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Beyond thriftiness: Independent and interactive effects of genetic and dietary factors on variations in fat deposition and distribution across populations

Krista Casazza, PhD, RD^a, T. Mark Beasley, PhD, and Jose R. Fernandez, PhD.^{a,b}

^aDepartment of Nutrition Sciences, University of Alabama at Birmingham, Birmingham, AL

^bDepartment of Biostatistics, University of Alabama at Birmingham, Birmingham, AL

Abstract

The thrifty genotype hypothesis initiated speculation that feast and famine cycling throughout history may have led to group-specific alterations of the human genome, thereby augmenting the capacity for excessive fat mass accrual when immersed in the modern-day obesogenic environment. Contemporary work, however, suggests alternative mechanisms influencing fuel utilization and subsequent tissue partitioning to be more relevant in the etiology of population-based variation in adipose storage. The objective of this study was to evaluate the independent and interactive contribution of ancestral admixture as a proxy for population-based genetic variation and diet on adipose tissue deposition and distribution in peripubertal children and to identify differences in racial/ethnic and sex groups. Two-hundred seventy-eight children (53% male) aged 7–12y, categorized by parental self-report as African- (n=91), European- (n=110), or Hispanic American (n=77), participated. Ancestral genetic admixture was estimated using 140 ancestry informative markers. Body composition was evaluated by dual-energy x-ray absorptiometry; energy expenditure by indirect calorimetry and accelerometry; and diet by 24h–recall. Admixture independently contributed to all adiposity parameters; i.e., estimates of European and Amerindian ancestries were positively associated with all adiposity parameters, whereas African genetic admixture was inversely associated with adiposity. In boys, energy intake was associated with adiposity, irrespective of macronutrient profile, whereas in girls, the relationship was mediated by carbohydrate. We also observed moderating effects of energy balance/fuel utilization of the interaction between ancestral genetic admixture and diet. Interactive effects of genetic and non-genetic factors alter metabolic pathways and underlie some of the present population-based differences in fat storage.

Keywords

Admixture; adiposity; diet; fuel utilization

Nearly a half century ago, it was proposed that “thrifty” genotypic adaptations relevant to metabolism induced naturally-selected phenotypes suited to “local” food-energy environments (i.e., cycles of scarcity/availability) (Neel, 1962). Hypothetically, the thrifty genotype would lead to selection of genes more “fit” for fuel utilization/storage in response to environmental pressures. Accordingly, because populations were exposed to different environments, genetic variation resulting from selective pressures across populations could account for respective variations in fat accumulation and distribution patterns. However,

recent work, including that of Neel himself (Neel, 1999), has challenged the original concept producing a wide range of alternative hypotheses as to why populations vary in obesity-related phenotypes.

Genetic variation

Heritability estimates maintain that modern day *intra*-population variability in obesity susceptibility is influenced at least in part by genetic factors (Haworth et al., 2008; Rankinen et al., 2006; Segal, 2007). Whether evolutionary genetic adaptations related to fat storage capacity account for *inter*-population variability has been widely investigated yet still remains unclear (Bonilla et al., 2005; Fernandez et al., 2003a; Fernandez et al., 2003b; Parra et al., 1998). Since Neel first proposed the hypothesis (Neel, 1962), a variety of polymorphisms attributed to local selective environmental pressures have provided some support for a genetic contribution to racial/ethnic variability in adiposity (Wells, 2007b; Wells, 2009b). In theory, genetic variants would have conferred a survival benefit within a small and geographically isolated population via altered metabolic signaling during food scarcity/availability cycles thereby impacting energy efficiency and fat deposition (Johnson et al., 2010). When these variants are subsequently immersed in the “inefficient” contemporary environment (i.e., high food availability, low energy expenditure requirement) the resulting aberrations in fuel utilization increase susceptibility of individuals within certain populations to obesity. However, the extent to which alleles differing in frequency among racial/ethnic groups are functional and truly along the causal path to altered metabolic phenotypes has not been determined (Bray et al., 2009; Rankinen et al., 2006). Further, many populations with high obesity prevalence have never experienced food scarcity/availability cycling (Speakman, 2007), therefore would not have been met with such selection pressures (and allelic variation), thus exposing a major flaw in the hypothesis. To date, although the comprehensive study of allelic variation has yielded some evidence for population differentiation, a consistent footprint of selection across any loci revealing genetic clues to population-based differences continues to elude researchers (Bray et al., 2009; Haworth et al., 2008; Parra et al., 1998; Rankinen et al., 2006). Accordingly, while the fervor to identify the thrifty gene(s) was initially very high, a number of weaknesses curbed the enthusiasm and counter viewpoints have since materialized.

Developmental phenotypic variation

The critical analysis and questioning of the genetic nature of the thrifty tendency to accumulate fat provided the impetus for the emergence of numerous alternative explanations for population-based variation in adiposity. Investigations into developmental origins of obesity, suggested that contrary to genotypic adaptations, metabolic (phenotypic) adaptations related to growth and development, particularly early in the life course, could trigger divergence among populations in obesity-related traits (Bray et al., 2009; Haworth et al., 2008; Parra et al., 1998; Rankinen et al., 2006). The thrifty *phenotype* (Barker) hypothesis, speculated that maternal (under)nourishment stimulates the “programming” *in utero* of anti-starvation mechanisms inducing greater fat storage and perturbed insulin homeostasis (Hales and Barker, 1992; Hales and Barker, 2001; Law, 1996; Watve and Yajnik, 2007). Subsequently, numerous epidemiological studies on peri-natal experiences have provided support for the thrifty phenotype family of hypotheses (Frisancho, 2009; Hales and Barker, 1992; Hales and Barker, 2001; Law, 1996; Painter et al., 2008; Ravelli et al., 2008; Roseboom et al., 2000; Varela-Silva et al., 2007; Watve and Yajnik, 2007; Wells, 2009a). Low birth weight, a proxy for maternal undernutrition differs among racial/ethnic groups and has been linked to adverse health outcomes (Crespi and Denver, 2005; Haworth et al., 2008; Solomons, 2009). An additional component of the thrifty phenotype hypotheses is that insulin resistance contributes to a thrifty metabolism leading to increased energy

storage in terms of fat at the expense of other tissues (e.g., muscle) and subsequent lower resting expenditure (Eriksson et al., 2010; Watve and Yajnik, 2007). Taken together, varied environmental stressors (e.g., food/resource availability) altered metabolic programming during developmental periods manifests into modified resource partitioning and theoretically could account for population-based differences in adiposity (Eriksson et al., 2010; Painter et al., 2008; Ravelli et al., 2008; Roseboom et al., 2000; Stoger, 2008). However, concordant with the thrifty genotype hypothesis, developmental models of *phenotypic* thriftiness are largely correlational, incapable of establishing causality and generally have not been universally supported as a viable explanation of population-based differences in adiposity (Eriksson et al., 2010; Kensara et al., 2005; Swinburn et al., 1996; Swinburn, 1996).

