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**EARLY-LIFE INFLUENCES ON AGE AT MENARCHE, BODY
COMPOSITION, AND METABOLIC ECONOMY**

by

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B.A., Economics, University of Michigan, 2004

M.S., Anthropology, University of New Mexico, 2006

DISSERTATION

Submitted in Partial Fulfillment of the
Requirements for the Degree of

**Doctor of Philosophy
Anthropology**

The University of New Mexico
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ABSTRACT

Prenatal energy balance and postnatal psychosocial experiences have been linked by separate literatures to maturational timing, adult body composition (e.g., height, skeletal muscle mass), and life-long differences in metabolic physiology. This dissertation examines the potential influences of prenatal energy balance and postnatal psychosocial experiences in simultaneous analyses designed to test whether they exert additive or interacting influences on adult body composition (chapters 2 and 4), metabolic physiology (chapter 3), and age at menarche (chapter 4) among samples of U.S. men and women. Evolutionary models that address human developmental plasticity are explored as possible explanations for the observed relationships.

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Chapter 1: Introduction

Small birth size, independent of gestational age or proximate cause, has been employed as an indicator of growth-limiting energy balance during fetal development (Barker, 1995). Differences in birth size have been linked to differences in female maturational tempo (Cooper et al., 1996; Ibanez et al., 2000, 2006; Morris et al., 2010; Ong et al., 2009; Ruder et al., 2010; Sloboda et al., 2007) and to life-long disparities in metabolic physiology (Barker, 1993; Hales and Barker, 1992; Hovi et al., 2007; Martyn and Greenwald, 1997; Osler et al., 2009; Yajnik et al., 2003) and body composition. In terms of body composition, these differences include deficits in muscle mass and height (Hediger et al., 1998; Kahn et al., 2000; Kuh et al., 2002; Sayer et al., 2004, 2008). This body of research suggests that prenatal experiences influence human developmental plasticity. Existing hypotheses attempting to explain these links have relied on evolutionarily adaptive as well as non-adaptive frameworks often with little empirical support. This dissertation aims to provide empirical tests of adaptive explanations for the observed links between birth size and the later-life outcomes listed above.

Because birth size may be linked to sociocultural factors that also influence qualities of the postnatal developmental environment (e.g., maternal socioeconomic status), a fundamental challenge to this type of human developmental plasticity research is isolating prenatal from postnatal effects and assessing, in cases when both effects are found, if they represent independent or interacting exposures. Regarding the outcomes examined by this dissertation, strong postnatal effects have been documented in the prediction of maturational timing (Belsky et al., 1991; Chisholm, 1993; Sheppard and

Sear, 2011; Wise et al., 2009), body composition (Euser et al., 2005; Kuh et al., 2002; Sachdev et al., 2005), and metabolic physiology (Cohen et al., 2007; Lemelin et al., 2009; Winkleby et al., 2007). In order to properly examine potential relationships between birth size and these outcomes, the models developed in this dissertation statistically control for postnatal experiences that have been linked, by previous research, to the outcomes of interest. Simultaneously examining birth size and postnatal factors in combined analyses, this dissertation examines not only whether they exert independent or interacting effects, but also allows comparison of their relative magnitudes of influence on the biological outcomes of interest.

Evolutionary Explanations for Human Developmental Plasticity

Life History Theory

Life History Theory posits a causal relationship linking environmental conditions to fitness-optimizing resource allocation decisions. The resources of interest to organisms include energy and, especially when future reproductive opportunities are uncertain, time. At every time-point across the life cycle, organisms invest whatever energy they currently possess into the discrete fitness-enhancing functions of maintenance and survival, growth, or reproduction. The cumulative impact of these allocation decisions summed across a lifetime is reflected in adult body size, the timing of reproductive maturation, the frequency of reproduction, longevity, and, of ultimate interest to evolutionary ecologists, the number of surviving offspring produced. Life History Theory provides a predictive framework for understanding variation in individual investment preferences, as reflected in these plastic life-history characteristics and events (body size, age at reproductive maturation, etc.), based on the expected fitness returns to investment

in competing priorities (survival, growth, reproduction) within the varying environments experienced by individuals.

Invoking Life History Theory, this dissertation proposes that developmental environments shape the investment preferences of growing youth and that these preferences explain observed variations in age at menarche, adult body composition (specifically height and skeletal muscle mass), and aspects of adult metabolic physiology. In all chapters, this dissertation tests the Life History-derived hypothesis that growth and maintenance are devalued within environments marred by health and survival hazards (in which expected reproductive lifespan may be reduced). The expected fitness returns to growth and maintenance are discounted within dangerous environments by the probability of dying prior to achieving said benefits. In these environments growth is predicted to cease earlier in life, allowing accelerated maturation and earlier reproduction. Earlier reproduction may improve the chances of successfully reproducing prior to death. This dissertation proposes that earlier cessation of growth should correlate with earlier age at menarche and reduced adult body size. By the same logic, adults (who have ceased growing) living in dangerous environments may reduce energetic investments in maintenance so that more energy may be invested in current reproductive effort. This dissertation proposes that reductions in maintenance costs should be observable as reduced caloric requirements in adults.

Fetal Programming Models

Fetal programming models suggest that prenatal conditions, particularly fetal energy balance, initiate developmental trajectories that track into adulthood and can explain observed phenotypic variations. A variety of fetal programming models are

addressed in this dissertation in attempts to explain observed variation in adult body size, metabolic physiology, and age at menarche.

Chapter 2 invokes a fetal programming model to predict permanent deficits in muscle mass among people who experienced energetic scarcity *in utero*. Limiting the development of muscle tissues *in utero* may be an adaptive fetal response to tightened energetic constraints if limited energy is preferentially re-allocated to other tissue types that provide a higher expected fitness return than muscle tissue.

Chapter 3 tests predictions derived from the *Predictive Adaptive Response* (PAR) fetal programming model as proposed by Gluckman and Hanson (2004, 2006). The PAR model suggests that fetal energetic scarcity induces life-long adjustments in metabolic physiology that serve the sole adaptive purpose of improving metabolic homeostasis during adulthood (Gluckman et al., 2007).

Chapter 4 attempts to test the idea that fetal energy balance influences female maturational timing reflected in age at menarche. Previous research has linked small birth size, an indicator of prenatal energetic scarcity, to earlier ages at menarche (Cooper et al., 1996; Ibanez et al., 2000, 2006; Morris et al., 2010; Ong et al., 2009; Ruder et al., 2010; Sloboda et al., 2007). Since women who achieved menarche at younger ages are shorter as adults (Georgiadis et al., 1997; Okasha et al. 2001; Onland-Moret et al., 2005; Sear et al. 2004), chapter 4 attempts to test whether fetal energy balance influences female adult stature independent of its impact of maturational timing.

Outline

This dissertation is organized into sections that describe tests of the adaptive hypotheses outlined above. Chapter two addresses the downstream influences of

developmental events on adult muscle mass, a component of body composition previously linked to birth weight. In an attempt to test the *Predictive Adaptive Response* model, chapter three examines adult metabolic sensitivity to negative energy balance in light of birth size while simultaneously controlling for life history-informed confounders. Chapter four characterizes the impacts of birth weight and childhood psychosocial experiences on age at menarche in a contemporary cohort of U.S. girls from NHANES 2007-2010. Then chapter four examines whether these same developmental experiences exert additional influences on women's height independent of their impact on age at menarche. Each chapter contains suggestions for improved study design and future research directions. A summary and synthesized conclusions are presented in chapter five.

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Chapter 2: Psychosocial stress, rather than birth weight, limits the development of human muscle mass

Introduction

Small birth size has been repeatedly linked to reduced skeletal muscle mass, an association that has been observed in both sexes and at every life stage from infancy through post-reproductive adulthood (Hediger et al., 1998; Kahn et al., 2000; Kuh et al., 2002; Sayer et al., 2004, 2008). The early appearance of this association and its persistence throughout the life course suggest that experiences prior to birth influence the development and growth trajectory of skeletal muscle tissues (Baker et al., 2010; Cameron & Demerath, 2002). Because birth size is considered an indication of fetal energy balance (Barker, 1995), it has been proposed that energetic scarcity *in utero* may interrupt normal muscle development during a critical window beyond which unrealized growth potential can never fully recover (Barker, 1995; Cameron & Demerath, 2002). Limited data generated from fetal autopsy (Stickland, 1981) and studies documenting postnatal muscle growth subsequent to small birth size (Baker et al., 2010; Sachdev et al., 2005; Sayer et al., 2004) support this idea. Human muscle development appears to follow the general mammalian trajectory according to which cell differentiation—including myofiber number, type, and bodily distribution—is largely fixed before birth (Bee, 2004; Jensen et al., 2007; Stickland, 1981). Thus, observed relationships between prenatal growth restriction and downstream reductions in muscle mass may reflect a general mammalian pattern rather than a specifically human adaptive relationship (Rehfeldt & Kuhn, 2006; Zhu et al., 2004).

While previous research linking early-life development to later musculature has often emphasized the impact of *prenatal* experience, there are a number of reasons to

suspect that *postnatal* growth plays an important role in the development of adult muscle mass as well. Weight gains in infancy and childhood have been linked to adult lean mass independent of birth size (Euser et al., 2005; Forsén et al., 2000; Kuh et al., 2002; Sachdev et al., 2005), suggesting that early postnatal muscle growth tracks into adulthood. While the number of skeletal muscle cells does not appreciably increase after birth (Appell et al., 1988; Kelley, 1996; Sjöström, et al., 1991) (except possibly under specific training regimes that are unlikely to occur naturally [Folland & Williams, 2007; Gonyea et al., 1986]), existing cells elongate and the total volume of each cell increases during periods of developmental hypertrophy (Jackowski et al., 2009; MacIntosh et al., 2006). Muscle growth is patterned after skeletal maturation in both boys and girls such that childhood represents a period of slow and steady accumulation of muscle volume followed by peak muscle growth velocity during adolescence (Jackowski et al., 2009; Webber & Barr, 2012; Xu et al., 2009). In adolescent boys, gonadal testosterone facilitates additional muscle gain such that muscle mass surpasses that of girls by Tanner Stage III and continues growing into early adulthood (Neu et al., 2002; Rogol et al., 2002). Assuming each myofiber has a limited size capacity, prenatally-fixed muscle cell number may limit total achievable muscle mass while conditions during periods of developmental hypertrophy may influence the body's "set point" of muscularity. Separated in time, prenatal impacts on hyperplasia (increased cell *number*) and postnatal impacts on hypertrophy (increased cell *size*) may represent independent predictors of downstream muscle mass. At least one published study suggests that periods of prenatal and childhood energetic scarcity reflect non-interacting exposures capable of independently shaping anatomical development (Bogin & Baker, 2012) and other

research suggests that downstream physiological trade-offs may originate *in utero* (Baker et al., 2010). However, at present, it remains unclear if and how prenatal and childhood nutrition might interact during the development of adult muscle mass.

In addition to the impacts of energy balance on muscle development, early-life cues that reduce a child's expectation of viable reproductive lifespan (i.e., health and longevity) may, by inducing a strategy that de-emphasizes 'growth and maintenance' in favor of other life-history objectives (Stearns, 1992), attenuate periods of muscle accumulation and reduce achieved adult muscle mass. Childhood psychosocial stress has been proposed as a signal of elevated local morbidity and mortality that may accelerate maturation and profoundly shift developmental trajectories (Coall & Chisholm, 2010; Coall et al., 2012; Nettle et al., 2011). Because achieved adult body size (kg) is the product of growth rate (kg/time) and the duration of growth (time), childhood stressors that inform maturational timing may reduce adult body size by accelerating maturation (reducing the duration of growth). Consistent with this hypothesis, epidemiological research suggests that adverse childhood experiences like abuse, removal of a parent from the home, and witnessing violence correspond to elevated local mortality rates (Adler et al., 1993; Chen et al., 2002), earlier reproductive senescence among women (Geronimus, 1987, 1992), and quantifiable reductions in lifespan (Brown et al., 2009; Felitti et al., 1998), providing a link between childhood psychosocial stress and reductions in viable reproductive lifespan. Elevated childhood adversity also predicts earlier ages at menarche (Belsky et al., 1991; Chisholm, 1993; Draper & Harpending, 1982) and first reproduction (Davis & Werre, 2007; Nettle et al., 2011; Sheppard & Sear 2011), suggesting a link between adversity and maturational timing. It is plausible that

stressful childhood experiences trigger earlier maturation at a smaller body size, reducing investments in skeletal muscle mass, perhaps in a manner independent of pre- and post-natal nutritional experiences (Bogin & Baker, 2012).

In response to a growth-limiting energy balance or an energy allocation paradigm that de-values ‘growth and maintenance’ in favor of competing fitness priorities, muscle tissue may be uniquely expendable. Muscle tissue is metabolically-active such that any reduction in muscle mass reduces basal energy requirements (Tzankoff & Norris, 1977). Each kilogram of skeletal muscle contributes approximately 13 kcals/day to the resting energy expenditure of adults (Elia, 1992). Thus, limiting energetic investment in muscle development reduces both the cost of growing the tissue and the daily costs required to maintain the tissue. A similar liberation of energy could only be achieved by limiting the development of other metabolically-active tissues (i.e., organs) (Galleghar et al., 1998). If the fitness benefit to the development of any of these tissues exceeds the fitness benefit to energetic investment in muscle development, individuals whose early-life physiology limited muscle growth due to such a ‘priority rule’ would be favored by selection (Zera & Harshman, 2001). One proposed beneficiary of sacrificed muscle development is the brain (Baker et al., 2010; Barker, 1993; Rudolph, 1984). Another proposed beneficiary is immune function, which could dramatically impact fitness by improving infant survivorship (Kuzawa, 1998; Kuzawa et al., 2007).

