Routledge
Taylor & Francis Group

Research Quarterly for Exercise and Sport

ISSN: 0270-1367 (Print) 2168-3824 (Online) Journal homepage: http://www.tandfonline.com/loi/urqe20

Top 10 Research Questions Related to Body Composition

Scott Going , Vinson Lee , Rob Blew , Deepika Laddu & Megan Hetherington-Rauth

To cite this article: Scott Going , Vinson Lee , Rob Blew , Deepika Laddu & Megan Hetherington-Rauth (2014) Top 10 Research Questions Related to Body Composition, Research Quarterly for Exercise and Sport, 85:1, 38-48, DOI: 10.1080/02701367.2013.875446

To link to this article: http://dx.doi.org/10.1080/02701367.2013.875446

Research Quarterly for Exercise and Sport, *85*, 38–48, 2014

ISSN 0270-1367 print/ISSN 2168-3824 online
DOI: 10.1080/02701367.2013.875446

Routledge
Taylor & Francis Group

SPECIAL TOPICS: Top 10 Research Questions

Top 10 Research Questions Related to Body Composition

Scott Going, Vinson Lee, Rob Blew, Deepika Laddu, and Megan Hetherington-Rauth
The University of Arizona

An understanding of body composition is crucial to understanding human health, disease, and function. Research in body composition has focused on the development of assessment methods, description of normal changes in body composition with growth and development and aging, and the changes that occur in body composition in response to challenges ranging from illness to planned interventions. Each focus is significant, and in a sense, they are interdependent, because technological advances allow more sophisticated questions to be addressed, which in turn drives the development of better methods. Significant advances have been made in each area, although perhaps surprisingly basic questions remain. For example, growth trajectories are often estimated from cross-sectional data, given the resources needed for long-term observational studies, and thus, longitudinal descriptive data are still needed. Along with advances in laboratory methods, development of field methods remains relevant for screening and clinical practice. Despite recognition of wide interindividual differences in intervention response, average outcomes continue to be emphasized. With technological advances, it is now possible to examine genetic along with nongenetic factors that underlie changes in body composition, and these techniques need to be applied in long-term, well-controlled trials. In this article, we review 10 key questions in related areas in which research is needed to continue to advance the field.

Keywords: adipose tissue, adults, bone, children, intervention response, methods, muscle, obesity, sarcopenia, standards

Nothing is more fundamental to understanding human health, disease, and function than our understanding of body composition. A person's composition reflects his or her net lifetime accumulation of nutrients and other substrates acquired from the environment and retained in the body. These components, ranging from elements to tissues and organs, are the building blocks that give mass and shape and confer function to all living things. Methods for body composition assessment allow scientists to quantify these components and describe how they change with age, growth, metabolic state, and acute and chronic illness. Clinicians rely on body composition measurements for diagnosis, predicting disease risk, and determining efficacy of therapies to improve clinical outcomes. Exercise physiologists, sports nutritionists, athletic trainers, and coaches rely on body composition measurements to assess fitness and follow adaptations to diet and exercise regimens. Epidemiologists and public health officials use body composition measures to assess the nutritional and health status of populations. Serial body composition measurements are a reliable indicator of nutritional recovery from uncomplicated malnutrition or illness as well as the response to dietary, exercise, pharmacological, or surgical

Correspondence should be addressed to Scott Going, Department of Nutritional Sciences, The University of Arizona, 1177 E. 4th St., Shantz 315A, Tucson, AZ 85721. E-mail: going@u.arizona.edu

interventions. Historically, body composition research has focused on the development of assessment methods, description of normal changes in body composition during life stages, and examination of changes in response to challenges ranging from illness to planned interventions. Many important advances have been made. Nevertheless, significant work remains to be accomplished in all of these areas of research. Based on our understanding of the literature, in the pages that follow, we endeavor to present the top 10 research questions in which research is needed to continue to advance the field.

TOP 10 RESEARCH QUESTIONS

1. What Are the Appropriate Reference Models of Body Composition?

There has long been interest in defining normal changes in body composition during growth, maturation, and senescence. Defining normal is vital to understanding abnormal, which is associated with disease. This proposition—defining normal—is challenging, given the large variation that occurs within and among healthy individuals and the difficulty separating age-related from disease-related changes in older persons. Most often, descriptions of normal age trajectories have been based on a composite built on data from multiple studies that are usually cross-sectional, employ different methods, and are not population-based. Few large-scale, population-based studies have been conducted to describe normal because of the cost and complexity of accurate body composition methods. Although some reference data have been developed using anthropometry, dual-energy X-ray absorptiometry (DXA), and bioelectric impedance measurements in large surveys like the National Health and Nutrition Examination Survey (NHANES) in the United States (Borrud et al., 2010; Kelly, Wilson, & Heymsfield, 2009; Kuczmarski et al., 2002), more longitudinal data are certainly needed.

By necessity, most human body composition assessment is based on indirect methods that rely on models derived from reference bodies to convert estimates of body properties or components to estimates of composition (Going, Hingle, & Farr, 2012). Application of these models (i.e., accuracy) depends on the validity of the underlying assumptions, with errors related to the "goodness of fit" of the reference body to the person being assessed. Application of densitometric methods, for example, whereby body density is converted to body composition, depends on knowing the composition and density of fat-free mass, which varies with age, maturation, and illness (Going, 2005). Significant work has been done in the last half of the last century to develop reference bodies and population-specific models and Equations (Going et al., 2012; Heymsfield, Lohman, Wang, & Going, 2005). Nevertheless, more work is needed, especially in "healthy" elderly and infants and most clinical populations, to develop models that are relevant in these groups. Less work is currently being done in this area, perhaps because underwater weighing, once considered the standard, has been replaced in many settings by DXA or air displacement plethysmography (ADP). All indirect methods, however, including DXA and ADP, depend on some sort of model, and thus, the idea that work on reference bodies is no longer needed is fallacious.