Interestingly, the racial/ethnic disparity observed in obesity prevalence is to some degree gender-specific. Independent of African American, Mexican or European race/ethnicity, adult male obesity prevalence rates are similar, whereas obesity prevalence in African American women exceeds both European American and Mexican American women (Flegal et al., 2010b; Flegal et al., 2010a). From a deterministic (i.e., genotypic or phenotypic) perspective, sexual dimorphism in obesity prevalence would be highly unlikely, but the metabolic (in)flexibility allowing for the diversion of dietary energy to the maintenance of reproduction may underpin this difference (Corbett et al., 2009). It is plausible that during critical periods of growth and development (e.g., the pubertal transition) interactions of diet (and subsequent fuel utilization), energy expenditure, developmental factors (e.g., birth weight) and genetic factors may alter the metabolic settings impacting adult phenotypes. Intriguingly, racial/ethnic differences and differences between sex groups oftentimes do not become readily apparent until puberty (Casazza et al., 2008; Kimm et al., 2001).

Proximate behavioral and physiologic responses

A recent analysis of factors underlying fat storage has concluded that the propensity to accrue greater fat mass among populations may be less metabolic and/or genetic and driven more by neuroendocrine and diet quality parameters (O'Rahilly and Farooqi, 2006; O'Rahilly and Farooqi, 2008). Indeed, genotypic and phenotypic factors predominate investigations into obesity-related traits; however, there are noticeable behavioral explanations for these associations. Increased availability of palatable, energy dense foods and concomitant reduced energy expenditure contributes to a state of positive energy balance, which over a period of time could provide sufficient force to shift obesity prevalence trends (Chakravarthy and Booth, 2004; Frisanchi, 2003; Varela-Silva et al., 2007). These changes independently may not, but synergistically may contribute to racial/ethnic variation in obesity prevalence trends. For example, national trends indicate a relatively stable caloric intake, with similar energy intake and physical activity independently assessed across populations (Crespo et al., 1996; Crespo et al., 2001; Pan and Pratt, 2008). However, African Americans and Hispanic American adults have obesity rates higher than their co-localized European American counterparts (Flegal et al., 2010b). Similar to the two- (or multiple-) hit hypothesis proposed for cancer development (Knudson, 2002), genotypic variants and/or phenotypic adaptation alone may not directly predispose populations to increased obesity susceptibility until additional factors usually derived from behavioral factors precipitate the condition.

Clearly, disentangling population-based differences in susceptibility to fat accumulation requires an integrated approach to investigating the origins of phenotypic, genotypic, and behavioral variability. The task of unraveling population-based differences in adiposity is exceedingly difficult, particularly as populations become more admixed. However, an approach that can be used to capture a proportion of population-based differences includes the use of estimate of ancestral genetic background, as a proxy for genetic contribution.

Although residual confounding (i.e., when two variables are associated, but one does not necessarily cause the other, rather is correlated because they are both influenced by a third variable) remains a concern, studying the effects in childhood allows for elucidation of these mechanisms before some modifiable lifestyle factors (e.g., smoking, alcohol consumption, etc.) further complicate relationships. Therefore, the objective of this study was to examine the independent and interactive effects of energy balance and genetic variance on population-based differences in adiposity in peri-pubertal children and to determine if these interactions differ by sex.

METHODS

Participants

Participants were 278 peripubertal children (53% male) aged 7–12 years from Birmingham, Alabama. Data includes all children measured as part of a cross-sectional study between 2004 and 2008 designed to evaluate genetic associations with diabetes risk factors. Children were recruited with community fliers and presentations, and newspaper advertisements. The participants were required to have no medical diagnoses that were contraindicated to study participation (including hypercholesterolemia, diabetes, or hypertension) and were not taking any medications known to affect body composition levels. Children were categorized into racial/ethnic groups according to parental self-report as African American (AA; n=91), European American (EA; n=110), or Hispanic American (HA; n=77). The children were pubertal stage ≤ 3 as assessed by a pediatrician according to the criteria of Marshall and Tanner (Marshall and Tanner, 1969; Marshall and Tanner, 1970b). Before participating in the study, the nature, purpose, and possible risks of the study were carefully explained. The children and parents then provided informed assent and consent, respectively. The protocol was approved by the Institutional Review Board for human subjects at the University of Alabama at Birmingham (UAB). All measurements were performed at the General Clinical Research Center (GCRC) and the Department of Nutrition Sciences at UAB between 2004 and 2008.

Protocol

Participants completed two testing sessions within 30 days of one another. In the first session anthropometric measurements, pubertal status, body composition, and physical fitness were assessed and a 24h dietary recall was obtained. Information on birth weight was also obtained by parental report. In the second (overnight) session, a second 24h dietary recall was obtained. Participants were admitted to the GCRC in the late afternoon for the visit. All participants were offered the same meal and snack foods. After 2000h, only water and/or non-caloric decaffeinated beverages were permitted until after morning testing. Upon completion of the overnight fast, blood samples were obtained for metabolic profile and DNA genotyping analysis.

Anthropometric measures

The same registered dietitian obtained anthropometric measurements on all children. Participants were weighed (Scale-tronix 6702W; Scale-tronix, Carol Stream, IL) to the nearest 0.1 kg in minimal clothing without shoes. Height was recorded also without shoes using a digital stadiometer (Heightronic 235; Measurement Concepts, Snoqualmie, WA). BMI percentile was calculated using CDC growth charts (<http://apps.nccd.cdc.gov/dnpabmi/>).