Based on this body of previous research, the current study investigates three avenues by which adult muscle mass might be modulated. First, birth weight is included as an indicator of prenatal nutrition (Barker, 1995) that may impact adult muscle mass by constraining myofiber hyperplasia *in utero*. Second, relative leg length (“RLL,” [height –

sitting height]/height x 100 as defined by Frisancho et al. [2001]) is used as an indicator of childhood nutrition (Wadsworth et al., 2002). The majority of childhood growth in stature occurs in the legs (Bogin, 1999; Leitch, 1951; Scammon, 1930) such that nearly 80% of adult leg length is achieved by age 10 (Tardieu, 2010). Because adult relative leg length is sensitive to disruptions in energy balance during infancy and childhood (Li et al., 2007; Wadsworth et al., 2002), RLL is increasingly used in epidemiological research as an indication of energy stability from birth to puberty (Bogin & Baker, 2012; Bogin & Varela-Silva, 2010). Adults with shorter RLLs presumably suffered nutritional constraints during pre-pubertal development. Because leg growth and pre-pubertal muscle hypertrophy overlap, it is reasonable to suspect that short RLL may correlate with reduced adult muscle mass, potentially capturing a relationship between growth-limiting childhood nutritional conditions and muscle mass development. Third, I assess the impact of adverse childhood psychosocial experiences on adult muscle mass by linking muscle mass to the results of a survey designed to capture the level of psychosocial adversity participants experienced during development. Assuming perceived stressful events inform energy allocation decisions that affect achieved adult body size, it is possible that the level of exposure to adverse childhood events might negatively correlate with adult body size and underlying components of adult body size including skeletal muscle mass.

Methods

Conceptual Model

During fetal life and early childhood, energetic scarcity constrains the energy budget available for investment in muscle development and other fitness-enhancing functions (e.g., growth of other tissue types including the brain, maintenance, survival

functions including immunity). Early-life energetic scarcity may, by itself, induce allocation decisions that favor ‘not muscle’ fitness-enhancing functions at the expense of muscle development. Any reduction in energy allocated to muscle development is made available for investment in competing priorities (Zera & Harshman, 2001). If the expected fitness benefit to investment in any of these competing priorities exceeds the expected fitness benefit to energetic investment in muscle development, individuals whose early-life physiology allowed economization of energy in this way would be favored by selection.

Childhood psychosocial stress that foreshadows reduced reproductive lifespan may limit investments in ‘growth and maintenance’ independent of energy balance (Sibley & Calow, 1986; Stearns, 1992; van Noordwijk & de Jong, 1986). This may reduce achieved adult body size specifically via components of body size that are both energetically-expensive to maintain and “expendable.” As explained above, muscle tissue fits this profile because it is metabolically-active and may be expendable if the fitness benefit to any competing priority exceeds the fitness benefit to investment in muscle development.

I propose that small birth size reflects fetal energetic scarcity (indifferent to causes related to placentation, maternal energetics, or the fetus’ ability to conduct cellular respiration). In line with much empirical research, fetal energetic scarcity is proposed to constrain fetal skeletal muscle development in such a way that reduces observed skeletal muscle mass later in life (Hediger et al., 1998; Kahn et al., 2000; Kuh et al., 2002; Sayer et al., 2004, 2008). Disruptions in energy balance throughout infancy and childhood are proposed to constrain the accumulation of muscle mass further—potentially independent

of fetal experience (Euser et al., 2005; Forsén et al., 2000; Kuh et al., 2002; Sachdev et al., 2005), which would appear as additive effects on observed adult muscle mass.

Subject Recruitment

The data for this study were collected as part of a larger exercise physiology research project. Subjects were recruited from the Albuquerque Metro Area by print and internet advertisements (e.g., craigslist, newspaper classifieds). Subjects included healthy men and women ages 18-38 who had access to accurate birth records (e.g., through a living mother). Subjects were weight-stable within the year preceding participation and had no history of diabetes or disorders of the heart, lungs, or kidneys. Female subjects were not currently pregnant or breastfeeding. Due to research questions not presented here, exclusion criteria included use of drugs known to alter metabolism (e.g., Adderall, nicotine) (PDR, 2008), except thyroid hormone therapies which were allowed so long as dosage had not changed within the 6 months preceding participation. Two subjects reported current thyroid therapy, both of whom were women being treated for hypothyroidism. Because hypothyroidism can be associated with muscle atrophy (Argov et al., 1988; Khaleeli et al., 1983), separate analyses were run including and excluding these two subjects. Subjects born under 6 lbs (~2700 g) were over-recruited in order to increase the number of lower birth weight subjects. This study was approved by the Human Research Review Committee at the University of New Mexico Health Sciences Center (HRPO #10-338).

Variables

All measurements were taken by the author (Workman) who completed training programs in nutrition assessment and exercise physiology laboratory methods at the

University of New Mexico (Department of Health, Exercise and Sports Science). Skeletal muscle mass was estimated from height and upper-arm muscle area using the sex-specific equations developed by Heymsfield et al. (1982). Mid-upper arm circumference and triceps skinfold were measured at the mid-point between acromion and olecranon processes (shoulder and elbow) of the subject's dominant arm using non-stretch tape (Mabis, Waukegan, IL). To minimize observation error, the average circumference and median skinfold values (to nearest mm) of 3-4 repeated measures were used for analyses. Weight (to the nearest 1/10th kg) was measured in minimal clothing, shoes off using the same digital scale for every subject (Seca, Chino, CA).

'Relative leg length' (RLL), as defined by Frisancho et al. (2001; $[(\text{Height} - \text{Sitting Height})/\text{Height}] * 100$), was used to indicate energy balance throughout infancy and childhood. Measurements of a subject's height and sitting height (to nearest mm) were recorded using the same wall-mounted stadiometer (Seca, Chino, CA). To reduce observation error, all heights were taken without shoes after aligning the subject's eyes and ears on a plane parallel to the floor. In keeping with previously published methods, subjects were defined as 'short RLL' if their RLL fell below the sample mean (Frisancho, 2007). The mean RLL of the sample was of 46.75%.

Birth weight (to the nearest g) was used to indicate fetal energy balance. Subjects were asked to contact their mother or to reference a birth record in order to accurately report their own birth weights. Subjects recorded their birth weights on a questionnaire and during follow up, were asked how they learned the information. Of the 50 subjects, 3 reported consulting an heirloom baby book, 1 consulted a family bible, 1 consulted an embroidered heirloom baby blanket, 1 consulted her maternal grandmother, and 44

reported consulting their mothers. The accuracy and reliability of maternally recalled birth weight is high in western societies regardless of maternal age, educational or socioeconomic status (Adegboye and Heitmann, 2008; Catov et al., 2006; Goffin et al., 2000). The accuracy of birth weight in other records is unknown. Subjects were defined as ‘small at birth’ if born under the mean birth weight of the sample. The mean birth weight of the sample was 3088g (6 lb 13 oz, s.d.=684 g), which is below the 25th percentile for U.S. births (Kuczmarski et al., 2000). Alternative analyses were run using the clinical definition of ‘low birth weight’ (<2500 g).

A retrospective questionnaire provided data on potential confounding variables and psychosocial stressors experienced between birth and age 15. Confounders included self-reported ethnicity (by checking options or filling in the “other” line), birth date, and habit of weightlifting exercise. Subjects were coded as ‘weightlifter’ if they replied “yes” to the question “Do you regularly lift weights?” Age at date of participation was calculated based on reported birth date (to the nearest 1/10th of a month).

The remainder of the questionnaire was designed to capture levels of psychosocial adversity experienced between birth and age 15 years. Modified from published questionnaires found to predict emotional and physiological responses to stress (Kohrt & Worthman, 2009), young adult mental health (Attar et al., 1994; Mayer et al., 2009), and cardiovascular disease risk (Krieger, 1990; Krieger & Sidney, 1996; Krieger et al., 2005), each question was intended to capture a distinct health or survival hazard. All questions are listed ad verbatim in Table 1. The same set of questions was repeated in triplicate in reference to the age ranges ‘birth to 5th birthday,’ ‘age 5 to 10th birthday,’ and ‘age 10 to 15th birthday.’ Analysis was run on the number of questions with at least one affirmative

response reported between birth and age 5, birth to age 10, and birth to age 15. This meant that a subject's total 'stress score' could range between 0 and 13 (because there were 13 questions total) despite answering "yes" repeatedly to the same question in reference to events experienced during multiple age ranges. In this way subjects were scored by the number of types of stressful experiences recalled rather than a cumulative number of events, a method commonly employed by studies linking early psychosocial stress to downstream outcomes (Brown et al., 2009; Coall & Chisholm, 2010; Danese et al., 2009; Felitti et al., 1998). Subjects were then classified as 'high stress' if they reported experiencing 4 or more types of adverse events prior to age 5 (n=6), 6 or more types prior to age 10 (n=6), and 8 or more types prior to age 15 (n=3). Similar thresholds have been used in published research linking childhood psychosocial adversity to later-life health outcomes (Brown et al., 2009; Felitti et al., 1998).

Predictions

A summary of operationalized concepts and hypotheses is provided in Table 2. Because growth-limiting energy balances *in utero* and between birth and puberty may constrain skeletal muscle development, I predict that small birth size and short relative leg length will correlate with reduced adult skeletal muscle mass after controlling for relevant confounders (e.g., sex, total body mass, intentional muscle-building exercise habits, age, ethnicity). High level of exposure to psychosocial stress prior to age 15 is also expected to correlate with reduced adult muscle mass independent of the effects of birth size and relative leg length.

Statistical Analyses

As an initial analytic step, descriptive statistics, bivariate correlation plots, and mean-by-groups plots were constructed. Pearson correlations were calculated between birth size, RLL, and each age range of 'high stress.' Multiple regression was used to assess the influence of predictor variables (birth size, RLL, and stress) on skeletal muscle mass while controlling for potential confounders (e.g., sex, exercise habits). This method allows examination of multiple simultaneous influences on a single outcome variable while considering the effects of every other predictor in the model (Belsley et al., 1980; Neter et al., 1999). Further, it allows comparison between the relative magnitudes of influence of each predictor on the outcome of interest, after controlling for all other effects (Neter et al., 1999). Potential confounders of the relationships linking prenatal, childhood nutritional, and psychosocial experiences to adult skeletal muscle mass included in the model selection procedure were: weight, sex, age, weightlifter status, Hispanic ethnicity, and Caucasian ethnicity (other ethnicities were under-represented in our sample). Backward elimination was employed by first fitting a model containing all predictors, then systematically eliminating one predictor at a time based on the highest p-value at each iteration. An ultimate cut-off criteria of $\alpha=0.05$ was employed for all variables included in the final model. I included all possible interaction terms in this process. Where eliminated, theory-motivated predictors were assessed using added variable plots (Cook, 1993, 1994; Zurlo et al., 1990), and, where graphically suggested, were reintroduced into the final model and tested for statistical significance before final elimination. No non-significant predictor was included in the final model because inclusion of non-informative predictors has been shown to bias the estimation of the

remaining coefficients in the model (Belsley et al., 1980). The final model was evaluated for colinearity graphically, using bivariate correlation plots between predictors, and formally, using variance inflation factors (Neter et al., 1999). General model fit was assessed using plots between predicted values and residuals as well as through histograms and normal probability plots of residuals (Cook, 1994; Neter et al., 1999). Errors were normally distributed and no dependency between fitted values and residuals was observed. Residuals associated with the final models presented in this paper did not deviate from normality based on Kolmogorov-Smirnov tests (Neter et al., 1999; Smirnov, 1948).

Results

The average skeletal muscle mass of men in this sample was 31.0 kg (S.E.=6.5kg, n=25). The average skeletal muscle mass of women in the sample was 19.3 kg (S.E.=4.4kg, n=25).

No correlations were found between ‘small birth size,’ ‘short relative leg length,’ and any age range of ‘high stress’ category (see Table 3), ensuring the linear independence of predictors included in the final analysis. As continuous variables, ‘birth weight,’ ‘relative leg length,’ and ‘cumulative types of adverse childhood experiences’ (any age range) failed to achieve statistical significance in the prediction of skeletal muscle mass. After controlling for total body mass, the parameters related to ethnicity, ‘short relative leg length,’ and ‘small birth size,’ failed to achieve significance as well.

The final regression model explaining skeletal muscle mass included predictors that achieved statistical significance at the $\alpha=0.05$ level (variance inflation factors did not exceed 2.0). In the final model, male sex, overall body size, age, and self-

identification as someone who routinely lifts weights positively correlated with muscle mass (see Table 4). Alone, these variables explained 79.5% of the observed variation in adult skeletal muscle mass (results not presented). In three separate models, each age range of ‘high stress’ was included in addition to these confounders of muscle mass. Although all ‘high stress’ definitions returned negative coefficients, only ‘high stress: birth-10yr’ (i.e., reported experiencing 6 or more types of adverse events prior to the 10th birthday) achieved statistical significance (final model presented in Table 4) and explained 10% of the remaining variation after controlling for sex, age, and weight-lifting status.

In the final model ($R^2=81.6\%$), men had 7.3 kg more muscle mass than women ($p<0.001$) and weightlifters enjoyed 4 kg more muscle mass than non-weightlifters ($p<0.001$) (after controlling for all other included predictors in the model). At baseline, subjects scored as ‘high stress: birth to age 10’ (i.e., accumulated 6 or more types of adverse childhood events within the first 10 years of life) had 4.1 kg less muscle mass than subjects who experienced fewer adverse events during this age range ($p=0.027$). For every 1 kg increase in total body weight, muscle mass increased by 0.24 kg ($p<0.001$) and for every 1 year increase in age, muscle mass increased by 0.31 kg ($p=0.003$).

Exclusion of the hypothyroid women did not alter the model.

One interaction term approached significance when added to the general model. ‘Weightlifter x High stress: birth-10yr’ was associated with a negative coefficient ($\beta=-6.221$, $p=0.052$) suggesting that weightlifters of high stress enjoyed less of an increase in skeletal muscle mass *due to their weightlifter status* than weightlifters of low stress.

Discussion

Our results suggest that, within an urban U.S. population, prenatal and childhood nutrition do not impact adult muscle mass. Instead, a high level of exposure to psychosocial stressors during the first ten years of life is associated with reduced adult muscle mass. After controlling for appropriate confounders (sex, age, total body mass, weightlifting habit), a high level of psychosocial stress experienced between birth and the 10th birthday predicted a 4.1 kg (>9 lb) deficit in skeletal muscle mass relative to individuals who reported less stressful childhoods. Among men in this sample, a 4.1 kg decline in total muscle mass reflects a 13% change from the mean. Among women, this represents a 21% decline from the mean skeletal muscle mass observed. Additionally, the strong negative impact of the interaction term ‘weightlifter x high stress: birth-10yr’ on adult muscle mass suggests that childhood stress may severely reduce the sensitivity of adult muscle mass to hypertrophy-inducing activities.