2. Which Field Methods Should Be Used for Body Composition Assessment?

Anthropometry and other low-cost portable methods are vital to body composition field research, large-scale surveys, and screening. Simple anthropometric measurements such as height, weight, and body mass index (BMI), as well as estimates of percent fat and lean mass from skinfolds or bioelectric impedance analysis (BIA) can be used to assess an individual's status against a standard, or relative to that person's "usual" over a specified period of time. These simple measures can contribute to fitness profiles and allow early detection of nutrient deficiencies or inadequate nutrient intakes so that nutritional status can be improved through an individualized nutrition plan before disease occurs. Reference data have been developed using anthropometry and BIA measurements obtained in NHANES (Janssen, Heymsfield, & Ross, 2002), and the anthropometric data have been used to describe age trajectories in the measured variables. With the advent of BIA, anthropometric approaches have "fallen out of favor" in part due to the training required for accurate measurements to be obtained. This development is unfortunate as simple measures like skinfold thickness provide direct estimates of subcutaneous adipose tissue that, unlike BIA, can be used to track regional changes in fatness. Many equations have been published for converting anthropometric measures to estimates of percent fat. Far less work has been done to test their utility in various group and cross-validation studies. A similar situation has developed with BIA with many published equations and far less work to test their generalizability. Research is also needed to develop alternative techniques for measuring regional as well as whole-body fatness outside the laboratory. Although there has been a proliferation of single-frequency BIA devices, the accuracy of many of these devices is limited.

Although single-frequency BIA is acceptable for estimating fatness in healthy individuals with an established gender-, age-, and race-appropriate equation, variability in hydration status and higher levels of adiposity increase error (Demura, Sato, & Kitabayashi, 2005; Neovius, Hemmingsson, Freyschuss, & Udden, 2006). Multifrequency bioelectrical impedance analysis (MFBIA),

although more expensive, may overcome the limitations of single-frequency BIA because MFBIA measures impedance over a range of frequencies and therefore has the potential to assess varied fluid distribution (Chumlea & Sun, 2005; Steijaert, Deurenberg, Van Gaal, & De Leeuw, 1997). Segmental MFBIA also has the potential to provide regional estimates of composition. Research in healthy adults is promising (Anderson, Erceg, & Schroeder, 2012; Demura, Sato, & Kitabayashi, 2004; Malavolti et al., 2003; Shafer, Siders, Johnson, & Lukaski, 2009), and there is some evidence suggesting that when an eight-electrode, segmental MFBIA is used in healthy euvolemic adults, population-specific equations may not be needed (Bosy-Westphal et al., 2013). More research in different healthy and clinical populations including obese persons is needed to cross-validate existing equations and to develop population-specific equations as needed (Shafer et al., 2009).

The portability and speed of body composition assessment with ultrasound have contributed to its emergence as an attractive field technique. Although studies have shown it to be accurate for measuring tissue thicknesses, with good agreement (standard error of estimate of 1.9%–3.0% for percent fat; Leahy, Toomey, McCreesh, O'Neill, & Jakeman, 2012) with laboratory techniques (Bullen, Quaade, Olessen, & Lund, 1965; Hawes, Albert, Healy, & Garrow, 1972; Muller et al., 2013; Pineau, Filliard, & Bocquet, 2009; Pineau, Guihard-Costa, & Bocquet, 2007; Stolk et al., 2001; Toomey, McCreesh, Leahy, & Jakeman, 2011; Wagner, 2013; Wang, Thornton, Kolesnik, & Pierson, 2000; Weiss & Clark, 1985), the United States has been limited by lack of uniform guidelines, and the results are dependent on technician skill and the force applied to the transducer (Wagner, 2013).

Recent work to develop a novel high-resolution brightness-mode ultrasound field technique has shown promising results in athletes and would potentially be of great value in clinical situations as well (Muller et al., 2013; Müller & Maughan, 2013). Improved field methods for body composition assessment in athletes are needed. Extremely low weight, rapid weight loss, and associated changes in body composition (and associated eating disorders) are important concerns in many sports. The ultrasound method could help overcome the measurement uncertainty due to compressibility and viscoelasticity of adipose tissue, a drawback of skinfold caliper measurements. The ultrasound method also allows determination of the amount of fibrous structures embedded in subcutaneous adipose tissue (SAT) and enables fat patterning analysis. Ultrasound has promise for determining total SAT and total body fat. Given its accuracy for measurements of uncompressed SAT, ultrasound may provide more accurate estimates of total body fat than other field methods. However, appropriate protocols and equations for ultrasound-based populations have not been developed and the predictive value of ultrasound must be determined using multicomponent body composition models.

3. How Should Health-Related Obesity Standards Be Determined and Improved?

Obesity and its attendant comorbidities may be our most important public health challenge. The crisis has reinvigorated efforts on all fronts to understand the epidemiology and etiology of obesity and develop efficacious strategies for prevention and treatment. It is surprising then that accepted definitions of obesity based on measures of total body fatness are not available. At all ages, the most common approach has been to use BMI, defined as the ratio of weight to height squared. In children and youth, to account for differences in lean and adipose-tissue trajectories during growth, age- and gender-specific percentiles are used to define overweight and obesity, whereas in adults, absolute levels are used (Kuczmarski et al., 2002).