Pubertal status

Tanner staging was based on pediatrician assessment according to the criteria of Marshall and Tanner (Marshall and Tanner, 1969; Marshall and Tanner, 1970a). Staging was according to both breast and pubic hair development in girls and genitalia and pubic hair development in boys. One composite number was assigned for Tanner staging, representing the higher of the two values defined by breast/genitalia and pubic hair (Malina RM and Bouchard C, 1991).

Adiposity parameters

Measures of adiposity (total body fat, percent body fat, and trunk fat) were assessed by DXA using a GE Lunar Prodigy densitometer (GE LUNAR Radiation Corp., Madison, WI). Participants were scanned in light clothing, while lying flat on their backs with arms at their sides. DXA scans were performed and analyzed using pediatric software (enCORE 2002 Version 6.10.029). Intra-abdominal adipose tissue (IAAT) and subcutaneous abdominal adipose tissue (SAAT) were measured by computed tomography scanning with a HiLight/ Advantage Scanner (General Electric, Milwaukee) as previously described (Kekes-Szabo et al., 1994). A 5mm abdominal scan was taken at the level of the umbilicus. Scans were analyzed for cross-sectional area (cm²) of adipose tissue using the density contour program with Hounsfield units for adipose tissue set at -190 to -30 (Goran et al., 1995).

Genetic admixture

Genotyping of 140 ancestry informative markers (AIMs) for the estimation of ancestral genetic admixture proportion for each subject was performed at Prevention Genetics (www.preventiongenetics.com) using the Chemicon Amplifluor SNPs Genotyping System (Myakishev et al., 2001) coupled with ArrayTape technology (www.global-array.com) as described elsewhere (Casazza K et al., 2009). The information from the AIMs was translated into estimates of African, European, and Amerindian admixture for each subject using maximum likelihood (ML) estimation based on the ML algorithm described by Hanis et al. (Hanis et al., 1986). In brief, the ML method estimates the proportion of genetic ancestry for an individual, using a range of proportions from 0 to 1 and identifies the most probable value of admixture based on the observed genotypes. Scientific evaluation of the uniqueness of population-based differences is challenging, in particular because in many contexts, delineation between biology and environment in the variable “race/ethnicity” is not clearly defined. Further, race/ethnicity changes according to historical periods, social structure, and as individuals become more admixed. Herein, we use admixture as a proxy for an estimate of the genetic contribution, yet are aware that although an objective measure, this estimate does not entirely transcend studies which merely include race/ethnicity. Notwithstanding, even when controlling for confounders associated with population-based variation it must be recognized that 1) not all intra- and inter-population confounders can be measured well, 2) statistical modeling techniques for the inclusion of such confounding may not function adequately, 3) there is a relative impossibility of identifying and including all potential confounders in any study (Kaufman et al., 1997). Accordingly, use of admixture estimates does not lead to the establishment of cause and effect relationships but does improve our ability to establish a meaningful, statistically valid connection between admixture and adiposity parameters.

Dietary intake

Diet composition was determined by two 24h recalls using the multiple pass method with cup and bowl sizes provided to help gauge portion sizes. Recalls were performed in person in the presence of at least one parent at each visit. A trained dietitian coded and analyzed dietary intake data using Nutrition Data System for Research software version 2006,

(Nutrition Coordinating Center, University of Minnesota, Minneapolis, MN) a dietary analysis program designed for the collection and analyses of 24h recalls. The average of the two days of intake for each nutrient was used in subsequent analyses.

Physical activity

The concept of thriftiness in energy storage would, hypothetically, not only include energy intake by also energy expenditure. Accordingly, physical activity, objectively measured by accelerometry, was included in statistical models as a potential moderator. The MTI Actigraph accelerometer (Actigraph GT1M – Standard Model 198-0100-02, ActiGraph LLC, Pensacola, FL and accompanying software) was used to measure physical activity levels and patterns for seven days prior to participant's inpatient visit at the GCRC as described (Casazza et al., 2009a). Epoch length was set at one minute and data expressed as counts per minute (counts min^{-1}). Daily and total counts per minute were summed and averaged.

Socioeconomic Status (SES)

Research suggests that SES influences adiposity and both sides of the energy balance equation. Although to adequately control for confounding due to socioeconomic status (SES) is nearly impossible (Kaufman et al., 1997), the variable SES was included in all statistical models as a covariate. SES was measured with the Hollingshead 4-factor index of social class (Cirino et al., 2002), which combines the educational attainment and occupational prestige for the number of working parents in the child's family. Scores range from 8 to 66 with the higher scores indicating higher theoretical social status.

Indirect calorimetry

Energy balance by definition includes not only intake, but also expenditure. Approximately 65% of total energy expenditure relates to resting energy expenditure (REE). Both REE and adiposity are influenced at least in part by substrate utilization. The respiratory quotient (RQ) is used in the calculation of REE and provides an estimate of fat vs. carbohydrate oxidation. Indirect calorimetry for the assessment for REE and RQ was performed in the morning immediately after awakening during the overnight visit. A computerized, open-circuit, indirect calorimetry system with a ventilated canopy (Delta Trac II; Sensor Medics, Yorba Linda, CA) was used. While lying supine on a bed, the head of the subject was enclosed in a Plexiglas canopy. Subjects were instructed not to sleep and remain quiet and still, breathing normally. One-minute average intervals of oxygen uptake (VO_2) and carbon dioxide production (CO_2) were measured continuously for thirty minutes.

Physical fitness

Oxygen utilization is partially dependent on physical activity but also strongly influenced by genetic factors, including historical geographic residence. Oxygen utilization is also influenced by exposure to hypoxia during development, which is dependent upon gestational and postnatal development and birthplace. Accordingly, aerobic capacity attained before adulthood may play a role in both behaviors and physiology related to fuel utilization and storage (Varela-Silva et al., 2007). At the first testing session, VO_{2-170} was determined by indirect calorimetry on a treadmill, as described by Gutin et al. (Gutin et al., 2004). The first four minutes of the test, as a mode of standardization, was at two-and-a-half miles per hour with no incline. Measurements were taken following the standardization period (at four minutes) and served as baseline for heart rate, VO_2 , and VCO_2 ; subjects then began exercising at three mph. The incline was subsequently increased by 2% every two minutes. Heart rate was measured with the Polar Vantage XL HR monitor (Polar Beat, Port Washington, NY). Based on this protocol, a measure of fitness was established for each

subject. For fitness, volumes of O₂ and CO₂ were measured continuously using open circuit spirometry until recording the VO₂ level at a heart rate of 170 beats/min. Data was analyzed with a Max-II metabolic testing system (PHYSIO-DYNE, Quogue, NY).