These profound deficits in muscle mass observed among individuals who experienced high childhood stress support the hypothesis that early exposure to psychosocial stressors reduces adult body size through reductions in muscle mass. In the sampled population, this effect appears independent of energy balance during development. If the assayed psychosocial stressors communicate reduced viable reproductive lifespan, as has been previously proposed (Coall & Chisholm, 2010; Ellis et al., 2009; Nettle, 2011), it is possible that they induce a condition-dependent energy allocation strategy that de-emphasizes ‘growth and maintenance’ in favor of alternative fitness-enhancing functions. Within this population, postnatal energy balance was likely not growth-limiting (indeed only one in fifty of the study participants answered

affirmatively to sections of the questionnaire that asked “Did you ever go hungry due to lack of food?” and this was a man who achieved a height of 1.82 m [6 ft]). A shift in energy allocation away from muscle hypertrophy *despite adequate energy intake to support growth* may, due to evolved life history tactics, take the form of accelerated maturation and increased reproductive effort. Although unknown within the current study sample, psychosocial stressors have been linked to accelerated maturation in similar well-fed populations (Belsky et al., 1991; Chisholm et al., 2005; Draper & Harpending, 1982; Sheppard & Sear, 2011). However, future research is needed to investigate whether elevated childhood psychosocial adversity may exert similar effects on maturational timing and achieved adult body size within populations suffering growth-limiting energetic scarcity, and whether or not these impacts are independent of developmental nutrition.

The current study also suggests a threshold effect of accumulated adverse events during childhood. Although limited in sample size (n=50), the results suggest a level of heightened adversity must be achieved before evidence of reduced muscle mass is observed. Larger studies document a similar cumulative impact of childhood adversities on adult morbidity and mortality (Brown et al., 2009; Danese et al., 2009). Such an effect would be expected if the development of a ‘non-stressed’ phenotype was robust and the induction of an alternative phenotype associated with stress required adequate (e.g., reliable) signals of environmental condition. In other words, the developing body appears able to “absorb” a certain level of psychosocial stress without observable phenotypic consequence. In the current study, 6 or more events prior to the 10th birthday impacted adult muscle mass but 8 or more events prior to the 15th birthday did not. Future research

may address whether the developmental timing of stressful events or the ‘rate of accumulation’ of events influences their impact on adult phenotype.

The absence of ‘small birth size’ from the final model predicting adult skeletal muscle mass is surprising given known links between birth weight and later lean tissue mass (Fewtrell et al., 2004; Kensara et al., 2005; Labayen et al., 2006, 2008; Sayer et al., 2004, 2008; Yliharsila et al., 2007). Adjusting the birth size category definition to ‘low birth weight’ matching the clinical threshold (<2500 g) did not change this result, nor did replacement of the categorical variable ‘small birth size’ with continuous birth weight (birth weight was negatively correlated with muscle mass, though did not approach significance). The omission of childhood ‘high stress’ from analyses did not cause birth weight or either category of ‘small birth size’ to achieve significance. One possible explanation for this result is that the current study employed tomography- and 24-hr creatinine-calibrated equations for the calculation of skeletal muscle mass *independent of other lean tissues* (Heymsfield et al., 1982). Among 20 reviewed research articles reporting reduced lean mass among those born small, only half measured direct indicators of muscle mass as opposed to the difference between total body and fat mass (Table 5). Of these 10, only 3 reported reduced muscle mass among those born small after controlling for total body mass (Kensara et al., 2005; Kuh et al., 2002; Sayer et al., 2008). Although valuable for its separation of skeletal muscle from other components of lean tissue mass, the method employed in the current study suffers from several limitations. Skeletal muscle mass was calculated as the product of sex-specific constants, upper-arm muscle area, and height (Heymsfield et al., 1982). Therefore, this method is not sensitive to differences in muscle mass outside of the upper-arm that have been reported

previously (Kahn et al., 2000). Further, small birth size has been reliably linked to shorter stature (Gale et al., 2001; Kensara et al., 2005; Kuh et al., 2002; Li et al., 2003; Loos et al., 2001, 2002; Sachdev et al., 2005; Sayer et al., 2004; Wells et al., 2005; Weyer et al., 2000). After adjustment of height for sex, our small birth size group was 5.5 cm shorter than our average birth size group ($p=0.010$, results not presented elsewhere). If the body composition of those born small alters the scaling relationship of skeletal muscle mass to height, then the predictive equations may be invalid. In other words, differences in body composition among people born small, who represent less than 25% of the U.S. population as defined by the current study (Kuczmarski et al., 2000), may reduce the accuracy of predictive equations developed from a random sample of American men and women.

Also surprising in our final model is the limited difference in muscle mass attributable to sex. Within our sample (ages 18-38 yr), men had 7.3 kg (16.1 lbs) more muscle mass than women after controlling for differences in overall body size, age, weightlifting status, and childhood stress. Omitting childhood stress from the model increased this sex-difference to 7.6 kg (results not shown, $p<0.001$), but this is still a smaller difference than has been reported in other urban North American populations of the same age range (12 kg difference) (Janssen et al., 2000). One reason to suspect skewed observations of skeletal muscle mass in our sample is the self-selection of research participants. These data were collected as part of a larger exercise physiology research project that provided participants with free results of otherwise expensive fitness testing and required a 32-hr fast from all calories. The current data were recorded at the start time of the fast prior to fasting-related dropout, but the prospect of fasting for 32

hours may have differentially impacted recruitment of men and women of different muscle masses. Although speculative, women interested in participating due to free fitness testing may have been more muscular than a random sample of women. Also speculative, the prospect of fasting may have prevented men of higher muscle mass from participating because their anticipated discomfort due to fasting may have been amplified by their elevated caloric requirement.

Conclusion

Among an urban U.S. population, variation in pre- and post-natal energy balance did not explain variation in adult skeletal muscle mass. Instead, high exposure to psychosocial adversity in the first decade of life predicted reduced muscle mass and attenuated increases in muscle mass attributable to a regular habit of weightlifting exercise. This study supports the hypothesis that early-life psychosocial stress induces an energy allocation pattern de-emphasizing ‘growth and maintenance’ in favor of other fitness priorities. To investigate whether childhood stress impacts adult body size, including muscle mass, independent of developmental energy balance, future research should explore the reported relationships within populations suffering growth-limiting nutrition.

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Tables

Table 2.1. Survey of stressful events experienced during development. The same set of questions was repeated 3 times, once for each age range. Below are the instructions for the age range birth to 5 years.

Instructions: Please indicate if any of the following events happened from the time you were born until your 5 th birthday by circling Y (yes) or N (no).	
Y or N	1. Did you have a serious physical injury?
Y or N	2. Were you a witness or victim of physical violence?
Y or N	3. Did you ever hide someplace because of violence in your home or neighborhood?
Y or N	4. Did a relative who you were very close to suffer serious physical illness or injury?
Y or N	5. Did a relative who you were very close to suffer serious mental illness?
Y or N	6. Did a relative who you were very close to pass away?
Y or N	7. Did a relative who you were very close to spend time in jail (or juvenile detention)?
Y or N	8. Did you or a close family member experience discrimination, get prevented from doing something, or get hassled or made to feel inferior because of your race, ethnicity, color, ancestry, sexual orientation, gender, sex, religious affiliation, citizenship, or country of birth?
Y or N	9. Did one (or both) of your parents/step-parents become unemployed for a time?
Y or N	10. Did a relative who you were very close to move out of your home?
Y or N	11. Did you go to live with a different relative or spend time in foster care?
Y or N	12. Did you and your family move from one place to another?
Y or N	13. Did your family's home or property get wrecked in a natural disaster, accident, or crime?

Table 2.2. Concepts and variables linked to hypotheses.

Variable	Concept Operationalized	Hypothesis Tested
Small birth size	Growth-limiting energy balance <i>in utero</i>	Prenatal energetic scarcity restricts skeletal muscle development
Short relative leg length	Growth-limiting energy balance from birth to age 10	Energetic scarcity from birth to puberty restricts skeletal muscle development
High psychosocial stress	Cues of reduced viable reproductive lifespan	Cues of reduced viable reproductive lifespan attenuate skeletal muscle development

Table 2.3. Correlations between potential predictor variables, no linear relationships are significant

<i>r</i> (<i>p</i>-value)	Small birth size	Short relative leg length
Short relative leg length	0.181 (0.209)	
High stress: birth-5yr	0.045 (0.758)	-0.050 (0.729)
High stress: birth-10yr	0.045 (0.758)	0.075 (0.603)
High stress: birth-15yr	-0.054 (0.708)	-0.034 (0.813)

Table 2.4. Regression analysis of the effects of early-life events on adult skeletal muscle mass, kg (n=50).

Parameter	Constant	β	Std Err coeff	p-value	Model R^2
Body mass, kg	-4.715	0.239	0.042	<0.001	81.6%
Male		7.275	1.309	<0.001	
Weightlifter		4.037	1.049	<0.001	
Age, yrs		0.310	0.100	0.003	
High stress: birth-10yr		-4.087	1.788	0.027	

Table 2.5. Literature review: the impact of birth size on skeletal muscle mass depends on method of assessment, sex, and correction for body size.

Citation	Population	Birth size indicator	Age	Methods	Body size correction	Correlation of birth size w/ lean tissue		Correlation of birth size w/ muscle	
						M	F	M	F
Hediger et al., 1998	USA	SGA	Infants	UAMA	(none)			+	+
Sayer et al., 2003	UK	Continuous	Elderly	FFM	(none)	+			
				Grip strength	(none)			+	
Li et al., 2003	Guatemala	BW z-score	Adults	FFM	(none)	+	+		
Weyer et al., 2002	Pima, USA	Continuous	Adults	FFM	(none)	+	+		
Labayen et al., 2008	Spain	BW z-score	Adolescents	FFM	height	0	+		
Singhal et al., 2003	UK	BW z-score	Adolescents	FFM	height	+	+		
			Children	FFM	height	+	+		
Sachdev et al., 2005	India, urban	Continuous	Adults	FFM	height	+	+		
Yliharsila et al., 2007	Finland	Continuous	Elderly	Grip strength	height			0	0
				FFM	height	+	+		
Euser et al., 2005	Netherlands	BW z-score	Adults	FFM	height	+	+		
Kahn et al., 2000	USA	Continuous	Adults	ThighMA	height			+	
Wells et al., 2005	Brazil, urban	BW quartiles	Children	FFM	height	+			
Fretwell et al., 2004	UK	Preterm (all <1850g)	Children	FFM	height	0	0		
				UAMA	height			0	0
Rogers et al., 2006	UK	Sex-specific BW z-score	Children	FFM	height	+	+		
Labayen et al., 2006	Spain	BW z-score	Adolescents	FFM	height	0	+		
Loos et al., 2001	Belgium	Continuous	Adults	FFM	weight	+			
Loos et al., 2002	Belgium	Continuous	Adults	FFM	weight		+		
Sayer et al., 2008	UK	Continuous	Elderly	CT of forearm	weight, height			+	0
				CT of calf	weight, height			0	0
Kensara et al., 2005	UK	<25 th %tile (vs. >75 th)	Elderly	DXA for SM	weight, height			+	
				UAMA	weight, height			0	
Gale et al., 2001	UK	BW tertiles	Elderly	FFM	weight, height	+	+		
Kuh et al., 2002	UK	Continuous	Adults	Grip strength	weight, height			+	+

SGA, small for gestational age; FFM, fat free mass=(total body mass – fat mass), measured by anthropometric equations, dual x-ray absorptiometry (DXA), or bioelectrical impedance (BIA); UAMA, upper-arm muscle area|upper-arm circumference, triceps skinfold thickness; ThighMA, thigh muscle area|thigh circumference, thigh skinfold thickness; CT, computerized tomography scan.

Chapter 3: The Predictive Adaptive Response Hypothesis Fails to Explain Fasting-Induced Changes in Calorie Requirements

Introduction

Over the past quarter century, deficits in birth size (regardless of gestational age) have been convincingly linked to reductions in adult body size (Hediger et al., 1998; Kahn et al., 2000; Kuh et al., 2002; Sayer et al., 2004, 2008) and to elevated incidence of chronic diseases known to result from long-term peripheral insulin resistance (e.g., type II diabetes, atherosclerosis) (Barker et al., 1989; Barker, 1993; Hales and Barker, 1992; Hovi et al., 2007; Martyn and Greenwald, 1997; Osler et al., 2009; Yajnik et al., 2003). Under the assumption that relative deficits in birth size reflect relative deficits in fetal energy balance (Barker, 1995), it has been proposed that the energy-limited fetus adjusts its metabolism and growth trajectory in order to survive within its lower-energy environment (Wells, 2010). It remains unclear, however, why these phenotypic adjustments should persist into adulthood.

The *Predictive Adaptive Response (PAR)* model suggests that observed relationships between small birth size and adult phenotypes reflect evolutionarily adaptive adjustments made in expectation of an energy-limited future environment (Gluckman and Hanson, 2006; Kuzawa, 2005, 2008; Kuzawa et al., 2007). According to the PAR model, phenotypic adjustments induced by fetal energetic scarcity persist because they confer relative energetic savings throughout adulthood, and these energetic savings are thought to improve relative reproductive success within energy-sparse environments (Gluckman and Hanson, 2007).

Because the phenotypes observed downstream of fetal energetic scarcity may support a variety scenarios, *PAR* and non-*PAR* alike, it has been difficult for researchers

to definitively test *PAR* hypotheses (Ellison and Jasienska, 2007). For instance, the reduced adult body size associated with fetal energetic scarcity may reflect phenotypic susceptibility to growth-limiting energetic constraints in a non-adaptive developmental damage scenario (Barker, 1994, 1995). Alternatively, reduced adult body size may reflect adaptive adjustments to growth trajectory or energy allocation patterns that maximize fitness within the tightened constraints imposed by early energetic scarcity (Baker et al., 2010; Godfrey and Barker, 2000). Under a bet-hedging scenario, reduced adult body size may reflect a phenotype that minimizes differences in fitness attributable to fluctuations in environmental conditions (Jones, 2005). But only the *PAR* model proposes that phenotypes induced by fetal energetic scarcity serve the specific adaptive function of down-regulating somatic energy requirements within energy-scarce adult environments (Gluckman et al., 2007):

If the signals in the developmental phase suggest limited nutrient availability, then the organism will adjust its developmental trajectory such that the mature individual has a metabolic homeostasis better adapted for survival in a sparse environment. (p. 7)

In order to test the plausibility of the *PAR* model, the current study examines whether phenotypes associated with small birth size serve their proposed energy-sparing adaptive function in adulthood. Relying on the definition outlined by Williams (1966) and Curio (1973), adaptations are distinguished by a clear relationship linking an exposure (fetal energetic scarcity) to a response (phenotypes induced by fetal energetic scarcity) that improves fitness *in the environment inducing that response*. Unique to the *PAR* hypothesis is the prediction that individuals who are ‘cued in’ to an energy-scarce future environment should enjoy fitness benefits *during energetic scarcity*. I propose that

fitness benefits associated with a ‘predictive adaptive’ phenotype may be achieved by improving the sensitivity of metabolic demands to bouts of acute negative energy balance. To test this hypothesis, I compared within-subject energy consumption rates before and after exposure to a period of fasting. The *PAR* hypothesis predicts that those born small should enjoy greater energetic savings during this bout of negative energy balance.