Although childhood obesity defined by BMI thresholds is predictive of adult obesity (Guo, Wu, Chumlea, & Roche, 2002; Laurson, Eisenmann, & Welk, 2011), a growing body of research has highlighted the shortcomings of BMI as a predictor of disease risk. As many as 24% of adults with normal BMI may be "metabolically unhealthy," whereas about half of overweight individuals are "metabolically normal" (Wildman et al., 2008). The failure of BMI to adequately capture differences in muscle, bone, and body fat at a given weight for height along with its failure to reflect variations in distributions of visceral and subcutaneous fat (Krakauer & Krakauer, 2012) explains many of these results. Moreover, variation in the age-, gender-, and race/ethnicity-related BMI–body fat relationship also limits the use of BMI for disease risk assessment in different populations (Deurenberg, Deurenberg-Yap, & Guricci, 2002; Going et al., 2011) and may result in misdiagnosis of metabolic comorbidities if the same standard is applied to all groups. The limitations of BMI underscore the need for obesity standards based on direct measures of body fat. In adults, percent-body fat standards have been published and are derived from the regression of BMI on percent fat (Gallagher et al., 2000). This "correlative approach" remains confounded by the limitations of BMI. An alternative approach is to determine cutpoints of percent fat, which predict elevated disease risk based on an appropriate health-related criterion—for example, against cardiometabolic disease risk factors (Gallagher et al., 2000; Going et al., 2011). This approach has been recently used to derive percent-fat cutpoints for risk for metabolic syndrome in U.S. youth (Laurson et al., 2011; Zhu, Wang, Shen, Heymsfield, & Heshka, 2003). These cutpoints are potentially useful as obesity standards, although more work is needed to validate them in other populations and in children. Similar work needs to be done in adults. Differences in the methods, samples, and criteria used to

define cutpoints have contributed to discrepancies in estimates of cutpoints (Laurson et al., 2011; Neovius & Rasmussen, 2008; Taylor, Jones, Williams, & Goulding, 2002; Zhu et al., 2003). Also, current definitions do not account for fat pattern, and fat pattern independent of levels of body fatness is more directly related to cardiometabolic risk. In addition, race/ethnicity-related variation in the relationship between adiposity and metabolic dysfunction may require the development of ethnicity-specific cutoffs or the use of different assessment indexes to predict future metabolic risk. Ultimately, longitudinal data are needed to determine how well cutpoints actually predict future disease.

4. What Is the Health- and Function-Related Standard for Muscle Mass?

Excessive muscle loss with aging, now commonly called sarcopenia (Rosenberg, 2011; Roubenoff, Heymsfield, Kehayias, Cannon, & Rosenberg, 1997), is a leading cause of frailty and disability in the elderly, with direct health care costs estimated at more than $18 billion in the United States annually (Fielding et al., 2011; Janssen, Shepard, Katzmarzyk, & Roubenoff, 2004). Although its consequences and impact are now well recognized, the lack of an objective definition of sarcopenia has limited research and diagnosis (Fielding et al., 2011). Baumgartner et al. (1998) were perhaps the first to put forth a quantitative definition using appendicular muscle mass measured by DXA divided by the square of height to derive a "relative skeletal muscle" index (RSMI). These authors defined sarcopenia as an RSMI of more than 2 standard deviations below the average from a young-adult reference group. Lauretani et al. (2003) proposed an alternative definition based on the recognition that muscle strength and function do not decline linearly with the loss of skeletal muscle mass. These authors defined sarcopenia as hand-grip strength 2 standard deviations below an adult mean and a walking speed measured at less than 0.8 m per second. Using an approach similar to Baumgartner et al.'s study, Janssen et al. (2002) used BIA data from a national survey to develop a skeletal muscle index (SMI) and determine risk for physical disability related to muscle loss defined by SMI. In this work, SMI was defined as absolute muscle mass normalized for height (muscle mass [kg]/[height in m]^2). Although these early studies elucidated the *bidimensional* character of sarcopenia, they failed to provide an accepted definition that can be used in research and by clinicians to diagnose sarcopenia in older populations.

Recently, the International Working Group on Sarcopenia (Cooper et al., 2013; Fielding et al., 2011) and the European Working Group on Sarcopenia in Older People (Cooper et al., 2013; Cruz-Jentoft et al., 2010) released independent consensus definitions for sarcopenia. Although both groups agree the definition should be based on loss of muscle mass and loss of muscle function, their definitions of "low muscle mass" and "low muscle function" differ. Other groups have also published consensus definitions of sarcopenia, including European Society for Clinical Nutrition and Metabolism special interest groups and the Society of Sarcopenia, Cachexia and Wasting Disorders (Cooper et al., 2013). Although these definitions are similar to the others, differences in definitions of "low muscle mass" and "low muscle function" remain to be resolved.

Although muscle loss and sarcopenia are not typically associated with childhood and adolescence when muscle mass is increasing, there are clinical populations (e.g., muscular dystrophy) in whom muscle loss is a critical issue. Reduced muscle mass in these groups and perhaps even in other (nonclinical) children may magnify the metabolic risks of obesity. Muscle mass is a major site of glucose disposal, and studies have shown muscle mass and strength are inversely related with insulin resistance, dysglycemia, and metabolic syndrome in adults (Atlantis et al., 2009; Srikanthan, Hevener, & Karlamangla, 2010; Srikanthan & Karlamangla, 2011). Muscle mass and strength are also strong predictors of bone mineral mass, density, and bone strength, and low muscle mass and strength are risk factors for impaired bone development. Research is needed to develop a definition of low muscle mass in children and youth that could be used in research and clinically in the prediction and treatment of disease.