Statistical analyses

Differences in descriptive statistics between self-reported racial/ethnic groups were analyzed using ANOVA with Tukey's post hoc analysis. Our primary analysis utilized multiple linear regression modeling to test independent relationships between genetic admixture and the measures of adiposity (total body fat, percent body fat, trunk fat, IAAT, SAAT). Next, the independent contribution for dietary variables (total energy intake and macronutrient composition) was explored. We then evaluated the relationships between admixture and adiposity parameters using mediating and moderating variables. Stratification by median intake of dietary variables served to clarify the mediating effect of the relationship between the independent and dependent variables. Regression models were stratified by the following diet-related variables: total energy intake, percent calories from carbohydrate, percent calories from fat, and percent calories from protein. Finally, to explore potential interactions of dietary variables on the relationship between ancestral genetic background and adiposity, five models were analyzed. Each of the five three-predictor models employed a single continuous potential energy-related variable, (i.e., energy expenditure, respiratory quotient, physical activity, physical fitness, birth weight), a measure of genetic admixture, and an admixture-by-energy-related (e.g., admixture by energy expenditure) centered cross-product interaction term.

Covariates—The main objective of our study was tested using multiple linear regression models with adiposity parameters as the dependent variables and admixture and dietary variables as the independent variables. Overall multiple regression models were adjusted for age, sex, race/ethnicity, pubertal stage, SES, and height. Sex was coded as 0 for males and 1 for females. Because the independent variables “Tanner” and “race/ethnicity” are nominal and included three levels, they were entered into the models as orthogonally coded dummy variables. Race/ethnic- and sex-specific models were also explored with respective covariates removed accordingly. All models were evaluated for residual normality and were logarithmically transformed as appropriate to conform to assumptions of linear regression. All data were analyzed using SAS 9.2 software (SAS Institute, Cary, NC).

RESULTS

General participant characteristics and body composition measures are presented in Table 1. Among racial/ethnic groups, there were no differences in age or weight. European Americans had the highest birth weight, followed by African Americans. African Americans were reproductively more mature. European Americans reported higher SES than African Americans, who in turn reported higher SES than Hispanic Americans. African genetic admixture was highest in African Americans and higher in Hispanic Americans than European Americans. European genetic admixture was highest in European Americans followed by Hispanic Americans. Amerindian admixture was highest in Hispanic Americans. Hispanic Americans presented with highest BMI z-score and greatest adiposity. There were no differences in daily physical activity, REE or RQ among racial/ethnic groups, but physical fitness was higher in Hispanic Americans relative to African Americans. Among sex groups, there were no differences in height, weight, BMI z-score, birth weight, SES, or any of the admixture variables. Girls were younger but reproductively more mature than boys. Girls had greater adiposity than boys in all depots. Boys had greater REE and physical fitness, whereas girls had higher respiratory quotient. Stratification within racial/

ethnic group by sex did not modify these differences; i.e. racial/ethnic differences upheld between boys and girls (data not shown).

Table 2 includes descriptive statistics for the total sample, by race/ethnicity, and sex for dietary intake variables. There were no differences in energy intake among racial/ethnic groups. African Americans reported the highest percentage intake of calories from fat, whereas Hispanic Americans reported the highest percentage intake of calories from protein, and European Americans reported highest percentage intake of calories from carbohydrate. Boys reported greater energy intake while girls reported consuming a greater proportion of their calories from fat. Further stratification within racial/ethnic group by sex did not modify these differences (data not shown).

Table 3 presents the multiple linear regression analyses evaluating relationships between admixture and adiposity measures in the total sample, stratified by race/ethnicity and sex groups. In the total sample, European genetic admixture was positively associated with all measures of adiposity. This relationship remained apparent in boys and marginal in African Americans for total body fat, i.e., boys (but not girls) with higher European admixture had higher adiposity and individuals self-classified as African American who had higher European admixture had greater total body fat. African genetic admixture was inversely associated with all measures of adiposity in the total sample, remained significant among African Americans and both sex groups. There was a positive relationship between Amerindian genetic admixture and adiposity parameters in the total sample, irrespective of sex; however, when stratified by race/ethnicity, the relationship was only observed for the measure of IAAT only in Hispanic Americans.

The independent contribution of dietary variables to adiposity parameters were evaluated and are presented in Table 4. Few significant associations were observed in the total sample, by race/ethnicity or sex.

Table 5 presents the relationship between genetic admixture and measures of adiposity for boys and girls with dietary variables stratified by median intake. In boys, the relationship between European genetic admixture and measures of adiposity appeared to be mediated by energy intake, such that in individuals with greater European admixture, increased energy was associated with greater adiposity. This relationship was independent of macronutrient profile, suggesting quantity, not necessarily quality may mediate adiposity in boys with greater European admixture. The relationship between African and Amerindian genetic admixture and dietary variables did not appear to be mediated by energy intake or macronutrient composition. In girls, the inverse relationship between African admixture and adiposity was attenuated in girls consuming a high proportion of their calories from carbohydrate and a low proportion of their calories from fat. Conversely, the positive relationship between Amerindian admixture and adiposity was attenuated in girls with these consumption patterns. Because a significant association between European admixture and adiposity parameters was not observed, mediation by dietary intake was not evaluated. For those variables in which a significant differential relationship was observed between groups with high and low intake, the interaction term consisting of the cross-product of the dietary variable and admixture was evaluated. The interaction term, energy intake by European admixture cross-product in boys was significant for all adiposity parameters and ($P < 0.01$, for all). In girls, the interaction term consisting of the cross-product of carbohydrate intake and African admixture was significant for total fat and SAAT ($P < 0.05$) and for Amerindian admixture by carbohydrate intake for IAAT and SAAT ($p < 0.05$).