Periods of fasting are known to modify metabolic demands at rest and during activity. Both resting energy expenditure (REE) and mechanical efficiency, the physical work that can be performed per calorie metabolized, are known to decline during fasting (Bahr et al., 1991; Elia et al., 1984; Kouda et al., 2006; Nair et al., 1987; Webber and MacDonald, 1994). Fasting-induced reductions of REE are thought to reflect a survival response whereby energy is diverted away from long-term fitness goals (e.g., reproduction) in order to support survival in the short-run. An illustrative example is the impairment of female fertility, modulated by ovarian hormone production, in response to negative energy balance (Ellison, 2003; Williams et al., 2010). Another example is the fasting-induced impairment of insulin sensitivity within skeletal muscles (Gjedsted et al. 2007; Newman and Brodows 1983; Mansell and Macdonald 1990), which is thought to preserve circulating glucose for consumption by insulin-independent tissues like the brain (Peters et al., 2004). The *PAR* hypothesis predicts that individuals ‘cued in’ to an energy-scarce environment enjoy relatively greater fasting-induced reductions in REE, allowing greater energetic savings (*Prediction 1*, see Table 1).

Mechanical efficiency refers to the amount of physical work that can be performed per calorie of energy consumed, analogous to the fuel economy of a vehicle.

In a fasted state, the added metabolic costs of gluconeogenesis and ketogenesis required to fuel metabolism in the absence of ingested carbohydrate drive mechanical efficiency down (Bahr et al., 1991; Elia et al., 1984; Webber and MacDonald, 1994). By increasing the metabolic costs of physical activity, fasting-induced reductions in mechanical efficiency likely exacerbate challenges faced during bouts of energetic scarcity (Cahill et al., 1996; Reaven, 1998). For example, impaired mechanical efficiency likely reduces the net return to energy-capture activities (Reaven, 1998). Hypothesized changes in phenotype congruent with a ‘predictive adaptive response’ may cushion mechanical efficiency from the negative impacts of calorie restriction (Stannard and Johnson, 2004; Wang and Mariman, 2008). Thus, the *PAR* hypothesis predicts relatively attenuated reductions in mechanical efficiency among those born small, allowing greater energetic savings while preserving physical performance (*Prediction 2*).

The *PAR* hypothesis belongs to the family of “fetal programming” models (Godfrey and Barker 2001; Lucas 1994) which treat fetal energetic constraint as the initiator mechanism responsible for phenotypes observed many years later. It remains unclear, however, whether fetal experience influences phenotype independent of postnatal experience. For instance, psychosocial stressors have been linked to type 2 diabetes, atherosclerosis, and coronary heart disease (Black, 2006; Chandola et al., 2006; Cohen et al., 2007; Krantz and McCeney, 2002; Lemelin et al., 2009; Vitaliano et al., 2002; Winkleby et al., 2007)—the identical suite of chronic metabolic illnesses linked to small birth size. Because it is plausible that small birth size and postnatal conditions covary (perhaps along sociocultural lines), it is necessary to assess whether birth size and postnatal experiences reflect independent exposures (Bogin and Baker, 2012). Because

indicators of an adjusted metabolism have been linked by separate literatures to prenatal energy balance and postnatal psychosocial stress, current evidence cannot distinguish whether these experiences exert independent or interacting effects on development.

Life History Theory provides an alternative explanation to fetal programming models for the persistence of energy-sparing phenotypes into adulthood. Life History Theory posits a causal relationship linking environmental conditions to energy allocation strategies. A phenotype characterized by reduced body size and limited energy consumption within insulin-dependent tissues (e.g., muscles) reflects a strategy that diverts energy away from somatic investment. Under Life History Theory, reduced somatic investment results from elevated risks to reproductive viability (e.g., mortality, infertility, senescence) (Charnov 1993, Roff 2002, Stearns 1992). If psychosocial stressors reflect risks to reproductive viability then they may contribute to the persistence of an energy-sparing phenotype throughout life. Consistent with this hypothesis, epidemiological research has demonstrated that adverse childhood experiences like abuse, removal of a parent from the home, and witnessing violence correspond to elevated local mortality rates (Adler et al., 1993; Chen et al., 2002), earlier reproductive senescence among women (Geronimus, 1987, 1992), and quantifiable reductions in lifespan (Brown et al., 2009; Felitti et al., 1998). These associations support the assumption that perceived childhood stressors signal actual risks to reproductive viability. Therefore, Life History Theory may motivate explanations for the observed links between childhood stress and altered metabolic phenotype, but current evidence cannot distinguish whether these effects occur independently of birth size.

To address the possibility that childhood psychosocial stressors, as indicators of risk to reproductive viability, independently impact the metabolic phenotypes observed during this study, I test the Life History-motivated hypothesis that elevated childhood psychosocial stress reduces somatic energy expenditure. I predict that this will be observable as reduced resting energy expenditure (*Prediction 3*) and greater mechanical efficiency (*Prediction 4*) among adults who experienced relatively increased levels of psychosocial stress during development. This Life History-motivated hypothesis does not directly inform our expectation of observed *sensitivity* of REE and mechanical efficiency to fasting. It may, however, predict that elevated childhood psychosocial stress will be linked to reduced somatic energy expenditure at all time points. This would appear as relatively reduced REE and relatively greater mechanical efficiency both before and after fasting among individuals who experienced greater psychosocial adversity during development.

Methods

Recruitment

Subjects were recruited from the Albuquerque Metro Area by internet and print advertisements (e.g., craigslist, newspaper classifieds), and included healthy men and women ages 18-38 who had access to an accurate record of their birth (e.g., through a living mother, written record). Subjects were weight-stable within the year preceding participation and had no history of diabetes or disorders of the heart, lungs, or kidneys. Female subjects were not currently pregnant or breastfeeding and women were asked not to schedule participation during menses. Women not on hormonal contraceptives were asked to schedule participation only during the luteal phase of their menstrual cycles.

Exclusion criteria included current participation in an elite athletic training program (e.g., pro cycling, NCAA sports) and regular use of drugs known to alter metabolism (e.g., Adderall, nicotine), except thyroid hormone therapies which were allowed so long as dosage had not changed within the 6 months preceding participation. Two subjects (both female) reported current treatment for hypothyroidism. Because hypothyroidism can affect muscle performance (Argov et al., 1988; Khaleeli et al., 1983) separate analyses were run including and excluding these two subjects (final model results did not significantly differ). Subjects were paid \$80 for completing the study. Those born under 6 lbs (~2700 g) were over-recruited in order to increase the number of small birth size subjects. No distinction was made between small birth size attributable to premature birth or other causes. This study was approved by the Human Research Review Committee at the University of New Mexico Health Sciences Center (HRPO #10-338).

Retrospective Data Collection

During the consent process that occurred no less than three days prior to metabolism testing, subjects received a questionnaire to take home. The questionnaire included sections on health history, drug and substance use (e.g., prescriptions, caffeine consumption, smoking), exercise habits, demographic information, birth circumstances, and adverse childhood experiences. Subjects were instructed to contact an older family member for help reporting early-life events they may not remember accurately. To improve confidentiality, questionnaires were returned in sealed envelopes only identified by participant ID number.

Experimental Design

Step 1: Metabolism Testing Controls

Throughout the recruitment and consent processes, subjects were informed of the fasting and lifestyle restrictions required during this study. At the time of consent that occurred no less than 3 days prior to testing, subjects were given verbal and written instructions to: (1) abstain from muscle-tearing activities (e.g., weightlifting, sprinting) and eating meat starting 3 days prior to metabolism testing, (2) abstain from metabolism-altering drug use (e.g., nicotine, caffeine, Ritalin, Adderall) starting 24 hours prior to metabolism testing, (3) eat a normal portion meat-free breakfast between 5 and 6 hours prior to the first round of metabolism testing with no calories thereafter, and (4) abstain from all forms of exercise on the mornings prior to metabolism testing. Subjects were also informed on the procedure for validating whether fasting had occurred (explained below) and that payment was contingent upon passing this validation procedure. All metabolism testing occurred between 1100 and 1400. Subjects were asked to schedule their metabolism tests to begin between 5 and 6 hours after their average daily waking time.

Step 2: Metabolism Testing Round 1, Pre-fast

Subjects reported to the University of New Mexico Exercise Physiology Laboratory (Albuquerque, NM) between 5 and 6 hours after their last consumption of calories (Compher et al., 2006). Data recorded included the subject's weight, height, sitting height, reported waking time, food recall of their last meal (to verify restrictions), and the approximate time at their last consumption of calories (to estimate the length of fasting).

Resting energy expenditure (REE, kcal/min) was assessed in real-time by indirect calorimetry using a TrueOne 2400 canopy system (*ParvoMedics*, Salt Lake City, UT).

Subjects were positioned under a ventilated canopy for 30-60 minutes while resting supine in a temperature-controlled room. After a period of acclimation to the testing environment (during which a subject's rate of breathing became steady), respiratory gas exchange was estimated from continuous sampling averaged over 5-second intervals. Comparison of carbon dioxide production (VCO_2 , l/min) to oxygen consumption (VO_2 , l/min) allowed calculation of resting energy expenditure (REE) within each 5s interval (McArdle et al. 2001, Weir, 1949), providing a time series of metabolic parameters for each subject. Controls were employed to improve the reliability of inter-test comparisons (see Compher et al. [2006] and Leonard [2012] for descriptions of indirect calorimetry best practice). The raw time series data were then averaged over 5-minute intervals and the 'minimum 5-min average REE' was used for analysis. This minimum REE occurred during steady state respiration for all subjects. Subjects achieved steady state respiration, during which oxygen consumption rate did not change by more than 15% within a continuous 5-minute period, after a variable period of acclimation. As subjects relaxed, their oxygen consumption rates fell until steady state was achieved. To avoid further drops in REE, subjects were monitored for 10 minutes after first achieving steady state. Then testing was stopped.

In addition to REE, this method of indirect calorimetry allowed estimation of respiratory quotient (RQ). RQ refers to the ratio of carbon dioxide exhaled to oxygen inhaled in a single breath and varies by the proportion of carbohydrate, lipid, and protein substrates fueling metabolism (McArdle et al. 2001). RQ values approach 1.0 when subjects are relying almost exclusively on carbohydrate sources of energy, which is typical in a fed state. Values approach 0.67 when subjects are relying almost exclusively

on adipolysis to fuel metabolism, which is typical in a fasted state. Subjects' RQ values were therefore expected to fall throughout the period of fasting (Webber and MacDonald, 1994). Failure of a subject's RQ to decrease from before to after fasting was grounds for disenrollment from the study under the assumption that fasting had not occurred (this is the fasting validation procedure mentioned above).

After the resting test, gross mechanical efficiency (energy produced per energy consumed in the whole body [Ettema and Loras, 2009]) was assessed during stationary cycling while connected to the TrueOne 2400 indirect calorimetry system via mouthpiece. The indirect calorimeter recorded breath-by-breath respiratory exchange ratios that were used to calculate calories of energy consumed throughout the task. A cycle ergometer (Excalibur Sport by *Lode*, Groningen, Netherlands) was programmed to force subjects to maintain constant work, or rate of energy output, during the task. Ergometers achieve constancy of energy output by continuously adjusting resistance to the subject's pedaling cadence. This method allowed real-time comparisons of 'energy consumed' (joules per second measured via indirect calorimetry) to 'energy produced' (joules per second controlled by the ergometer). Analogous to the fuel efficiency of a vehicle, this method allows calculation of the fuel efficiency of the body during stationary cycling (joules produced per second / joules consumed per second = % efficiency).

The cycle was fitted to each subject by a trained technician (MW) in order to achieve maximal knee extension without injury. Subjects cycled in normal shoes (i.e., not clipped in) for 27 minutes total, which included 2 minutes of low intensity warm-up followed by five 5-minute 'stages.' At each stage, the ergometer was programmed to a

different level of energy output rate (i.e., watts of work). All stages were sub-maximal in intensity, initially set to 20, 30, 40, 50, and 60 percent of the subject's estimated maximum oxygen consumption, and then adjusted based on actual oxygen consumption during testing. Maximum oxygen consumption estimates, measured in metabolic equivalents or "METs," were based on resting heart rate and other inputs employing the standard equations developed by Jurca et al. (2005) and the American College of Sports Medicine (Whaley et al., 2005). In this way, exercise testing was controlled for the subject's cardiovascular fitness level.

Efficiency was calculated in keeping with previous exercise physiology research (Bell and Ferguson, 2009; Cannon et al., 2007; Coyle et al., 1992). Breath-by-breath energy consumption estimates were averaged over the final 3 minutes of each stage. Each of the 5 stages of cycling produced a data point relating 'energy consumed' to an experimentally-fixed level of 'energy produced' (held constant by the ergometer). The slope of the line fitted through a subject's five data points represents the number of calories produced by a unit increase in calories consumed. This slope is the subject's gross mechanical efficiency during stationary cycling.

After testing, subjects left the lab with instructions to go about their normal lives with the exceptions noted in *Step 1* above. During the fast, they were permitted to drink zero-calorie, caffeine-free beverages *ad libitum* (e.g., water, herbal tea, diet caffeine-free soda).

Step 3: Metabolism Testing Round 2, Post-fast

Subjects returned to the lab for an identical round of testing beginning at the same time next day. This final round of testing occurred an average of 29 hours after the

subject's last consumption of calories. Immediately following the REE test, a subject's post-fast RQ was compared to their pre-fast RQ in order to determine the likelihood that fasting had occurred. Two individuals (1 male, 1 female) failed this validation procedure (i.e., RQ did not decrease) at which point no further testing was performed and all data collected from these two subjects were excluded from analyses. For the stationary cycling test, all stages were of identical workload and occurred in the same order as on day 1.