5. What Is the Relationship Between Fat Distribution and the Health Risks of Obesity?

Excess adiposity rather than excess weight per se increases risk for metabolic comorbidities. Additional risk is explained by variation in fat distribution as some fat depots are more pathogenic than others (Despres, 2006). Abdominal visceral adiposity (VAT) and intramyocellular fat, in particular, are associated with increased release of cytokines and low-grade inflammation, making measurements of these fat depots critical for the early detection of metabolic health risks, even among normal-weight individuals (Ahima & Lazar, 2013; Despres, 2006). Other so-called "ectopic" fat depots—for example, pericardial and perirenal fat—confer risk but are less commonly studied. In contrast, appendicular adiposity is associated with higher amounts of subcutaneous fat, normal insulin sensitivity, and less risk for cardiovascular disease and type 2 diabetes (Wildman et al., 2008), which is related to the lower rate of lipolysis in the subcutaneous adipose tissue in the femoral/gluteal and abdominal regions compared with VAT. On the basis of these regional differences in the regulation of lipolysis (Van Pelt, Evans, Schechtman, Ehsani, & Kohrt, 2002), which contributes to differences in the cytokine profile (O'Connell et al., 2010; Wajchenberg, 2000), it is possible that increased subcutaneous fat may confer protective effects against metabolic dysfunction, although more work

is needed to clarify this possibility. Similarly, although there is little debate that cardiometabolic risk is strongly influenced by fat distribution, more work is needed to understand how the relationships are modified by age, gender, race, and genetic profile. This is especially true in children and youth in whom far less research has been done compared with adults. The consequences of differences in fat distribution on bone development is an emerging area with some data suggesting that higher levels of VAT and skeletal muscle fat compromise bone mineral accrual and bone strength (Farr et al., 2011; Farr, Laddu, Blew, Lee, & Going, 2013; Pollock et al., 2010).

6. What Is the Body Composition Exercise-Dose Response?

Regular exercise has a significant albeit modest effect on body weight, with substantially greater effects on components of body composition depending on exercise mode, intensity, and energy expenditure (Williams, Teixeira, & Going, 2005). In sufficient amounts, exercise can lead to substantial decreases in body fat and visceral fat with concomitant improvement in cardiometabolic risk factors. Although evidence supports a dose–response relationship between exercise and these changes (Slentz et al., 2004; Slentz, Houmard, & Kraus, 2009)—that is, more exercise lends to additional benefits—further research is needed to develop targeted exercise prescriptions for specific outcomes. Surprisingly, few prospective controlled trials have been designed to test the benefits of different levels of exercise on various components of body composition, and this is particularly true in children and adolescents. Consequently, the dose–response information needed to formulate evidence-based public health recommendations for children is not available, although one recent study suggested dose–response benefits of aerobic training on general and VAT in previously sedentary overweight or obese children (Davis et al., 2012). The amount of exercise needed to prevent weight gain remains controversial, and the amount of exercise required to sustain significant weight loss may be difficult for most individuals to achieve (American College of Sports Medicine [ACSM], 1998; Ross & Bradshaw, 2009). Initial weight and composition influence results, as significant results are more often found in overweight and obese individuals. Often, exercise studies have been done in lean individuals, or if conducted with overweight/obese individuals, the exercise energy expenditure was small (Ross & Bradshaw, 2009). These limitations led to the notion that exercise resulted in only small changes in weight without an added diet intervention. However, in adults, several studies of exercise only compared with diet only have shown that weight loss is similar when the same degree of energy deficiency is achieved (Ross et al., 2000). Studies of this kind are needed in children and youth as exercise would be preferred over dietary restriction during growth. In adults, significant metabolic improvement occurs with modest or no weight loss, which has led to strong support for targeting healthy lifestyle, including exercise, rather than weight reduction *per se* for treating obesity and its comorbidities (Donnelly et al., 2013; Ekelund, Franks, Sharp, Brage & Wareham, 2007; Ross et al., 2000). Similar benefits are likely in children, although far less research has been done with young children and youth.

Perhaps the exercise dose–response relationship is best established for the response of skeletal muscle to progressive resistance exercise in adults (ACSM, 1998). Adolescents respond in much the same way as adults do, whereas the benefits of resistance exercise in children continue to be debated (Faigenbaum et al., 2009). Far less work has been done on the exercise-dose response for human skeletal outcomes. Significant work has been done in animal models to describe the mechanical loading characteristics (strain magnitude, repetitions, interval, and system saturation) that stimulate osteogenesis and mineral accrual, and these characteristics have been largely adapted to human exercise prescription without systematic investigation. Progressive resistance exercise has significant effects on bone mineral mass and density, especially in adults (ACSM, 1998). Recent work in children and youth suggests exercise that elicits significant ground reaction forces may promote structural adaptations that increase bone strength (MacKelvie, Khan, & McKay 2002). This proposition has not been tested in dose–response experimental designs.

7. Is Lifestyle Modification a Better Target Than Weight Loss for Improving Health?

Intentional weight loss in most adults is associated with a reduction in many of the health complications of obesity, and weight loss is recommended as a primary treatment for obesity reduction and its comorbidities. Typical weight loss goals range from 5% to 10% of body weight. Although attempts to lose weight are common, even modest weight loss has proved challenging for most individuals to maintain the focus on weight loss as the main outcome of exercise or dietary interventions fails to recognize the heterogeneous nature of obesity and that excess visceral fat explains much of the health risks of obesity (Despres, Lemieux, & Prud'homme, 2001). Growing evidence supports the proposition that adoption of a lifestyle characterized by greater levels of physical activity and a healthy diet can reduce visceral fat, waist circumference, and cardiometabolic risk factors with little or no weight loss (Janiszewski & Ross, 2007; Lee et al., 2005; Ross & Bradshaw, 2009). For example, in a recent review, Ross & Bradshaw (2009) showed a clear dissociation between weight loss and corresponding reductions in waist circumference and/or visceral fat across a number of randomized, controlled trials,