The underlying effect of diet on the relationship between genetic background and adiposity may be moderated by fuel utilization. Accordingly, we tested the interactive contribution of

diet and admixture on adiposity as moderated by variables associated with fuel utilization: REE, RQ, physical activity and fitness. In boys, the relationship between diet and admixture (European, African, and Amerindian) on adiposity was attenuated by the inclusion of physical fitness or REE in the models ($p > 0.15$). In girls, the association between carbohydrate intake and admixture (African and Amerindian) on adiposity was attenuated by inclusion of REE, RQ and daily physical activity ($P > 0.10$) in the models.

Lastly, as a proxy to estimate maternal nutrition and subsequent “fetal programming” the effect of birth weight on the observed relationships between diet and admixture was evaluated. In boys, but not girls, the association between energy intake and admixture (European and Amerindian, but not African) on adiposity was attenuated with birth weight ($P > 0.10$) in the models.

DISCUSSION

Genetic contributors to population-based differences in fat storage

Though the validity and applicability of the thrifty genotype hypothesis remains controversial, its proposal provided the impetus for investigations into the etiology of population-based differences in fat storage. Subsequently, a variety of alternative explanations for variations in fat storage across populations emerged, some of which are equally contentious. The results presented herein identify ancestral genetic admixture as a contributor to population-based differences in adipose tissue deposition and distribution. The positive relationship between Amerindian admixture and adiposity allows for a potential genetic contribution, and the speculative possibility that climate-related adaptive processes may alter energy metabolism among would-be descendants of seemingly agriculturally-subsistent populations (e.g., Amerindians) (Acuna-Alonzo et al., 2010). However, the inverse relationship between African admixture and adiposity measures in light of current obesity prevalence estimates (Flegal et al., 2010a) in African Americans (particularly females), challenges the notion that selected genetic adaptations are in the causal pathway of racial/ethnic differences in fat storage capacity, rendering metabolic/phenotypic mechanisms related to fat storage a plausible explanation for adiposity differences.

Developmental adaptations of metabolic phenotypes

The metabolic cost of storing fat is lower and accordingly, the advantages for growth, development and reproduction are significant in partitioning of resources between tissues (i.e., fat, bone, lean mass). The sexual dimorphism observed between admixture and energy balance further elucidates the collective contribution of various factors in population differences in adiposity. During critical periods of development (e.g., puberty) metabolic inflexibility (i.e., carbohydrate vs. fat oxidation) may be the result of an adaptive response to efficient fat storage (Berk et al., 2006) to ensure evolutionary fitness in terms of reproductive success. This is particularly salient during the pubertal transition and may underlie the differential response between girls and boys to variables evaluated. Factors that affect survival or reproduction at a young age have greater effects on the fitness of an individual than do aspects with the same magnitude of effect expressed later in life (Chakravarthy and Booth, 2004; Goedecke et al., 2009). Racial/ethnic differences in reproductive hormone concentrations (e.g., estradiol, androgens) and growth factors (e.g., insulin, insulin-like growth factor) early in the life course may provide some insight into altered metabolic phenotypes during critical periods of development (Casazza et al., 2009b; Crespi and Denver, 2005; Frisano, 2009; Suliga, 2009). Further, the mediation of the relationship between macronutrient content and admixture as well as moderation of the association by variables associated with energy balance (i.e., REE, RQ) suggest genetic and non-genetic factors act in concert to alter metabolic pathways (Casazza et al., 2010; Acuna-

Alonzo et al., 2010; Gower et al., 2003; Johnson et al., 2010). Accordingly, although genetics (i.e., ancestral genetic background) certainly plays a role, it is clear that non-genetic factors are involved interactively in obesity susceptibility across groups.

Proximate/behavioral modifications influencing energy efficiency

Indeed, caloric intake plays a major role in establishing energy balance influencing fat mass accrual. However, dietary intake has not changed dramatically in the past few decades in terms of quantity, but the quality significantly differs (e.g., carbohydrate quality, degree of processing), particularly from that which existed during metabolic physiology evolution (Crespo et al., 2001) (Johnson et al., 2010). In our sample, similar to that which has been observed by others, (Chakravarthy and Booth, 2004; Eaton et al., 2009; Gardner and Rhodes, 2009) energy intake and daily physical activity was comparable across racial/ethnic groups. Differences in macronutrient intake between groups can influence substrate oxidation, resource partitioning and feeding behaviors especially during growth and development and impact fat deposition (Corbett et al., 2009; Varela-Silva et al., 2007; Wells, 2007a; Wells, 2007b). Humans with a higher RQ have been reported to gain more weight than those with a lower RQ (Galgani et al., 2008a; Ravussin, 1995; Weyer et al., 1999b; Weyer et al., 1999a). Our findings of a moderating effect of RQ, particularly with Amerindian admixture and macronutrient intake among girls may indicate some degree of preferential carbohydrate oxidation and provide a potential explanation for the greater adiposity observed in these groups. When stratified by sex, girls consumed a greater proportion of their calories from fat. Interestingly, we also observed a greater RQ (greater carbohydrate oxidation) and lower REE in girls relative boys. Physical activity has consistently demonstrated to influence fat mass accrual as well as fat oxidative capacity (Chakravarthy and Booth, 2004; Galgani et al., 2008b; Weyer et al., 2000). Although we did not observe racial/ethnic differences in physical activity, the attenuation of the relationship between admixture and energy intake on adiposity in boys supports energy expenditure being a core catalyst to physiologically regulate adipose storage (Chakravarthy and Booth, 2004). This relationship was not identified in girls perhaps due to the relatively low level of physical activity among the girls in this sample. Interestingly, Smith and colleagues reported that low activity coupled with high fat intake delays fat oxidation and increases fat storage (Smith et al., 2000). The extent to which substrate oxidation translates into health outcomes has not been fully elucidated, the level of physical activity needed to generate health benefits and if this level differs across groups has not been determined.