Predictions

Table 1 presents our theory-motivated predictions. According to the *PAR* hypothesis, prenatal energetic scarcity induces a phenotype that minimizes fitness disadvantages experienced in response to future bouts of negative energy balance. Accordingly, I predict that those exposed to prenatal energetic scarcity, i.e., those born small (Barker, 1995), will enjoy relatively greater energetic saving during fasting. This will be achieved via enhanced fasting-induced reductions in REE and attenuated fasting-induced reductions in gross mechanical efficiency.

According to the Life History hypothesis, postnatal experiences that signal elevated risks to reproductive viability inspire physiological adjustments that reduce somatic energy expenditure. Accordingly, I predict that those who experienced greater psychosocial adversity throughout development will enjoy relatively reduced metabolic demands both before and after fasting. This will include reduced REE and greater gross mechanical efficiency at all time points, relative to individuals who experienced less-stressed childhoods.

Variables

Table 3 provides lists of the theory-motivated predictors and confounders considered in each analysis. Birth weight (reported to the nearest ounce then converted to grams) was used to indicate fetal energy balance. Subjects were asked to contact a family member or to reference a birth record in order to accurately report their own birth weights. Subjects recorded their birth weights on a questionnaire and during follow up, were asked how they learned the information. Of the 42 subjects included in analysis, 4 reported consulting a written family record (e.g., heirloom baby book) and 38 reported consulting their mothers. The accuracy and reliability of maternally recalled birth weight is high in western societies regardless of maternal age, educational or socioeconomic status (Adegboye and Heitmann, 2008; Catov et al., 2006; Goffin et al., 2000). The accuracy of birth weight in family records is unknown.

A retrospective questionnaire provided data on potential confounding variables and psychosocial stressors experienced between birth and age 15. Confounders included self-reported ethnicity (by checking options or filling in the “other” line), sex, birth date, and exercise habits. Age at date of participation was calculated based on reported birth date (to the nearest 1/10th of a month). Subjects were coded as ‘weightlifter’ if they replied “yes” to the question “Do you regularly lift weights?” Subjects were coded as ‘cyclist’ if they indicated that they “routinely” ride a bicycle, stationary cycle, or attend spin classes. Subjects were coded as ‘sedentary’ if they indicated that they routinely perform vigorous aerobic exercise no more than 1 time per week (duration of bouts not reported). Immediately preceding their first round of testing, subjects were asked to estimate the time at which they consumed their last calorie. This allowed calculation of

‘fast length’ (to the nearest 1/10 of an hour). Actual fast lengths ranged from 27.2 to 30.3 hours. Two subjects were excluded from analysis due to over-long periods of fasting (actual fast length >33 hours).

The remainder of the questionnaire was designed to capture levels of psychosocial adversity experienced between birth and age 15 years. Questions were modified from published questionnaires found to predict emotional and physiological responses to stress (Kohrt and Worthman, 2009), young adult mental health (Attar et al., 1994; Mayer et al., 2009), and cardiovascular disease risk (Krieger, 1990; Krieger and Sidney, 1996; Krieger et al., 2005). Questions are listed *ad verbatim* in Table 2. The same set of questions was repeated in triplicate in reference to the age ranges ‘birth to 5th birthday,’ ‘age 5 to 10th birthday,’ and ‘age 10 to 15th birthday.’ Analysis was run on counts of the number of questions with an affirmative response reported within the age range. Therefore analysis was run on three separate stress variables (one for each age range), for which scores could range between 0 and 13 (because there were 13 questions total). In this way, subjects were scored on the number of *types* of stressful experiences recalled rather than a cumulative number of events, a method commonly employed by studies linking early psychosocial stress to downstream outcomes (Brown et al., 2009; Coall and Chisholm, 2010; Danese et al., 2009; Felitti et al., 1998).

All anthropometric and metabolism testing measurements were performed by the author (MW) who completed training programs in nutrition assessment and exercise physiology laboratory methods at the University of New Mexico (Department of Health, Exercise and Sports Sciences). Weight (to the nearest 1/10th kg) was measured in minimal clothing, shoes off using the same digital scale for every subject (*Seca*, Chino,

CA). Metabolic testing outcome variables included REE and gross mechanical efficiency at the beginning of the period of fasting (within 5-6 hr of the last consumption of calories) and at the end of the fast (~29 hr after last consumption of calories). The pre-fasting values were used to predict the post-fasting values. In this way, fasting-induced changes in REE and efficiency could be attributed to theory-motivated predictors *while controlling for baseline values*. Resting energy expenditure was included in the model selection procedures for efficiency in case *net* mechanical efficiency, efficiency just within those motor units responsible for cycling, was affected by predictor variables but *gross* mechanical efficiency was not (for further explanation, the reader is referred to a review of cycling efficiency calculations by Ettema and Loras [2009]).

Statistical Analyses

As an initial analytic step, descriptive statistics, bivariate correlation plots, and means-by-group plots were constructed. Then, multiple regression was used to assess the influence of theory-motivated predictors (birth size and stress scores) on outcomes while controlling for potential confounders (e.g., sex, exercise habits). This method allows examination of multiple influences on a single outcome variable while simultaneously considering the effects of every other predictor in the model (Belsley et al., 1980; Neter et al., 1999). Further, it allows comparison between the relative magnitudes of influence of each predictor on the outcome of interest, after controlling for all other effects (Neter et al., 1999). For all outcomes, potential confounders included: weight, sex, age, weightlifter status, sedentary status, Hispanic ethnicity, and Caucasian ethnicity (other ethnicities were under-represented in our sample). The model selection procedure for post-fasting outcomes additionally included the potential confounders: ‘length of fast’

and 'pre-fasting value.' Mechanical efficiency models also included cycling status and that day's resting energy expenditure. Backward elimination was employed by first fitting a model containing all potential predictors, then systematically eliminating one parameter at a time based on the highest p-value at each iteration. An ultimate cut-off criteria of $\alpha=0.05$ was employed for all variables included in the final model. Where eliminated, theory-motivated predictors (birth weight and stress scores) were assessed using added variable plots (Cook, 1993, 1994; Larsen and McLeary, 1972) and, where graphically suggested, were reintroduced into the final model and tested for statistical significance before final elimination. No non-significant predictor was included in the final model because inclusion of non-informative predictors biases the estimation of the remaining coefficients in the model (Belsley et al., 1980) limiting the model's interpretability for biological significance. The final model was evaluated for colinearity graphically, using bivariate correlation plots between predictors, and formally, using variance inflation factors (Neter et al., 1999). Final model fits were graphically assessed by plotting residuals against predicted values and examining normal probability plots of residuals (Cook, 1994). For all final models, errors were normally distributed and no dependency between fitted values and residuals were observed. In other words, residuals associated with each of the final models presented in this paper did not deviate from normality based on Kolmogorov-Smirnov tests (Neter et al., 1999; Smirnov, 1948) and no patterns were observed amidst the scatterplots of the residuals versus the fitted values of each final model.

Results

Table 4 presents the final regression models explaining resting energy expenditure (REE). At the beginning of the period of fasting (5-6 hr after the last consumption of calories), REE did not depend on birth weight or developmental psychosocial stress after controlling for body mass. In the final model of pre-fasting REE, weightlifters required 233 kcal/day more energy than non-weightlifters ($p<0.001$) and men required 831 kcal/day more energy than women ($p=0.001$). The energetic demands attributable to increases in body mass depended on sex; the interaction term 'Body mass x Male' ($\beta=-9.5$, $p=0.005$) discounts the increase in pre-fasting REE associated with additional kilograms of body mass in men. Controlling for all other predictors in the model, each additional kilogram of body mass cost women 18 kcal more per day but cost men only 8 kcal more per day ($p<0.001$).

Variation in the sensitivity of REE to fasting is explained by predictors included in the final model of post-fasting REE after controlling for observed differences in the pre-fasting REE value. At the end of the fast (an average of 29 hr after the last consumption of calories), REE depended heavily on the pre-fasting REE value ($\beta=0.95$, $p<0.001$), which alone explained 85% of observed variation in post-fasting REE. A pre-fasting REE coefficient less than 1 indicates a reduction in REE from before to after fasting since each 1 kcal/day increase in pre-fasting REE contributes <1 kcal/day to post-fasting REE. Male sex and the number of types of psychosocial stressors reportedly experienced in the early adolescent age range 10-15 yr ('Stress:10-15yr') explained 31% of the variation remaining after controlling for pre-fasting REE. Contrary to the *PAR* prediction (*Prediction 1*), birth weight did not approach significance in the model

examining sensitivity of REE to fasting. In alternative analyses replacing continuous birth weight with the categorical variables ‘low birth weight’ (<2500 g) or ‘small birth size’ (<sample mean), these indicators of pre-natal energetic scarcity failed to approach significance as well.

In the final model controlling for sex and ‘Stress:10-15yr,’ each additional 1 kcal/day of pre-fasting REE only contributed 0.75 kcal/day to the post-fasting REE ($p<0.001$) suggesting that REE fell in response to fasting (i.e., post-fasting REE only achieved 75% of its pre-fasting value). At the end of the fast (controlling for all other predictors included in the model), men required 171.31 kcal/day more energy than women ($p=0.004$) and, interestingly, each additional type of psychosocial stress reportedly experienced during the early adolescent age range 10-15 yr predicted 50.70 kcal/day more energetic demand ($p=0.003$). This model suggests that REE falls in response to fasting, but that male sex and psychosocial stressors experienced between ages 10-15 yr decrease the sensitivity of resting metabolic demands to fasting. According to this model, birth weight does not impact the sensitivity of REE to fasting.

Table 5 presents the final regression models explaining gross mechanical efficiency. At the beginning of the period of fasting, no parameters approached significance in the prediction of mechanical efficiency except birth weight. Each additional kilogram of birth weight predicted a 1.86% improvement in pre-fasting mechanical efficiency ($p=0.034$). Birth weight alone explained 10.7% of observed variation in pre-fasting mechanical efficiency. Contrary to the Life History-motivated prediction (*Prediction 4a*), pre-fasting efficiency was not affected by developmental psychosocial stress.

Variation in the sensitivity of gross mechanical efficiency to fasting is explained by predictors included in the final model of 'post-fasting efficiency' after controlling for differences in the 'pre-fasting efficiency' value. At the end of the fast, mechanical efficiency depended heavily on its pre-fasting value ($\beta=0.97$, $p<0.001$), which alone explained 68% of observed variation in post-fasting efficiency. In the final model, each 1.0% of pre-fasting efficiency only contributed 0.94% to post-fasting efficiency ($p<0.001$), suggesting that efficiency fell in response to fasting (i.e., post-fasting efficiency achieved only 94% of its pre-fasting value). After controlling for this effect, 'Stress:10-15yr' explained 16% of the remaining variation observed in post-fasting efficiency. In the final model after controlling for pre-fasting efficiency, each additional type of psychosocial stress reportedly experienced in the early adolescent age range 10-15 yr predicted a fall in mechanical efficiency of 0.74% ($p=0.020$) (recall that decreases in efficiency reflect increased metabolic demands during physical work). Contrary to the *PAR* prediction (*Prediction 2*), birth weight did not approach significance in the model examining sensitivity of mechanical efficiency to fasting (the lack of effect was also apparent in alternative models replacing continuous birth weight with categorical variables 'low birth weight' [<2500 g] or 'small birth size' [$<\text{sample mean}$]). This model suggests that gross mechanical efficiency falls in response to fasting and that psychosocial stressors experienced between ages 10-15 yr amplify this effect.

Discussion

This research demonstrates that birth weight does not predict the sensitivity of metabolic demands to fasting. Because reduced birth weight is the diagnostic indicator employed by the *PAR* hypothesis to assess fetal energetic scarcity (Gluckman and

Hanson, 2006), the *PAR* model predicts that adults of smaller birth size should display relatively greater energetic savings in response to current energetic scarcity. Energetic savings are generally considered advantageous because they allow redistribution of scarce resources to meet the needs of competing fitness-enhancing functions (Zera and Harshman, 2001). Fetal energetic scarcity that results in small birth size is known to induce phenotypic adjustments (Barker, 1993; Hales and Barker, 1992; Hediger et al., 1998; Hovi et al., 2007; Kahn et al., 2000; Kuh et al., 2002; Martyn and Greenwald, 1997; Osler et al., 2009; Sayer et al., 2004, 2008; Yajnik et al., 2003). In order to ascribe the adaptive function to these adjustments that the *PAR* hypothesis proposes, they must demonstrate fitness advantages during similar energy-scarce conditions in adulthood (Williams, 1966; Curio, 1973). I found no evidence that this occurred, in the form of energetic savings, either at rest or during physical activity. Contrary to predictions derived from the *PAR* hypothesis, our results demonstrate that birth weight does not impact the reductions in resting energy expenditure or gross mechanical efficiency known to occur in response to fasting (Bahr et al., 1991; Elia et al., 1984; Kouda et al., 2006; Nair et al., 1987; Webber and MacDonald, 1994).

Additionally, our results demonstrate a positive correlation between birth weight and gross mechanical efficiency independent of postnatal experiences. Because efficiency reflects the amount of physical work that can be performed per calorie of energy consumed by the body, this relationship suggests that phenotypic adjustments associated with small birth size *impair* the amount of physical labor that can be supported by equivalent energy budgets. This effect is in direct opposition to the predictions of the *PAR* model as considered in this paper. Impairment was not mediated by current energy

balance (as explained above) and did not depend on postnatal psychosocial stress, body mass, sex, age, or any other potential predictor listed in Table 3. A heightened energy requirement associated with physical work more reasonably represents a fitness handicap than a fitness-enhancing response. Because this negative impact of small birth size on adult efficiency was observed independent of current energy balance or any other postnatal experiences tested, it may reflect phenotypic concessions made in response to early energetic constraints (though the current study design cannot distinguish between developmental damage, adjusted energy allocation paradigm, or bet-hedging scenarios).

