing overweight and obesity in children, adolescents, and adults has received substantial attention, yet are largely ineffective in the short term and have unknown long term effects (Levri et al. 2005; Park et al. 2009). While behavior modification-based interventions can be difficult to implement, they represent the likeliest way to address obesity when carried out across several levels (e.g., individual-, family-, community-) and work across sectors (e.g., government and policy, health care, industry) (Frieden et al. 2010). However, given that systematic reviews have found past interventions to be limited in their effects (Blake-

Lamb et al. 2016; Bluford et al. 2007; Ciampa et al. 2010; Redsell et al. 2016; Waters et al. 2011), it is clear that efforts should focus on determining more efficatious intervention options and validation of currently accepted approaches. Further, it is worth considering how, at a population-level, we can draw attention away from assigning individual responsibility for obesity and move towards greater recognition of how broader social and cultural values affect health and well being. The results reported herein suggest that population-level health disparities that are attributed to race/ethnicity and socioeconomic status reflect intergenerational transmission of inequities through their downstream impacts on physiology.

Chapter 5 References

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