regardless of sex or age. A focus on average effects only, which were small, would be misleading, as there was considerable variation in individual response. Perhaps the most convincing results come from studies in which individuals with abdominal obesity exercised under supervision and were required to increase caloric intake to prevent exercise-induced weight loss (Ross et al., 2000, 2004). In these studies, lean and obese men and women experienced reduction in total fat, abdominal fat, and waist circumference in the absence of weight loss. In addition, improvements were observed in skeletal muscle mass and cardiorespiratory fitness. Whether an increase in fitness is necessary to achieve improvement in cardiometabolic risk factors deserves further research in youth and adults as some work has shown improvement independent of change in fitness (Ekelund et al., 2007). A better description of changes in skeletal and muscle mass is also warranted as these compartments are not often assessed. Weight loss is potentially deleterious for the skeleton, and thus, promotion of healthy lifestyle rather than weight loss presumably has skeletal benefits. A better understanding of the factors underlying the individual response is crucial to targeted interventions, as is more knowledge concerning the amount of exercise to achieve the desired results. Although there is some evidence of a dose response (Slentz et al., 2009), there are limited data on this question, particularly in youth.

8. What Is the Role of Different Types of Adipose Tissue in Obesity Prevention and Metabolic Health?

Recent work with sophisticated imaging techniques has shown that adults possess brown adipose tissue (BAT) at sites (e.g., thyroid/tracheal, mediastinal, paracervical/supraclavicular, parathoracical, suprarenal and perirenal) where BAT is found in neonates (Ahmadi et al., 2013; Enerback, 2010). This finding has broadened research on the relationship (and associated mechanisms) of fat distribution with metabolic health (Bartelt & Heeren, 2013). Extensive research on animals has shown that BAT, the primary organ for heat production through nonshivering thermogenesis, has beneficial effects on adiposity, insulin resistance, and hyperlipidemia (Nedergaard & Cannon, 2010). Recent work suggests a positive effect on bone as well (Rahman et al., 2013). Findings of low BAT in obese patients and patients with diabetes have stimulated interest in BAT as a therapeutic target—for example, by enhancing recruitment and retarding involution. Beige adipocytes (also called inducible brown or brown in white), another type of adipocyte, are found in brown and white adipose tissue (WAT). Accumulation of beige adipocytes in WAT is referred to as the "browning" of WAT. The idea of using beige adipocytes and the browning of WAT therapeutically has gained attention as the amount of BAT is usually quite low. Beige adipocytes are generated by de-novo recruitment of progenitor cells and transdifferentiation from white adipocytes—independent and reversible processes that are stimulated by cold and exercise (Bartelt & Heeren, 2013). The question of whether induction of browning is an avenue for obesity prevention and treating metabolic disorders in humans is an emerging area of significant research effort.

9. What Are the Inter-Relationships ("Crosstalk") Among Muscle, Bone, and Adipose Tissue?

Muscle, bone, and adipose tissue are interdependent and inter-regulatory. Despite the growing body of work describing the factors that mediate crosstalk between the cells of the different tissues, significant research is left to be done. The effect of excess adiposity on bone, for example, has emerged as an important area of research driven by the need to understand all the health ramifications of the obesity epidemic. In children and youth, it is unclear whether excess fat augments or impairs bone during development as some evidence suggests excess adiposity impairs bone development (Goulding et al., 2000; Manias, McCabe, & Bishop, 2006), while other evidence suggests adiposity is protective of the skeleton (Sayers & Tobias, 2010). In adults, a positive fat–bone relationship has been widely accepted, with proponents claiming that adiposity protects bone against fracture risk by mechanisms of increased mechanical stress on bone and positive metabolic effects on mineral accrual by hormones secreted by adipocytes (Petit et al., 2008; Zhao et al., 2008). More recently, this traditional paradigm of an "osteoprotective" effect of fat on bone has been challenged by evidence suggesting a higher incidence of fracture in children (Goulding, Grant, & Williams, 2005; Goulding, Jones, Taylor, Piggot, & Taylor, 2003; Goulding et al., 2000) and adults with higher adiposity (Di Monaco, Vallero, Di Monaco, Tappero, & Cavanna, 2007; Hsu et al., 2006) and lower muscle strength (Fielding et al., 2011; Nguyen, Pongchaiyakul, Center, Eisman, & Nguyen, 2005). Adults with high muscle fat content also have higher marrow fat content (Pluijm et al., 2001), which has been linked to a weaker skeleton (Kuk, Saunders, Davidson, & Ross, 2009). The interaction between obesity and bone metabolism originates in the bone marrow microenvironment. Adipocytes and osteoblasts develop from a common progenitor, mesenchymal stromal cells, which have an equal propensity to differentiate into adipocytes through the adipogenic pathway, which is associated with suppression of myogenesis and osteogenesis, or the osteogenic pathway, which promotes osteoblast differentiation while also inhibiting adipogenic differentiation (Zhao et al., 2008). The balance of this differentiation is predominately regulated by localized release of cytokines (i.e., TGF-α) and hormones (e.g., leptin and estrogen) related to osteogenesis and adipogenesis (Cao, 2011; Zhao et al., 2008). Although the activity and nature of the adipocytokines depends on the location and the type of fat depot (i.e., visceral, skeletal muscle fat vs. subcutaneous fat masses), further research is

needed to understand whether the activity of the cytokines has only localized or systemic effects on the skeleton.