This research also demonstrates that adverse postnatal experiences, in the form of stressful childhood events, do not reduce metabolic demands. Because psychosocial stress is associated with risks to reproductive viability (Adler et al., 1993; Brown et al., 2009; Chen et al., 2002; Felitti et al., 1998; Geronimus, 1987, 1992), Life History Theory may be invoked when proposing that developmental exposure to psychosocial stressors should predict reductions in somatic energy expenditure (Stearns, 1992). Contrary to our Life History-derived hypothesis, developmental psychosocial stress did not predict reductions in baseline resting energy expenditure or gross mechanical efficiency. However, stressful experiences accumulated during early adolescence (ages 10-15 yr) *increased* metabolic demands during fasting, both at rest and during physical activity. Importantly, this effect was independent of birth size.

The increased metabolic demand—during fasting—associated with increasing numbers of early adolescent stressful events was unanticipated. Previous studies investigating the sensitivity of adult stress responses to the timing of stressful experiences accumulated during development suggest that the transition from juvenility to adulthood

represents a period of unique vulnerability to the developmental influences of physiological and psychological stress (Lupien et al., 2009; McCormick et al., 2010; Romeo 2010). Steinberg (2010) suggests that the plasticity of human brain development during adolescence, especially in the frontal cortex, may explain observed links between adolescent experiences and downstream physiological responses to stress. Although speculative, because negative energy balance represents a physiological stressor, it is possible that adolescent experiences that have ‘tuned’ the body’s stress response influence the sensitivity of adult metabolic demands to fasting. Future research is needed to investigate the mechanism and potential evolutionary significance linking early adolescent psychosocial stress to the sensitivity of adult metabolism to sudden energetic scarcity.

This study suffered from several limitations. First, our results linking adolescent stress to metabolic outcomes, rather than earlier occurrences, may reflect a recall bias if participants more accurately reported events that occurred more recently in time. Because prospective data collection is often infeasible, future research could address this problem by validating assays of early-life stress that are independent of conscious memory (e.g., biomarkers). One method that may prove useful toward this end is a metric of accumulated lifetime stress called allostatic load. Allostatic load is calculated from co-occurring cardiovascular, metabolic, and inflammatory biomarkers (Seeman et al., 2004) and has been linked, in longitudinal studies beginning in childhood, to accumulating numbers of stressful lifetime experiences (Caspi et al., 2006; Evans et al., 2007). Future Life History-motivated research may examine potential associations between allostatic load and indicators of somatic investment.

This study also suffers from a lack of information about participants' early postnatal growth. Data were generated from a healthy, urban U.S. sample that was not likely calorie-restricted during postnatal development (Polhamus et al., 2009) and likely enjoyed low-pathogen environments. These circumstances may increase the possibility of catch-up growth subsequent to small birth size, which is known to impact the physiology contributing to chronic metabolic disease risk in adulthood (Eriksson et al., 1999, 2006; Ibáñez et al., 2006; Meas et al., 2008; Ong et al., 2000). Although it seems unlikely because catch-up growth is thought to exacerbate, rather than moderate, the physiological adjustments associated with small birth size, it is possible that the effects of catch-up growth on adult physiology masked the relationships I attempted to examine between birth weight and adult metabolism. Future research is required to rule out the possibility that catch-up growth subsequent to small birth size impacts the results reported herein.

Conclusion

The results of this study contradict the *PAR* hypothesis in that individuals exposed to fetal energetic scarcity enjoyed no enhanced energetic savings in response to current energetic scarcity. These results argue against the ascription of adaptive function to phenotypes induced by fetal energy balance at the cautions of Baker (2011), Curio (1973), Jones (2005), Kuzawa (2005), Wells (2010), and Williams (1966). Moreover, this study suggests that small birth size is associated with a fitness handicap—reduced level of physical work that can be supported by equivalent energy budgets. The negative impact of this handicap was not mediated by current energy balance or postnatal psychosocial experiences (i.e., it was evident in *all* downstream environments). Also

important, this study demonstrates that post-natal stress can independently and significantly influence adult metabolism.

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Tables

Table 3.1. Hypotheses, predictions tested in this paper, and results.

Hypotheses		Predictions Tested	Results
Predictive Adaptive Response	Prenatal energetic scarcity induces a phenotype that minimizes the fitness disadvantages that occur during bouts of negative energy balance	Small birth size should be linked to: (1) Fasting-induced reductions in resting energy expenditure (2) Preserved mechanical efficiency during fasting	(1) rejected (2) rejected
Life History Theory	Cues of risk to reproductive viability inspire physiological adjustments that reduce somatic energy expenditure	Psychosocial stress experienced during development should be linked to: (3) Reduced resting energy expenditure (a) Pre-fasting (b) Post-fasting (4) Greater mechanical efficiency (a) Pre-fasting (b) Post-fasting	(3a) rejected (3b) rejected (4a) rejected (4b) rejected

Table 3.2. Survey of stressful events experienced during development. The same set of questions was repeated 3 times, once for each age range. Below are the instructions for the age range birth to 5 years.

Instructions: Please indicate if any of the following events happened from the time you were born until your 5 th birthday by circling Y (yes) or N (no).	
Y or N	1. Did you have a serious physical injury?
Y or N	2. Were you a witness or victim of physical violence?
Y or N	3. Did you ever hide someplace because of violence in your home or neighborhood?
Y or N	4. Did a relative who you were very close to suffer serious physical illness or injury?
Y or N	5. Did a relative who you were very close to suffer serious mental illness?
Y or N	6. Did a relative who you were very close to pass away?
Y or N	7. Did a relative who you were very close to spend time in jail (or juvenile detention)?
Y or N	8. Did you or a close family member experience discrimination, get prevented from doing something, or get hassled or made to feel inferior because of your race, ethnicity, color, ancestry, sexual orientation, gender, sex, religious affiliation, citizenship, or country of birth?
Y or N	9. Did one (or both) of your parents/step-parents become unemployed for a time?
Y or N	10. Did a relative who you were very close to move out of your home?
Y or N	11. Did you go to live with a different relative or spend time in foster care?
Y or N	12. Did you and your family move from one place to another?
Y or N	13. Did your family's home or property get wrecked in a natural disaster, accident, or crime?

Table 3.3. Potential predictors included in each model selection procedure.

Outcome Models:	Resting energy expenditure		Gross mechanical efficiency	
	at beginning of fast	at end of fast	at beginning of fast	at end of fast
Theory-Motivated Predictors	Birth weight Stress: birth-5yr Stress: 5-10yr Stress: 10-15yr	Birth weight Stress: birth-5yr Stress: 5-10yr Stress: 10-15yr Pre-fasting REE	Birth weight Stress: birth-5yr Stress: 5-10yr Stress: 10-15yr	Birth weight Stress: birth-5yr Stress: 5-10yr Stress: 10-15yr Pre-fasting efficiency
Confounders	Male Body mass Weightlifter Sedentary Hispanic Caucasian Age	Male Body mass Weightlifter Sedentary Hispanic Caucasian Age Length of fast	Male Body mass Weightlifter Sedentary Hispanic Caucasian Age Cyclist Pre-fasting REE	Male Body mass Weightlifter Sedentary Hispanic Caucasian Age Cyclist Post-fasting REE Length of fast

Table 3.4. Regression analysis explaining variation in resting energy expenditure, kcal/day (n=39).

	Parameter	Constant	β	Std Err coeff	p-value	Model R^2
At beginning of fast	Body mass, kg	963.2	17.51	2.56	<0.001	86.7%
	Weightlifter		232.58	41.18	<0.001	
	Male		830.80	219.40	0.001	
	Body mass x Male		-9.50	3.16	0.005	
At end of fast	Pre-fasting REE, kcal/day	285.3	0.75	0.08	<0.001	89.5%
	Stress: 10-15yr, count		50.70	15.76	0.003	
	Male		171.32	55.02	0.004	

Table 3.5. Regression analysis explaining variation in gross mechanical efficiency, % (n=42).

	Parameter	Constant	β	Std Err coeff	p-value	Model R^2
At beginning of fast	Birth weight, kg	21.53	1.86	0.85	0.034	10.5%
At end of fast	Pre-fasting efficiency, %	2.59	0.94	0.10	<0.001	72.5%
	Stress: 10-15yr, count		-0.74	0.31	0.020	

Chapter 4: Does birth weight impact height independent of its influence on age at menarche?

Introduction

Small birth size and earlier age at menarche have each been linked to reductions in women's heights (Labayen et al., 2006; Loos et al., 2002; Sachdev et al., 2005; Weyer et al., 2002; Georgiadis et al., 1997; Okasha et al., 2001; Onland-Moret et al., 2005; Sear et al., 2004). Because small birth size may predict an accelerated pace of maturation leading to earlier menarche (Cooper et al., 1996; Ibanez et al., 2000, 2006; Morris et al., 2010; Ong et al., 2009; Ruder et al., 2010; Sloboda et al., 2007), it remains unclear whether the observed reductions in height among women born small are attributable to earlier menarche alone, or if birth size exerts an additional effect on adult height independent of its influence on menarcheal timing. The timing of menarche also appears highly sensitive to psychosocial adversities experienced during childhood (Belsky et al., 1991; Bergevin et al., 2003; Chisholm, 1993; Chisholm et al., 2005; Ellis, 2004; Mendle et al., 2011; Pesonen et al., 2008; Romans et al., 2003; Surbey, 1990; Turner et al., 1999; Villamor et al., 2009; Wise et al., 2009). This study attempts to separate the impacts of birth weight, level of exposure to childhood psychosocial adversities, and age at menarche in the prediction of height among a contemporary cohort of U.S. young women.

Conceptual Model and Predictions

Because first birth predictably follows menarche within natural fertility populations (several examples reviewed by Walker et al., 2006), the timing of menarche in a women's life course is studied as a transition event marking the end of the juvenile growth phase and the beginning of the reproductive phase of her life. Menarche occurs

after the adolescent growth spurt (Ellison, 1981, 2001) and is among the latest-occurring physical changes reflecting reproductive maturation in girls (Ellison, 2001). For these reasons, age at menarche may accurately reflect the duration of the growth phase of life. All else equal, earlier menarche, reflecting reduced duration of growth, should produce shorter heights. Often within cohorts, the women who achieved menarche earlier are indeed shorter (Georgiadis et al., 1997; Okasha et al., 2001; Onland-Moret et al., 2005; Sear et al., 2004). Because deficits in birth weight have been associated (in separate literatures) to both earlier menarche (Cooper et al., 1996; Ibanez et al., 2000, 2006; Morris et al., 2010; Ong et al., 2009; Ruder et al., 2010; Sloboda et al., 2007) and reduced height among women (Labayen et al., 2006; Loos et al., 2002; Sachdev et al., 2005; Weyer et al., 2002), it is plausible that girls born small end up shorter solely due to a reduction in their duration of growth (see Figure 1).

In addition to its link with small birth size, earlier menarche has been associated with several types of childhood psychosocial adversities. For instance, earlier menarche is associated with exposure to violence during childhood in the forms of elevated homicide rates (Villamor et al., 2009) and physical and sexual abuse (Bergevin et al., 2003; Mendle et al., 2011; Romans et al., 2003; Turner et al., 1999; Wise et al., 2009). Earlier menarche is also predicted by childhood separation from a parent, inconsistent parental discipline, and other indicators of a low quality parent-child relationship (Belsky et al., 1991; Chisholm, 1993; Chisholm et al., 2005; Ellis, 2004; Surbey, 1990). Because level of childhood exposure to psychosocial adversity positively correlates, in many cases, with health and mortality hazards (Adler et al., 1993; Brown et al., 2009; Chen et al., 2002; Felitti et al., 1998; Geronimus, 1987, 1992), previous explanations have relied

on the Life History-motivated hypothesis that maturation accelerates in response to cues of reduced reproductive lifespan (Chisholm, 1993; Chisholm et al., 2005; Ellis et al., 2009). If childhood adversity reduces a girl's expected reproductive lifespan, she may "accept" cessation of growth at a shorter stature because the benefits to increases in body size are discounted by the probability of dying prior to reproduction. All else equal, the reductions in 'target adult size' induced by childhood adversities should produce earlier menarche. But it remains unclear whether birth size and level of childhood adversity reflect separate exposures each capable of independently influencing age at menarche (see Figure 2).

Based on this body of previous research, I predict that deficits in birth weight and elevated exposure to childhood psychosocial adversity independently predict earlier menarche (controlling for appropriate confounders). If this is the case, each exposure will significantly correlate with observed age at menarche in a combined multivariate analysis, and the potential two-way interaction between them will be insignificant. Additionally, I predict that age at menarche alone explains adult height without additional impacts from birth weight or level of exposure to childhood psychosocial adversity. If this is the case, an instrumental variable calculated from these exposures (and appropriate confounders) will explain observed variation in women's heights after controlling for relevant confounders.

Methods

The study sample was limited to 15-year-old girls (ages 180-191 months at the time of examination) who fasted prior to participation in the Mobile Examination Centers of the U.S. National Health and Nutrition Examination Survey (NHANES) between

2007-2010 (n=122). This cohort is the only age for which birth weight was recorded and all girls interviewed had already achieved menarche. Due to missing data, analysis was limited to 99 young women (see Table 1). Sample weights were calculated based on published NHANES guidelines to adjust analytical results so that they represent the civilian non-institutionalized U.S. population at year-end 2008 (NCHS, 2006). Children in this population generally enjoy high energy balances (Polhamus et al., 2009), but data on individual childhood growth rates were unavailable.

Reported birth weight (to nearest ounce, converted to grams) and reported age at menarche (to nearest year) were recorded during structured interviews by trained NHANES personnel. Standing heights (to nearest 0.1 cm) were assessed by NHANES health technicians using wall-mounted stadiometers with digital displays (NHANES, 2009). Level of exposure to psychosocial adversity during childhood was estimated by allostatic load score.

Allostatic Load Score

Allostatic load considers the long-term impact of repeated stress on multiple physiological regulatory pathways (Stewart, 2006). Repeated exposure to psychosocial stress is thought to permanently activate physiological stress-coping mechanisms, permanently exacerbating levels of biomarkers associated with elevated lifetime stress (Crimmins et al., 2003). Thus, allostatic load is a metric that combines metabolic, cardiovascular, and inflammatory biomarkers to quantify individual-level differences in cumulative lifetime exposure to psychosocial stress (Crimmins et al., 2003; Geronimus et al., 2006; Gruenewald et al., 2006; Seeman et al., 2010; Stewart, 2006). Given the young age of the cohort studied (i.e., 15-year-olds have spent the majority of their lives as

children), I operated under the assumption that differences in allostatic load scores reflect differences in levels of childhood exposure to psychosocial stress. Supporting this assumption, previous longitudinal studies have shown that the physiological effects first noted in response to childhood adversity persist through adolescence and into young adulthood, independent of later environment (Caspi et al., 2006; Evans et al., 2007). Additionally, retrospective studies have linked increasing numbers of recalled childhood and adolescent adversities to increasing cardiovascular, inflammatory, and metabolic disease risk factors in adults while controlling for adult experiences (e.g., occupation, smoking) (Alastalo et al., 2009; Chen et al., 2006; Danese et al., 2007, 2009).