A major strength of the study is the identification of population-based differences in fat deposition using robust body composition measurement techniques and distribution identified early in the life course. Nevertheless, several limitations of this study warrant mention. As is true for most prior multi-ethnic studies, there are relevant confounding factors that differ among groups that influence health and cannot be completely and accurately accounted for by a single estimates of variables such as admixture, diet, or SES. In addition, the cross-sectional nature of our samples prevents us from assessing how adiposity changes with time, which is critical to establishing causality. Planned, future follow-ups will help clarify whether adiposity early in development predicts future health risks and shed some light as to the extent an adaptive response during critical periods (i.e., the pubertal transition) may be the body's mechanistic approach to "synchronize" genotypic and phenotypic expression best suited for the "environment."

CONCLUSIONS

Proximate (mechanistic) and ultimate (evolutionary) underpinnings of population-based differences in obesity have been debated since Neel first proposed the thrifty genotype hypothesis a half decade ago. The work of Lasker (Lasker, 1969), presaged many of the

contemporary investigation of variation in adiposity between populations speculating that at least three modes underlie adaptive or thrifty process that influence differences. A variety of genetic factors (variants), attributed to local selective pressures deriving from particular ecological or agricultural circumstances, may contribute racial/ethnic variability in adipose tissue accumulation. However, the effects exerted on energy balance via genotypic, phenotypic and behavioral variation are not independent fundamental agents, rather different levels of the same causal framework. Although obesity itself may not have been an adaptive response, the mechanisms which were established based upon selective pressures may have conferred adaptive changes. These mechanisms collide synergistically to promote fat deposition in an environment created by contemporary, technologically advanced societies. Within the context of our past, and not at the level of fatness today, fuel utilization patterns that enhance fat deposition may have had metabolic benefits in some groups and reproductive benefits in females. Although strides have been made in understanding the mechanistic and evolutionary cause of population-based differences in adiposity, a general consensus has not been reached on molecular or relative contributions of different evolutionary processes.

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Table 1

Descriptive statistics and adiposity measures in the total sample and by self-reported race/ethnicity (mean±SE)

	Total (n=278)	EA (n=110)	AA (n=91)	HA (n=77)	Boys (n=146)	Girls (n=132)
Age (yrs)	9.5±0.1	9.6±0.1	9.6±0.1	9.3±0.2	9.7±0.1 ^d	9.3±0.1 ^e
Height (cm)	139.4±0.6	140.0±1.0 ^a	140.8±1.0 ^a	136.9±1.2 ^b	140.0±0.8	138.8±0.9
Weight (kg)	36.6±0.5	35.4±0.8	37.2±1.0	37.6±1.1	37.0±0.8	36.1±0.7
BMI z-score	-0.04±0.06	-0.23±0.08 ^b	-0.02±0.10 ^b	0.37±0.11 ^a	-0.04±0.1	-0.04±0.1
BMI percentile	66.4±1.5	60.0±2.4	63.9±2.7	79.2±2.0	66.4±2.0	66.0±2.2
Birth weight (g)	3296.7±40.7	3520.0±50.4 ^a	3194.8±70.1 ^b	3067.2±91.8 ^c	3324.7±59.9	3265.7±58.2
Tanner	1.49±0.04	1.34±0.06 ^b	1.75±0.08 ^a	1.40±0.07 ^b	1.37±0.04 ^e	1.6±0.1 ^d
SES	38.8±0.8	49.3±0.9 ^a	37.0±1.1 ^b	25.7±1.3 ^c	38.7±1.1	38.7±1.3
Total PA (min/d)	286.9±3.2	288.1±4.7	290.9±6.4	280.8±6.1	287.4±4.7	286.3±4.5
EUADM	0.55±0.02	0.96±0.01 ^a	0.15±0.01 ^c	0.35±0.02 ^b	0.52±0.03	0.53±0.03
AFADM	0.31±0.02	0.01±0.00 ^c	0.82±0.01 ^a	0.09±0.01 ^b	0.30±0.03	0.29±0.03
AMINADM	0.14±0.01	0.03±0.00 ^b	0.03±0.00 ^b	0.56±0.03 ^a	0.18±0.02	0.18±0.02
Total fat (kg)	8.9±0.3	8.2±0.5 ^d	8.1±0.6 ^d	10.9±0.6 ^c	8.4±0.5 ^e	9.6±0.4 ^d
Percent fat (kg)	23.5±0.5	22.5±0.8 ^b	20.4±1.0 ^b	28.4±0.9 ^a	21.1±0.8 ^e	26.1±0.7 ^d
Trunk fat (kg)	3.7±0.2	3.2±0.2 ^b	3.1±0.3 ^b	4.9±0.3 ^a	3.4±0.2	4.0±0.2
IAAT (g)	33.4±1.6	34.4±2.7 ^b	26.9±2.1 ^c	42.2±3.4 ^a	32.9±2.2	34.0±2.2
SAAT (g)	93.1±5.2	86.5±8.6 ^b	79.2±8.7 ^b	124.2±8.6 ^a	78.6±6.3 ^e	110.1±8.2 ^d
REE	1191.8±13.9	1181.7±22.3	1190.2±21.4	1209.3±30.0	1238.6±20.3 ^d	1140.4±17.8 ^e
RQ	0.88±0.01	0.88±0.01	0.87±0.01	0.88±0.01	0.87±0.01 ^d	0.89±0.01 ^e
Fitness (VO170)	1068.6	1060.1±29.9 ^{ab}	1011.5±32.5 ^b	1143.8±36.6 ^a	1132.9±27.9 ^d	992.6±23.6 ^e

^a superscripts indicate significant differences among self-identified racial/ethnic category, p<0.05^b superscripts indicate significant differences among self-identified racial/ethnic category, p<0.05^c superscripts indicate significant differences among self-identified racial/ethnic category, p<0.05

^d superscripts indicate significant differences among sexes, $p < 0.05$. EA=European American, AA=African American, HA=Hispanic American, BMI=body mass index, IAAT=intra-abdominal adipose tissue, SAAT=subcutaneous adipose tissue, EUADM=European admixture, AFADM=African Admixture; AMINADM =American Indian Admixture; SES=socioeconomic status; PA=physical activity; REE = Resting Energy Expenditure; RQ = Respiratory Quotient; VO170 = volume of oxygen used at heart rate 170 beats per minute on graded treadmill test