In contrast to the relationship between adipose tissue and bone, the positive effects of muscle on bone are better understood. In particular, the structural and material properties that underlie bone quality and bone strength underscore the prevailing notion of a tight, functional relationship between muscle and bone. The relationship requires a continuous balance between bone strength and the mechanical forces that challenge bone stability (Schoenau, Neu, Beck, Manz, & Rauch, 2002). Greater muscle strength, or the muscle force, on bone directly influences acquisition of bone strength during growth and helps to preserve bone strength and quality later in life (Ashby, Adams, Roberts, Mughal, & Ward, 2011; Schoenau et al., 2002). A central component of bone remodeling is the adaptive feedback loop that exists between bone tissue strain (deformation) and bone strength. A combination of factors, including bone marrow mediators and signaling molecules, link the muscle–bone unit, while nonmechanical mediators, such as hormones, nutrition, behavior, and environment, modulate the modeling and remodeling threshold by determining when and where adaptive bone strength is needed so that varying peak loads that can be tolerated. Thus, the adaptive gains in bone strength are secondary to gains in muscle mass and muscle strength (Rauch, Bailey, Baxter-Jones, Mirwald, & Faulkner, 2004), and declines in muscle mass and strength, associated with physical inactivity and aging, may result in decreased mobility, impaired physical function, and deteriorating bone quality (Lang et al., 2010; Yerges-Armstrong et al., 2010). Future studies that investigate whether the osteogenic influences of muscle are enhanced or hindered by the additional mechanical loading of adipose tissue on bone will provide insight regarding the effects of soft tissue on bone and the crosstalk that occurs between muscle, fat, and bone.

10. What Factors Best Explain Individual Response to Interventions?

Wide interindividual variation in response is a hallmark of intervention studies (Going et al., 2012), regardless of the intervention or component of body composition that is studied. For example, in an investigation of aerobic exercise (400 kcal/session or 600 kcal/session with a constant diet) for weight loss, average weight loss was 4% to 6% depending on the exercise energy cost, while the individual response ranged from 1% to 4% weight gain to 15% to 20% weight loss (Donnelly et al., 2013). Similar ranges of individual responses have been seen in studies with muscle and bone outcomes (Going et al., 2003). Although intervention adherence explains some of the variation, even when all members of the exercise group are exposed to the same volume of exercise, significant individual differences remain. Clearly, multiple genetic and non-genetic factors contribute to the variation in response (Bouchard, 2012; Rankinen & Bouchard, 2012). These differences are greater than measurement error, are not random, and are informative of the adaptive mechanisms involved. What is less clear is the exact nature of the mechanisms responsible for the heterogeneity in response. Human genetic differences appear at the level of sequence variation (single nucleotide polymorphisms), chromosomal structural variation (copy number variation, deletions, inversions, insertions, duplications), and epigenetic variation (DNA methylation, histone acetylation), and variation at these levels effects the change in body composition and other outcomes of diet and physical activity. Conversely, diet and physical activity can affect how these gene differences are regulated at the level of gene transcription, protein expression, and metabolism (Kussmann, Raymond, & Affolter, 2006).

Evidence for a strong genotype dependency of the ability to respond to regular exercise was described more than 30 years ago in a series of experimental studies with pairs of monozygotic twins (Bouchard, 2012). In these studies, there was consistently more variance in training responses between twin pairs than was observed within pairs. The heterogeneity in responsiveness to a standardized exercise program was also demonstrated in the HEalth, RIsk factors, exercise Training And GEnetics (HERITAGE) Family Study, which continues to be the most comprehensive study of individual differences in trainability, with data from 742 healthy sedentary participants who undertook endurance training for 20 weeks. The remarkable heterogeneity in response was characterized by a strong familial aggregation. In HERITAGE, the association of the fat mass obesity gene (FTO; Loos & Bouchard, 2008) with changes in body composition induced by exercise was studied. Homozygotes for the risk allele have a 1.67 times greater risk for obesity than do those that do not contain the allele. After 20 weeks of exercise, individuals with the FTO genotype lost 0.1% of their fat mass, while their counterparts without the FTO genotype lost 4% (Rankinen, Rice, Teran-Garcia, Rao, & Bouchard, 2010). Although there are many other genes and markers with evidence of an association and linkage to body composition, few have been tested in standardized controlled training studies, and more studies like HERITAGE based on larger sample sizes with uniform methodologies are needed to draw further conclusions on these associations and linkages (Rankinen & Bouchard, 2012).

Many past studies to identify genetic variants affecting training responsiveness were based on a candidate gene approach, with limited success (Rankinen & Bouchard, 2012). Technological advances have made it possible to conduct detailed genomewide screening of DNA sequence and gene transcripts abundance, which supports objective, unbiased association studies. Large observational genome-wide association studies are under way, and knowledge of gene–physical activity interactions will increase

significantly when the findings are reported. Progress with intervention studies, a much stronger approach to test for genotype–exercise interaction on the change in body composition, will be slower because of the much higher cost. These kinds of studies are needed, however, to fully understand the genetics and biology underlying changes in components of body composition with exercise, and to confirm gene–exercise interactions found in observational studies. This information is needed if we are to improve upon current exercise recommendations with the formulation of targeted and personalized exercise prescriptions.

In summary, significant technological advances have made it possible to study complex issues such as how various tissues "communicate" and counter-regulate in response to various challenges and what the factors (genetic as well as nongenetic) are that underlie the responses. Although much has been learned through the application of these techniques, there is still significant work to be done before we can predict who will respond and the magnitude of response, with the goal of providing personalized interventions. In addition, there continues to be a need to develop simple methods that can be used for field research, in large-scale surveys, and for risk assessment in clinical practice, and longitudinal data are needed to refine trajectories of change in body composition during different life stages and to better understand the long-term effects of interventions. Work is needed in all key questions outlined in this article to continue to move body composition research ahead.