Allostatic load scores were calculated for each young woman based on the levels of her cardiovascular, inflammatory, and metabolic regulatory system biomarkers. In keeping with previously published methods, one point was assigned for each biomarker exceeding the *a priori* thresholds listed in Table 2. The biomarkers chosen to calculate allostatic load in the current study match those used in previous research. They include systolic and diastolic blood pressures, resting heart rate, and whole blood concentrations of total cholesterol, HDL cholesterol, glycosylated hemoglobin, and c-reactive protein (Crimmins et al., 2003, 2009; Evan, 2003; Geronimus et al., 2006; Merkin et al., 2009; Seeman et al., 1997, 2010a). Among the biomarkers for which elevated levels are associated with stress-induced poor health, thresholds were defined as greater than 1 standard deviation above the weighted sample mean. Because elevated HDL cholesterol is considered protective of health, the HDL threshold was defined as less than -1 standard deviation below the weighted sample mean. To incorporate the complex NHANES

sampling design, standard deviations were calculated from the weighed variances.

Weighted variance was defined by the formula:

$$[\sum w_i(x_i - \mu)^2] / [(\sum w_i) - 1], \quad (\text{eq. 1})$$

Where w_i is the sample weight of the i^{th} individual, x_i is her biomarker value, and μ is the weighted sample mean of the biomarker.

Among the biomarkers available for 15 year olds in the NHANES 2007-2010 database, those chosen for inclusion in our allostatic load metric were known not to change with maturational status in the direction of our *a priori* thresholds. Before including an available biomarker in our calculation of allostatic load, I plotted its weighted sample means against age for girls ages 8 through 17 (by year) in the NHANES 2007-2010 sample (see Figure 3). Among biomarkers for which elevated levels are associated with poor health, I excluded those that predictably increased with age. For instance, elevated BMI is often included in scores of allostatic load as an indicator of metabolic dysregulation in adults (Crimmins et al., 2003, 2009; Geronimus et al., 2006). But because women predictably gain BMI throughout adolescence (Hill and Hurtado, 1996; Howell 2010; Marlowe, 2010), a BMI above any pre-defined threshold may simply reflect accelerated maturation—confounding analysis of our outcomes of interest. For this reason, I did not include BMI in the calculation of allostatic load. Because blood pressure increases with height throughout development (NHLBI, 2012), and height increases with maturational status, systolic and diastolic blood pressures were corrected for height before graphically assessing their feasibility for inclusion. Blood pressures

corrected for height did not increase predictably with age (see Table 3), suggesting that height-corrected blood pressures greater than a pre-defined threshold do not simply reflect advanced maturational status. Thus, systolic and diastolic blood pressures corrected for height were included in analysis. Similarly, among biomarkers for which diminished levels are associated with poor health (e.g., HDL), I excluded those that predictably decreased with age. Mean-by-age plots of biomarkers used in our calculation of allostatic load are shown in Figure 3. Formal trend analysis linking weighted mean biomarker values to age are displayed in Table 3. No significant increasing linear trends with age (or decreasing, in the case of HDL) were found, suggesting that elevated levels (or decreased levels, in the case of HDL) are not simply attributable to relatively advanced maturational status compared to cohort peers.

Statistical Analysis

A two-stage regression analysis was performed whereby the first-stage model predicted age at menarche and the second-stage model predicted height based on the ‘predicted age at menarche’ calculated from the first-stage regression equation.

In the first stage, sample weighted multiple regression analysis (DuMouchel and Duncan, 1983) assessed the influence of birth weight (kg) and allostatic load scores (counts, 0-7 possible) on age at menarche (years) while controlling for the potential confounding effects of ethnicity and socioeconomic factors. Ethnicity categories reported in NHANES 2007-2010 included: Non-Hispanic White, Non-Hispanic Black, Mexican American, Other Hispanic, and Other Ethnicity. Socioeconomic status indicators included in model selection procedures were: the young woman’s U.S. citizenship status, the total number of people living in her household, the head-of-household’s gender (to control for

dual income), the head-of-household's education level, and the family of the girl's income-to-poverty ratio. Income-to-poverty ratio is the ratio of total family income to the level of income required for the family to be eligible for federal public assistance. This threshold poverty level is federally defined per family size, location of residence (based on cost of living), and is adjusted yearly to account for inflation (NHANES, 2011a). Backward elimination was employed by first fitting a model containing all potential predictors, then systematically eliminating one parameter at a time based on the highest p-value at each iteration. The selected model included only predictors significant at the $p < 0.05$ level. Then, two-way interaction terms between predictors included in the selected model were added one at a time and examined for significance.

In the second stage, an identical model selection procedure was employed to estimate height. The initial model included 'predicted age at menarche' (calculated from the first-stage regression equation) and parameters not chosen for inclusion in the first-stage model. At each iteration, one parameter was eliminated from the model based on the highest p-value. Due to the limited sample size, the selected model included only predictors significant at the $p < 0.1$ level. Finally, two-way interaction terms between predictors included in the selected model were added one at a time and examined for significance.

Results

Table 4 presents the first-stage regression model selected to estimate age at menarche. During the model selection procedure, birth weight, ethnicities, U.S. citizenship status, household size, and head-of-household education level were eliminated because they did not approach significance at the $\alpha = 0.1$ level. According to the final

model, allostatic load score, family income-to-poverty ratio, and head-of-household sex explained 22% of the observed variation in age at menarche. Supportive of our hypothesis, each point increase in allostatic load score corresponded to a 5 month earlier age at menarche ($p=0.001$) after controlling for other effects. Controlling for the effect of all other predictors in the model, each point decrease in family income-to-poverty ratio corresponded to a 2.4 month earlier age at menarche ($p=0.009$), and girls living in a female-headed household achieved menarche 7 months earlier ($p=0.013$). No two-way interaction terms between these predictors approached significance, suggesting that all reported effects are additive. Pearson correlations confirmed that no two predictors in this model were linearly dependent (see Table 5). Additional univariate analysis confirmed that age at menarche was not linearly dependent on birth weight (Pearson's $r=-0.950$, $p=0.300$).

Table 6 presents the second-stage regression model selected to estimate height. The instrumental variable 'predicted age at menarche' did not linearly co-vary with the other predictors included in this model (see Table 7 for Pearson correlations). Controlling for all other effects, each year delay in the 'predicted age at menarche' corresponded to a 3.7 cm boost in height ($p<0.001$). This effect alone explained 13% of observed variation in height. Although the other effects did not achieve statistical significance at the $\alpha<0.05$ level, these predictors were included in the final model due to their potential biological relevance. Controlling for all other effects, each 1 kg deficit in birth weight predicted a 2 cm deficit in height ($p=0.052$), and Mexican American ethnicity predicted a 4.2 cm deficit in height ($p=0.053$). No interaction terms approached significance.

Discussion

To our knowledge, this study is among the first to simultaneously examine birth weight and childhood psychosocial experience in the prediction of age at menarche (although see Blell et al., 2008). The results of our first-stage regression model suggest that family poverty, living in a female-headed household, and elevated exposure to childhood psychosocial adversity can independently hasten female reproductive maturation. Contrary to our hypothesis, birth weight did not influence age at menarche among 15 year-olds in the NHANES 2007-2010 sample.

A female-headed household and the income-to-poverty ratio of a girl's family were negatively associated with age at menarche suggesting that girls living in poorer socioeconomic conditions matured earlier. This result matches previous research (Braithwaite et al., 2009; James-Todd et al., 2010). The link between accelerated menarche and elevated childhood psychosocial adversity that remained after controlling for these indicators of socioeconomic status (SES) also finds support in the literature (Coall and Chisholm, 2010; Ellis and Essex, 2007). Because low SES and childhood psychosocial adversities positively correlate, in many cases, with health and mortality hazards (Adler et al., 1993; Brown et al., 2009; Chen et al., 2002; Felitti et al., 1998; Geronimus, 1987, 1992), previous explanations have relied on the Life History-motivated hypothesis that maturation accelerates in response to cues of reduced reproductive lifespan (Chisholm, 1993; Chisholm et al., 2005; Ellis et al., 2009). Reflecting the fundamental tradeoff of current versus future reproduction, this body of evidence suggests that the duration of growth is reduced (in order to mature and reproduce sooner) when future reproductive opportunities are uncertain. Our results are consistent with this

model under the assumption that earlier ages at menarche reflect reduced durations of the growth period.

The lack of association between birth weight and age at menarche in the current sample finds support in the literature (Boyne et al., 2010; Dos Santos Silva et al., 2002; Persson et al., 1999; Terry et al., 2009; Wehkalampi et al., 2011), although other studies report earlier menarche among girls born lighter (Cooper et al., 1996; Ibanez et al., 2000, 2006; Morris et al., 2010; Ong et al., 2009; Ruder et al., 2010; Sloboda et al., 2007). None of these previous reports simultaneously considers the impact of childhood psychosocial experiences on female maturational tempo. Although speculative, the inconsistency with which birth weight has been linked to age at menarche previously may, in part, be explained by a failure to control for the independent effect of childhood stress on menarcheal timing.

In our second-stage model, Mexican American ethnicity, birth weight, and ‘predicted age at menarche’ (calculated from the first-stage regression equation) exerted independent effects on height at age 15. Similar deficits in stature among Mexican Americans, independent of SES, were observed in a previous wave of HANES data (Ryan et al., 1990). Previous research also supports the observed deficit in stature among women who achieved menarche earlier than their peers (Georgiadis et al., 1997; Okasha et al. 2001; Onland-Moret et al., 2005; Sear et al. 2004). Controlling for Mexican American ethnicity and predicted age at menarche, birth weight was positively correlated with height at age 15: girls who were born 1 kg lighter were 2 cm shorter. Consistent reductions in height associated with small birth size have been reported previously (Gale et al., 2001; Labayen et al., 2006; Loos et al., 2002; Sachdev et al., 2005; Weyer et al.,

2002). Loos et al. (2002) report a 3.26 cm reduction in height among women per 1 kg deficit in birth weight.

Contrary to our predictions, these results suggest that birth weight influences height independent of maturational timing. Although a constant rate of linear growth across the entire period of development is unrealistic, height at age 15 can be simplified as the product of ‘average growth rate’ by ‘duration of growth.’ Assuming age at menarche reflects the duration of the growth phase, our results suggest that women who were born lighter experienced a reduced ‘average growth rate’ (averaged from conception until the time of observation at age 15). By documenting differences in the growth schedules of girls born different sizes, future research may tease apart this rather unsatisfying observed reduction in ‘average growth rate’ among women born lighter.

Our interpretation that deficits in birth weight predict slower average growth rates appears, at first blush, inconsistent with previous reports documenting relatively rapid childhood growth among those born small (Chakraborty et al., 2007; Dos Santos Silva et al., 2002). Previous research has demonstrated that, in environments of sufficient nutritional quality to sustain rapid growth, individuals born small may grow relatively rapidly during infancy and childhood (Chakraborty et al., 2007) catching-up to or surpassing the heights of peers born heavier (Casey et al., 1991; Dos Santos Silva et al., 2002; Hack et al., 2005). However, these accelerated rates of growth do not persist after early childhood (Casey et al., 1991; Knops et al., 2005) and at least one published longitudinal study found that the absolute differences in female adult height attributable to difference in birth weight were achieved prior to age 8 (Ibanez et al., 2006). Upon adulthood, deficits in birth weight reliably predict deficits in stature among both women

(Adair, 2007; Gale et al., 2001; Labayen et al., 2006; Loos et al., 2002; Sachdev et al., 2005; Weyer et al., 2002) and men (Adair, 2007; Gale et al., 2001; Kensara et al., 2005; Li et al., 2003; Loos et al., 2001; Sachdev et al., 2005; Sayer et al., 2004; Weyer et al., 2002).

The current study is limited by our assumption that allostatic load scores at age 15 accurately reflect childhood exposure to psychosocial stressors that signal reduced reproductive lifespan for girls in the study population. However, this type of biomarker-based method for assaying childhood stress offers two advantages over common alternative techniques that rely on conscious memory and self-reported information. Previous research addressing the developmental consequences of childhood stress has often relied on retrospective questionnaires or interviews. These techniques have been criticized for potential recall biases and subjective interpretations of, even self-deception regarding, events that may have caused significant stress during childhood (Bergevin et al., 2003). Additionally, a biomarker-based method of assaying childhood stress extends the possibility of studying childhood stress within existing databases that were originally assembled for other purposes, as I have done herein using data collected by the NHANES.

Conclusion

Data collected from a contemporary U.S. cohort suggest that birth weight does not predict age at menarche, childhood exposure to psychosocial stress accelerates maturation independent of SES, and deficits in stature attributable to deficits in birth size occur independent of age at menarche. Our interpretation of these results is that childhood stress reduces the ‘target adult height’ that a girl in good nutritional condition

will likely achieve prior to ceasing growth and that differences in birth weight predict differences in growth schedules that impact final height but not age at menarche.

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Tables and Figures

Table 4.1. Inclusion criteria for girls in the sample.

Description	n	<i>n missing</i>
Girls who were between 180-191 months of age at the time of MEC examination	140	0
...who fasted	122	18
...for whom all allostatic load biomarkers were available	113	9
...who reported age at menarche to nearest year	108	5
...whose family's income-to-poverty ratio was reported	101	7
...whose family's head of household gender was reported	99	2

Table 4.2. Biomarkers used in calculation of ‘Allostatic Load’ metric for 15-year-old U.S. women examined during NHANES 2007-2010.