^e superscripts indicate significant differences among sexes, $p < 0.05$. EA=European American, AA=African American, HA=Hispanic American, BMI=body mass index, IAAT=intra-abdominal adipose tissue, SAAT=subcutaneous adipose tissue, EUADM=European admixture, AFADM=African Admixture; AMINADM =American Indian Admixture; SES=socioeconomic status; PA=physical activity; REE = Resting Energy Expenditure; RQ = Respiratory Quotient; VO170 = volume of oxygen used at heart rate 170 beats per minute on graded treadmill test

Table 2

Descriptive Statistics of Dietary Intake (mean±SE)

	Total (n=278)	EA (n=110)	AA (n=91)	HA (n=77)	Boys (n=146)	Girls (n=132)
Energy (kcal)	1888.2±26.8	1877.3±38.5	1,889.6±50.7	1906.0±52.4	1945.8±38.2 ^d	1826.0±36.9 ^e
CHO (%)	51.2±0.4	53.0±0.6 ^a	49.6±0.8 ^b	50.5±0.9 ^b	51.6±0.6	50.7±0.6
Fat (%)	35.0±0.3	34.0±0.5 ^b	36.8±0.6 ^a	34.2±0.7 ^b	34.3±0.5 ^e	35.7±0.5 ^d
Protein (%)	15.0±0.2	14.3±0.3 ^b	14.7±0.3 ^b	16.5±0.4 ^a	15.2±0.2	14.8±0.3

^a superscripts indicate significant differences among self-identified racial/ethnic category, p<0.05.

^b superscripts indicate significant differences among self-identified racial/ethnic category, p<0.05.

^c superscripts indicate significant differences among self-identified racial/ethnic category, p<0.05.

^d superscripts indicate significant differences among sex category, p<0.05. EA=European American, AA=African American, HA=Hispanic American, CHO=carbohydrate; Fat quality (0–4) derived from total energy intake, calories from fat, saturated fat, trans fat; CHO quality (0–4) derived from total energy intake, percent calories from CHO, glycemic load, fructose.

^e superscripts indicate significant differences among sex category, p<0.05. EA=European American, AA=African American, HA=Hispanic American, CHO=carbohydrate; Fat quality (0–4) derived from total energy intake, calories from fat, saturated fat, trans fat; CHO quality (0–4) derived from total energy intake, percent calories from CHO, glycemic load, fructose.

Table 3

Multiple linear regression analysis for the effect of genetic admixture on body composition in the entire sample (n=278) and stratified by self-reported race/ethnicity

	Total Body Fat			% Body Fat			Trunk Fat			IAAT			SAAT		
	β	p-value		β	p-value		β	p-value		β	p-value		β	p-value	
EUADM															
Total Sample	0.19	<0.01	0.22	<0.01	0.14	0.03	0.24	<0.01	0.25	<0.01	0.25	<0.01	0.25	<0.01	
EA (n=110)	-0.07	0.38	0.09	0.31	0.06	0.48	0.09	0.50	0.06	0.62					
AA (n=91)	0.16	0.06	0.19	0.05	0.10	0.35	0.19	0.10	0.18	0.09					
HA (n=77)	-0.06	0.55	-0.03	0.84	-0.02	0.86	-0.14	0.37	0.06	0.72					
Boys (n=146)	0.23	<0.01	0.25	0.01	0.17	0.07	0.35	<0.01	0.32	<0.01					
Girls (n=132)	0.14	0.11	0.19	0.06	0.10	0.31	0.14	0.28	0.16	0.20					
AFADM															
Total Sample	-0.30	<0.01	-0.35	<0.01	-0.31	<0.01	-0.35	<0.01	-0.35	<0.01					
EA	-0.09	0.32	-0.08	0.39	-0.05	0.56	-0.09	0.49	-0.15	0.24					
AA	-0.20	0.02	-0.23	0.02	-0.18	0.06	-0.29	0.01	-0.23	0.03					
HA	-0.05	0.59	-0.09	0.45	-0.12	0.23	-0.08	0.22	-0.19	0.19					
Boys	-0.33	<0.01	-0.36	<0.01	-0.29	<0.01	-0.41	<0.01	-0.39	<0.01					
Girls	-0.25	<0.01	-0.34	<0.01	-0.34	<0.01	-0.29	<0.01	-0.33	<0.01					
AMINADM															
Total Sample	0.34	<0.01	0.38	<0.01	0.41	<0.01	0.36	<0.01	0.36	<0.01					
EA	-0.05	0.58	0.07	0.45	0.05	0.60	-0.06	0.65	0.01	0.98					
AA	0.12	0.17	0.17	0.17	0.07	0.48	0.25	0.13	0.24	0.03					
HA	0.09	0.40	0.12	0.07	0.09	0.45	0.28	0.02	0.09	0.58					
Boys	0.39	<0.01	0.43	<0.01	0.40	<0.01	0.34	<0.01	0.36	0.01					
Girls	0.27	<0.01	0.36	<0.01	0.43	<0.01	0.40	<0.01	0.38	<0.01					

Bolded values indicate a significant relationship between the admixture and adiposity measures ($p \leq 0.05$). All models adjusted for age, sex, pubertal stage, SES, and height. EA=European American, AA=African American, HA=Hispanic American, IAA=intra-abdominal adipose tissue, SAAT=subcutaneous adipose tissue, EUADM=European admixture, AFADM=African admixture, AMINADM=American Indian admixture

Table 4

Independent contribution of dietary variables to body composition parameters in the total sample and stratified by self-reported race/ethnicity.