REFERENCES

Ahima, R. S., & Lazar, M. A. (2013). Physiology. The health risk of obesity—better metrics imperative. *Science*, *341*, 856–858.

Ahmadi, N., Hajsadeghi, F., Conneely, M., Mingos, M., Arora, R., Budoff, M., & Ebrahimi, R. (2013). Accurate detection of metabolically active "brown" and "white" adipose tissues with computed tomography. *Academic Radiology*, *20*, 1443–1447.

American College of Sports Medicine. (1998). ACSM position stand on exercise and physical activity for older adults. *Medicine and Science in Sports and Exercise*, *30*, 992–1008.

Anderson, L. J., Erceg, D. N., & Schroeder, E. T. (2012). Utility of multifrequency bioelectrical impedance compared with dual-energy x-ray absorptiometry for assessment of total and regional body composition varies between men and women. *Nutritional Research*, *32*, 479–485.

Ashby, R. L., Adams, J. E., Roberts, S. A., Mughal, M. Z., & Ward, K. A. (2011). The muscle-bone unit of peripheral and central skeletal sites in children and young adults. *Osteoporosis International*, *22*, 121–132.

Atlantis, E., Martin, S. A., Haren, M. T., Taylor, A. W., Wittert, G. A., & Members of the Florey Adelaide Male Ageing Study. (2009). Inverse associations between muscle mass, strength, and the metabolic syndrome. *Metabolism: Clinical and Experimental*, *58*, 1013–1022.

Bartelt, A., & Heeren, J. (2013). Adipose tissue browning and metabolic health. *Nature Reviews Endocrinology*, Advance online publication. doi:10.1038/nrendo.2013.204

Baumgartner, R. N., Koehler, K. M., Gallagher, D., Romero, L., Heymsfield, S. B., Ross, R. R., … Lindeman, R. D. (1998). Epidemiology of sarcopenia among the elderly in New Mexico. *American Journal of Epidemiology*, *147*, 755–763.

Borrud, L. G., Flegal, K. M., Looker, A. C., Everhart, J. E., Harris, T. B., & Shepherd, J. A. (2010). Body composition data for individuals 8 years of age and older: U.S. population, 1999–2004. *Vital and Health Statistics*, *11*, 250.

Bosy-Westphal, A., Schautz, B., Later, W., Kehayias, J. J., Gallagher, D., & Muller, M. J. (2013). What makes a BIA equation unique? Validity of eight-electrode multifrequency BIA to estimate body composition in a healthy adult population. *European Journal of Clinical Nutrition*, *67* (Suppl. 1), S14–S21.

Bouchard, C. (2012). Genomic predictors of trainability. *Experimental Physiology*, *97*, 347–352.

Bullen, B. A., Quaade, F., Olessen, E., & Lund, S. A. (1965). Ultrasonic reflections used for measuring subcutaneous fat in humans. *Human Biology*, *37*, 375–384.

Cao, J. J. (2011). Effects of obesity on bone metabolism. *Journal of Orthopaedic Surgery and Research*, *6*, 30. doi:10.1186/1749-799X-6-30

Chumlea, W. C., & Sun, S. S. (2005). Bioelectrical impedance analysis. In S. B. Heymsfield, T. G. Lohman, Z. Wang, & S. B. Going (Eds.), *Human body composition* (2nd ed., pp. 79–88). Champaign, IL: Human Kinetics.

Cooper, C., Fielding, R., Visser, M., van Loon, L. J., Rolland, Y., Orwoll, E., … Kanis, J. A. (2013). Tools in the assessment of sarcopenia. *Calcified Tissue International*, *93*, 201–210.

Cruz-Jentoft, A. J., Baeyens, J. P., Bauer, J. M., Boirie, Y., Cederholm, T., Landi, F., … European Working Group on Sarcopenia in Older People. (2010). Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. *Age and Ageing*, *39*, 412–423.

Davis, C. L., Pollock, N. K., Waller, J. L., Allison, J. D., Dennis, B. A., Bassali, R., … Gower, B. A. (2012). Exercise dose and diabetes risk in overweight and obese children: A randomized controlled trial. *Journal of the American Medical Association*, *308*, 1103–1112.

Demura, S., Sato, S., & Kitabayashi, T. (2004). Percentage of total body fat as estimated by three automatic bioelectrical impedance analyzers. *Journal of Physiological Anthropology and Applied Human Science*, *23*, 93–99.

Demura, S., Sato, S., & Kitabayashi, T. (2005). Estimation accuracy of percent total body fat and percent segmental fat measured by single-frequency bioelectrical impedance analysis with 8 electrodes: The effect of difference in adiposity. *Journal of Sports Medicine and Physical Fitness*, *45*, 68–76.

Despres, J. (2006). Is visceral obesity the cause of the metabolic syndrome? *Annals of Medicine*, *38*, 52–63.

Despres, J. P., Lemieux, I., & Prud'homme, D. (2001). Treatment of obesity: Need to focus on high risk abdominally obese patients. *British Medical Journal*, *322*, 716–720.

Deurenberg, P., Deurenberg-Yap, M., & Guricci, S. (2002). Asians are different from Caucasians and from each other in their body mass index/body fat per cent relationship. *Obesity Reviews*, *3*, 141–146.

Di Monaco, M., Vallero, F., Di Monaco, R., Tappero, R., & Cavanna, A. (2007). Fat mass and skeletal muscle mass in hip-fracture women: A cross-sectional study. *Maturitas*, *56*, 404–410.