Biological Regulatory System	Biomarker	Weighted Mean	Weighted S.D.	Threshold	
Inflammatory	C-reactive protein, mg/dL	0.1289	0.4170	> +1 S.D.	0.5459
Metabolic	Total cholesterol, mg/dL	159.0023	26.0143	> +1 S.D.	185.0166
	HDL cholesterol, mg/dL	50.2413	11.9365	< -1 S.D.	62.1778
	Glycosylated hemoglobin (HbA1c), %	5.1481	0.1117	> +1 S.D.	5.2598
Cardiovascular	Height-corrected systolic blood pressure, mmHg/cm	0.6570	0.0734	> +1 S.D.	0.7304
	Height-corrected diastolic blood pressure, mmHg/cm	0.3940	0.0817	> +1 S.D.	0.4757
	Pulse, beats/min	78.9658	1.3360	> +1 S.D.	80.3018

Table 4.3. Weighted means by age of allostatic load biomarkers observed among female participants in NHANES 2007-2010.

Cohort	CRP	TC	HDL	HbA1c	Systolic/Ht	Diastolic/Ht	Pulse
8	0.1750	164.3327	52.2918	NA	0.7486	0.3883	87.4153
9	0.1212	164.4385	52.0235	NA	0.7323	0.3836	86.1281
10	0.1152	161.6123	51.9688	NA	0.7032	0.3727	85.0903
11	0.1239	159.6676	50.8792	NA	0.6889	0.3735	83.5705
12	0.0733	159.5577	52.7894	5.2522	0.6756	0.3615	81.5339
13	0.1023	157.2138	54.1082	5.2632	0.6499	0.3695	80.0532
14	0.1363	154.5615	52.5225	5.2302	0.6629	0.3782	80.8512
15*	0.1417	158.3897	50.5129	5.1444	0.6556	0.3925	78.7709
16	0.1470	160.7685	53.0357	5.1519	0.6529	0.3869	78.2270
17	0.1782	164.2875	54.7309	5.1879	0.6486	0.3664	77.6013
Beta trend	0.0025	-0.3629	0.1697	-0.0212	-0.0109	-0.0003	-1.1204
p-trend	0.513	0.347	0.256	0.070	<0.001	0.795	<0.001

CRP, c-reactive protein (mg/dL); TC, total cholesterol (mg/dL); HDL, high-density lipoprotein cholesterol (mg/dL); HbA1c, glycosylated hemoglobin (%), data not collected from participants under 12 years of age; Systolic/Ht, height-corrected systolic blood pressure (mmHg/cm); Diastolic/Ht, height-corrected diastolic blood pressure (mmHg/cm); Pulse, resting heart rate (beats/minute).

*Note: Inconsistency between weighted means displayed in Tables 2 and 3 are due to current inclusion of girls excluded from regression analysis due to missing data (see Table 1). Table 2 thresholds were defined using only girls included in analysis.

Table 4.4. Final weighted first-stage regression model explaining age at menarche (in years) among 15-year-old U.S. women examined during NHANES 2007-2010 (n=99).

Parameter	Model Constant	β	S.E. of Coefficient	p- value	Model R ²
Allostatic load (count)	12.697	-0.434	0.129	0.001	22.0%
Income:Poverty Ratio		0.197	0.073	0.009	
Female head of household		-0.603	0.238	0.013	
<i>Allostatic load x Income:Poverty Ratio</i>				*	
<i>Allostatic load x Female head of household</i>				*	
<i>Income:Poverty Ratio x Female head of household</i>				*	
<i>U.S. citizenship</i>				*	
<i>No. people living in household</i>				*	
<i>Head of household educational status</i>				*	
<i>Non-Hispanic White</i>				*	
<i>Non-Hispanic Black</i>				*	
<i>Mexican American</i>				*	
<i>Other Hispanic</i>				*	
<i>Other Ethnicity</i>				*	
<i>Birth weight (kg)</i>				*	

Table 4.5. Pearson correlations between predictors selected for inclusion in first-stage model.

Pearson's r (p-value)	Female head of household	Income:Poverty Ratio
Income:Poverty Ratio	-0.134 (0.129)	
Allostatic load score	-0.017 (0.858)	0.091 (0.354)

Table 4.6. Final weighted second-stage regression model of height (cm) considering predicted age at menarche for 15-year-old U.S. women examined during NHANES 2007-2010 (n=102). Birth weight impacts height, controlling for predicted age at menarche.

Parameter	Model Constant	β	S.E. of Coefficient	p- value	Model R ²
Predicted age at menarche (years)	112.31	3.723	1.007	<0.001	21.2%
Birth weight (kg)		1.990	1.010	0.052	
Mexican American		-4.203	2.147	0.053	
<i>Predicted age at menarche x Birth weight</i>				*	
<i>Predicted age at menarche x Mexican American</i>				*	
<i>Birth weight x Mexican American</i>				*	
<i>U.S. citizenship</i>				*	
<i>No. people living in household</i>				*	
<i>Head of household educational status</i>				*	
<i>Non-Hispanic White</i>				*	
<i>Non-Hispanic Black</i>				*	
<i>Other Hispanic</i>				*	
<i>Other Ethnicity</i>				*	

Table 4.7. Pearson correlations between predictors selected for inclusion in second-stage model.

Pearson's <i>r</i> (p-value)	Birth weight	Predicted Age at Menarche
Predicted Age at Menarche	0.157 (0.114)	
Mexican American Ethnicity	0.044 (0.605)	-0.046 (0.644)

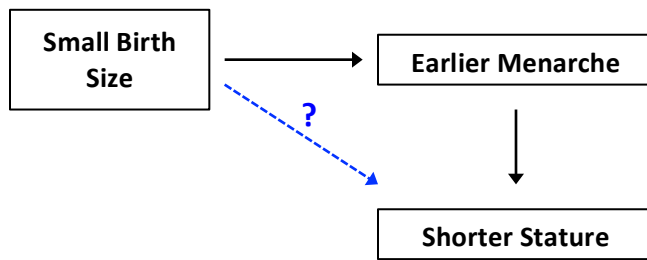


Figure 4.1. Conceptual model 1. Separate literatures link small birth size to earlier menarche and shorter stature. It is plausible that the deficits in stature among women born small result solely from the earlier cessation of growth implied by earlier menarche.

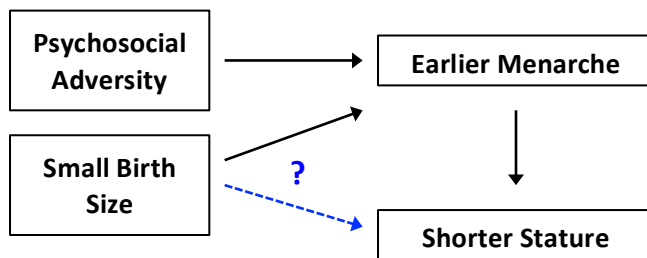


Figure 4.2. Conceptual model 2. Elevated exposure to psychosocial adversity predicts earlier menarche, potentially independent of birth size. Earlier menarche predicts shorter adult stature.

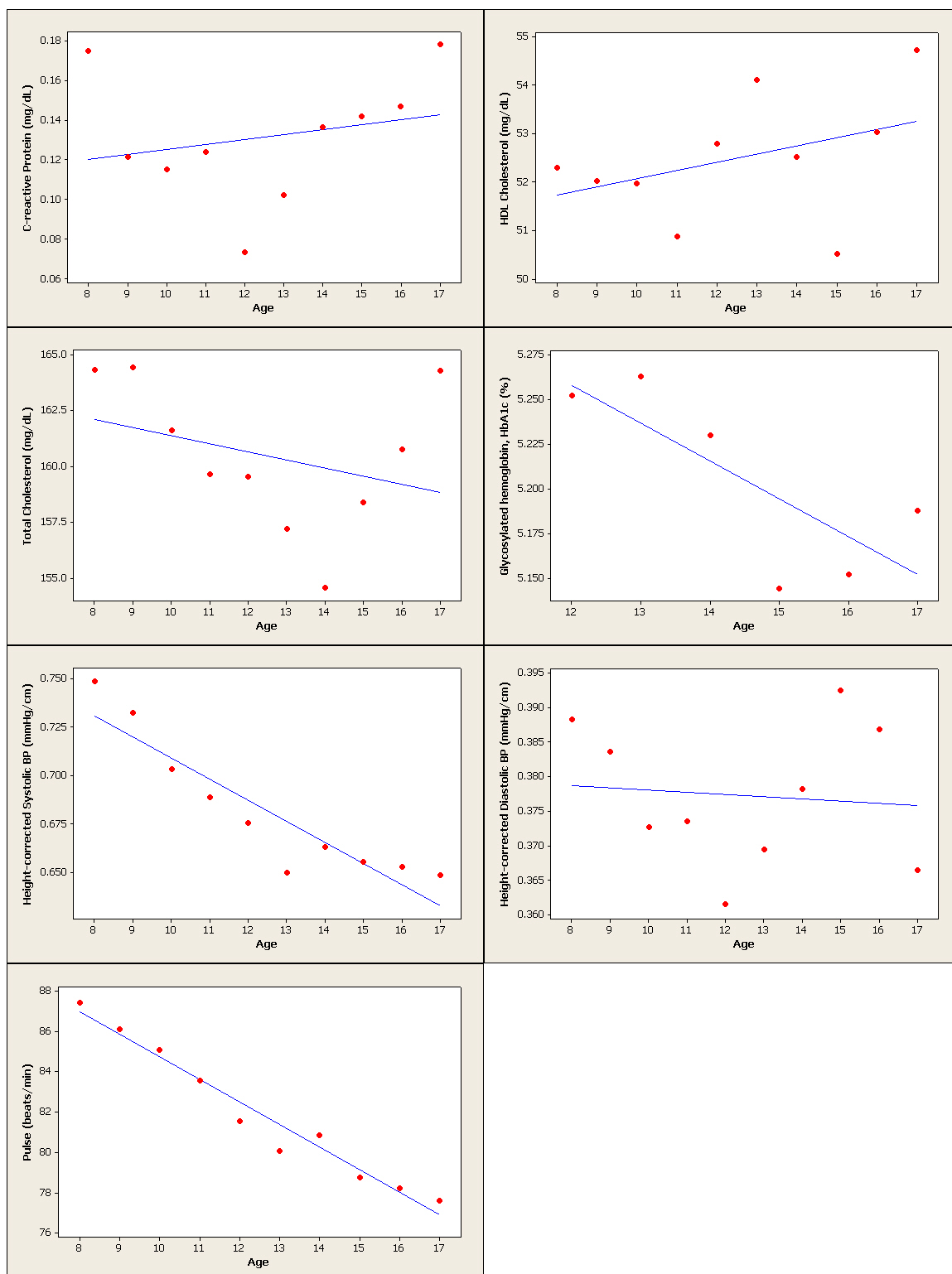


Figure 4.3. Mean-by-age plots (sample weighted) of allostatic load biomarkers observed among female participants in NHANES 2007-2010. Tests for trend significance shown in Table 2. Among biomarkers for which significant linear trends with age are found (height-corrected systolic blood pressure, pulse, glycosylated hemoglobin), none are in

the direction that would inflate allostatic load score among girls of advanced maturational status.

Chapter 5: Conclusion

The analyses presented in this dissertation combined birth weight and indicators of postnatal developmental conditions to examine the relationships between early-life experiences and adult phenotypes. While previous research has highlighted associations between birth size and the later-life outcomes examined in this dissertation (adult height and lean tissue mass, age at menarche, metabolic physiology), this dissertation presents evidence that post-natal experiences independently and significantly affect these phenotypes as well. In some instances (explained below), controlling for post-natal experiences eliminated the correlations previously reported between birth size and the outcome of interest.

Review of Results

Chapter 2 explains that neither birth weight, indicating prenatal energy balance, or relative leg length, indicating childhood energy balance, predicted adult skeletal muscle mass while controlling for level of childhood psychosocial adversity. Independent from indicators of early-life nutrition, a high level of psychosocial adversity experienced in the first decade of life predicted reductions in muscle mass and diminished returns to muscle-building habits of weightlifting exercise. These effects did not depend on sex or ethnicity. The absence of a link between birth weight and later muscle mass contradicts previous research, although much previous research fails to control for overall body size or childhood psychosocial experience.

Chapter 3 presents evidence that deficits in birth weight predict deficits in gross mechanical efficiency such that individuals born lighter can perform only a proportion of the physical work that heavier-born peers can support on an equivalent energy budget.

This effect was not mediated by postnatal experiences, suggesting that prenatal energy balance independently and significantly alters a phenotype reflected in mechanical efficiency.

Chapter 3 also explains that psychosocial stress during the early-adolescent period, between ages 10-15 yr, predicts metabolic sensitivity to acute negative energy balance (i.e., fasting). This sensitivity of metabolic economy, both at rest and during moderate activity, was not mediated by birth weight. This suggests that postnatal psychosocial experiences ‘program’ adult metabolic sensitivity to energetic stress (independent of prenatal energy balance).

Chapter 4 presents evidence that childhood exposure to psychosocial stress, as indicated by allostatic load score at age 15, accelerates maturation independent of birth weight. Nevertheless, birth weight predicted differences in stature at age 15 (independent of age at menarche) suggesting that prenatal energy balance impacts postnatal growth schedules that contribute to final height but not age at menarche. The positive correlation found between birth weight and women’s height is consistent with previous research.

Generalizability

All analyses presented in this dissertation rely on data collected from contemporary U.S. young adults. This population is generally well-fed (Polhamus et al, 2009) and children in the U.S. are increasingly likely to suffer health consequences from consistent positive energy balances (Ogden et al., 2002). Phenotypic correlations observed within U.S. young adults, therefore, likely reflect developmental processes that were less constrained by energy abundance than is typical in other populations. It is plausible that the associations reported herein between developmental psychosocial

experiences and adult phenotypes—and the lack of associations with pre- and post-natal nutrition—reflect only what happens when energetic constraints on development are extremely relaxed.

Conclusion

In a well-fed population where childhood energy balance is high and stable, developmental experience of psychosocial stress significantly affected age at menarche, adult muscle mass, and sensitivity of calorie requirements to fasting. These effects appear independent of prenatal energy balance inferred from birth weight. In the case of adult muscle mass, birth weight did not explain observed variation after controlling for childhood psychosocial stress, which contradicts previous research informed by fetal programming models. The association previously reported between birth weight and adult height was confirmed in this population, even after controlling for developmental psychosocial experiences that impact age at menarche. Birth weight was also found to significantly influence gross mechanical efficiency despite controlling for postnatal experiences. These results support the fetal programming idea that prenatal energy balance (inferred from birth weight) influences growth trajectory of height and contributes to adult metabolic physiology. The body of work presented in this dissertation suggests that prenatal and postnatal experiences reflect independent exposures that can each significantly contribute to adult phenotype.

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