	Total Fat		% Fat		Trunk Fat		IAAT		SAAT	
	β	α	β	α	β	α	β	α	β	α
Total Sample										
<i>Energy kcal</i>	-0.05	0.27	-0.06	0.24	-0.06	0.22	-0.05	0.49	-0.08	0.22
% <i>CHO</i>	-0.09	0.07	-0.09	0.07	-0.05	0.32	-0.10	0.14	-0.09	0.18
% <i>Fat</i>	0.07	0.19	0.06	0.25	0.02	0.69	0.05	0.44	0.03	0.62
% <i>Protein</i>	0.067	0.18	0.09	0.10	0.06	0.23	0.15	0.04	0.40	0.04
EA										
<i>Energy kcal</i>	-0.04	0.72	-0.01	0.96	-0.05	0.13	0.09	0.48	-0.02	0.99
% <i>CHO</i>	-0.10	0.30	-0.13	0.14	-0.09	0.31	-0.22	0.07	-0.15	0.22
% <i>Fat</i>	0.13	0.19	0.17	0.06	0.12	0.18	0.22	0.08	0.16	0.19
% <i>Protein</i>	0.01	0.96	-0.01	0.88	-0.01	0.92	0.15	0.22	0.08	0.48
AA										
<i>Energy kcal</i>	-0.09	0.41	-0.09	0.36	-0.15	0.15	-0.14	0.27	-0.12	0.33
% <i>CHO</i>	-0.16	0.12	-0.05	0.57	-0.06	0.57	0.03	0.79	-0.05	0.67
% <i>Fat</i>	0.04	0.45	-0.11	0.222	-0.10	0.3	-0.11	0.37	-0.07	0.51
% <i>Protein</i>	0.29	<0.01	0.20	0.03	0.26	<0.01	0.26	0.02	0.20	0.06
HA										
<i>Energy kcal</i>	0.14	0.20	-0.01	0.92	0.03	0.74	0.02	0.92	-0.06	0.69
% <i>CHO</i>	-0.05	0.66	-0.16	0.18	-0.06	0.61	-0.06	0.68	-0.08	0.55
% <i>Fat</i>	0.04	0.76	0.10	0.40	0.06	0.57	0.07	0.64	0.01	0.92
% <i>Protein</i>	0.04	0.69	0.14	0.21	0.02	0.98	-0.03	0.84	0.15	0.30
Boys										
<i>Energy kcal</i>	-0.03	0.67	-0.05	0.44	-0.06	0.37	-0.03	0.71	-0.05	0.52
% <i>CHO</i>	-0.07	0.36	-0.09	0.21	-0.02	0.759	-0.04	0.65	-0.08	0.36
% <i>Fat</i>	0.05	0.52	0.08	0.25	0.01	0.988	0.01	0.91	0.03	0.71
% <i>Protein</i>	0.08	0.26	0.03	0.63	0.04	0.578	0.11	0.28	0.15	0.12
Girls										

	Total Fat		% Fat		Trunk Fat		IAAT		SAAT	
	β	α	β	α	β	α	β	α	β	α
<i>Energy kcal</i>	-0.04	0.67	-0.07	0.36	-0.06	0.473	-0.07	0.54	-0.11	0.32
% <i>CHO</i>	-0.06	0.51	-0.11	0.19	-0.10	0.203	-0.17	0.13	-0.11	0.32
% <i>Fat</i>	0.02	0.83	0.03	0.70	0.06	0.481	0.13	0.25	0.03	0.79
% <i>Protein</i>	0.08	0.42	0.15	0.09	0.10	0.241	0.17	0.16	0.04	0.79

Bolded values indicate a significant relationship between the dependent (adiposity) and independent variables (diet). Italicized values indicate a trend towards a significant relationship between the dependent (adiposity) and independent variables (genetic admixture) ($p < 0.10$). All models adjusted for age, sex, pubertal stage, SES, and height. EA=European American, AA=African American, HA=Hispanic American, IAAT=intra-abdominal adipose tissue, SAAT=subcutaneous adipose tissue, CHO=carbohydrate.

Table 5

Mediating effects of dietary variables on measures of adiposity.

	Total Body Fat		% Body Fat		Trunk Fat		IAAT		SAAT	
	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls
European Admixture										
<i>Energy Intake</i>										
<i>Low</i>	↔	NS	↔	NS	↔	NS	↔	NS	↔	NS
<i>High</i>	↑	NS	↑	NS	↑	NS	↑	NS	↑	NS
<i>% CHO</i>										
<i>Low</i>	↔	NS	↔	NS	↔	NS	↔	NS	↔	NS
<i>High</i>	↑	NS	↑	NS	↑	NS	↑	NS	↑	NS
<i>% Fat</i>										
<i>Low</i>	↔	NS	↔	NS	↔	NS	↔	NS	↔	NS
<i>High</i>	↑	NS	↑	NS	↑	NS	↑	NS	↑	NS
<i>% Protein</i>										
<i>Low</i>	↔	NS	↑	NS	↑	NS	↑	NS	↑	NS
<i>High</i>	↑	NS	↔	NS	↔	NS	↔	NS	↔	NS
African Admixture										
<i>Energy Intake</i>										
<i>Low</i>	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓
<i>High</i>	↔	↓	↔	↓	↔	↓	↔	↓	↔	↓
<i>% CHO</i>										
<i>Low</i>	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓
<i>High</i>	↓	↔	↓	↔	↓	↔	↓	↔	↓	↔
<i>% Fat</i>										
<i>Low</i>	↓	↔	↓	↔	↓	↔	↓	↔	↓	↔
<i>High</i>	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓
<i>% Protein</i>										
<i>Low</i>	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓
<i>High</i>	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓

	Total Body Fat		% Body Fat		Trunk Fat		IAAT		SAAT	
	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls
Amerindian Admixture										
<i>Energy Intake</i>										
<i>Low</i>	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑
<i>High</i>	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑
<i>% CHO</i>										
<i>Low</i>	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑
<i>High</i>	↑	↔	↑	↔	↑	↔	↑	↔	↑	↔
<i>% Fat</i>										
<i>Low</i>	↑	↔	↑	↑	↑	↑	↑	↑	↑	↑
<i>High</i>	↑	↑	↑	↔	↑	↔	↑	↔	↑	↔
<i>% Protein</i>										
<i>Low</i>	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑
<i>High</i>	↑	↑	↑	↑	↑	↔	↑	↔	↑	↔

All models adjusted for age, pubertal status, SES and height. Adjustment for admixture component as presented. ↑ indicates a positive relationship between the dependent (adiposity) and median dietary intake (p<0.05). ↓ indicates an inverse relationship between the dependent (adiposity) and median dietary intake (p<0.05). ↔ indicates attenuation of the relationship between the dependent (adiposity) and median dietary intake (p<0.05). IAAT = intra-abdominal adipose tissue, SAAT = subcutaneous adipose tissue, CHO = carbohydrate. NS = non-significant.