Donnelly, J. E., Honas, J. J., Smith, B. K., Mayo, M. S., Gibson, C. A., Sullivan, D. K., … Washburn, R. A. (2013). Aerobic exercise alone results in clinically significant weight loss for men and women: Midwest Exercise Trial 2. *Obesity*, *21*, 219–228.

Ekelund, U., Franks, P. W., Sharp, S., Brage, S., & Wareham, N. J. (2007). Increase in physical activity energy expenditure is associated with reduced metabolic risk independent of change in fatness and fitness. *Diabetes Care*, *30*, 2101–2106.

Enerback, S. (2010). Human brown adipose tissue. *Cell Metabolism*, *11*, 248–252.

Faigenbaum, A. D., Kraemer, W. J., Blimkie, C. J., Jeffreys, I., Micheli, L. J., Nitka, M., & Rowland, T. W. (2009). Youth resistance training: Updated position statement paper from the National Strength and

Conditioning Association. *Journal of Strength Conditioning and Research*, *23*(Suppl. 5), S60–S79.

Farr, J. N., Funk, J. L., Chen, Z., Lisse, J. R., Blew, R. M., Lee, V. R., … Going, S. B. (2011). Skeletal muscle fat content is inversely associated with bone strength in young girls. *Journal of Bone and Mineral Research*, *26*, 2217–2225.

Farr, J. N., Laddu, D., Blew, R. M., Lee, V. R., & Going, S. B. (2013). Effects of physical activity and muscle quality on bone development in girls. *Medicine and Science in Sports and Exercise*, *45*, 2332–2340.

Fielding, R. A., Vellas, B., Evans, W. J., Bhasin, S., Morley, J. E., Newman, A. B., … Zamboni, M. (2011). Sarcopenia: An undiagnosed condition in older adults. Current consensus definition: Prevalence, etiology, and consequences. International Working Group on Sarcopenia. *Journal of the American Medical Directors Association*, *12*, 249–256.

Gallagher, D., Heymsfield, S. B., Heo, M., Jebb, S. A., Murgatroyd, P. R., & Sakamoto, Y. (2000). Healthy percentage body fat ranges: An approach for developing guidelines based on body mass index. *American Journal of Clinical Nutrition*, *72*, 694–701.

Going, S. B. (2005). Hydrodensitometry and air displacement plethysmography. In S. B. Heymsfield, T. G. Lohman, Z. M. Wang, & S. B. Going (Eds.), *Human body composition* (2nd ed., pp. 17–33). Champaign, IL: Human Kinetics.

Going, S., Hingle, M., & Farr, J. (2012). Body composition. In B. C. A. C. Ross, R. J. Cousins, K. L. Tucker, & T. R. Ziegler (Eds.), *Modern nutrition in health and disease* (11th ed., pp. 635–648). Baltimore, MD: Lippincott, Williams & Wilkins.

Going, S. B., Lohman, T. G., Cussler, E. C., Williams, D. P., Morrison, J. A., & Horn, P. S. (2011). Percent body fat and chronic disease risk factors in U.S. children and youth. *American Journal of Preventive Medicine*, *41*(Suppl. 2), S77–S86.

Going, S., Lohman, T., Houtkooper, L., Metcalfe, L., Flint-Wagner, H., Blew, R., … Weber, J. (2003). Effects of exercise on bone mineral density in calcium-supplemented postmenopausal women with and without hormone replacement therapy. *Osteoporosis International*, *14*, 637–644.

Goulding, A., Grant, A. M., & Williams, S. M. (2005). Bone and body composition of children and adolescents with repeated forearm fractures. *Journal of Bone and Mineral Research*, *20*, 2090–2096.

Goulding, A., Jones, I. E., Taylor, R. W., Piggot, J. M., & Taylor, D. (2003). Dynamic and static tests of balance and postural sway in boys: Effects of previous wrist bone fractures and high adiposity. *Gait and Posture*, *17*, 136–141.

Goulding, A., Taylor, R. W., Jones, I. E., McAuley, K. A., Manning, P. J., & Williams, S. M. (2000). Overweight and obese children have low bone mass and area for their weight. *International Journal of Obesity and Related Metabolic Disorders*, *24*, 627–632.

Guo, S. S., Wu, W., Chumlea, W. C., & Roche, A. F. (2002). Predicting overweight and obesity in adulthood from body mass index values in childhood and adolescence. *American Journal of Clinical Nutrition*, *76*, 653–658.

Hawes, S. F., Albert, A., Healy, J. R., & Garrow, J. S. (1972). A comparison of soft-tissue radiography, reflected ultrasound, skinfold calipers, and thigh circumference for estimating the thickness of fat overlying the iliac crest and greater trochanter. *Proceedings of the Nutrition Society*, *31*(3), 91A–92A.

Heymsfield, S., Lohman, T. G., Wang, Z. M., & Going, S. B. (Eds.). (2005). *Human body composition: Methods and findings* (2nd ed.). Champaign, IL: Human Kinetics.

Hsu, Y. H., Venners, S. A., Terwedow, H. A., Feng, Y., Niu, T., Li, Z., … Xu, X. (2006). Relation of body composition, fat mass, and serum lipids to osteoporotic fractures and bone mineral density in Chinese men and women. *American Journal of Clinical Nutrition*, *83*, 146–154.

Janiszewski, P. M., & Ross, R. (2007). Physical activity in the treatment of obesity: Beyond body weight reduction. *Applied Physiology, Nutrition, and Metabolism*, *32*, 512–522.

Janssen, I., Heymsfield, S. B., & Ross, R. (2002). Low relative skeletal muscle mass (sarcopenia) in older persons is associated with functional impairment and physical disability. *Journal of the American Geriatrics Society*, *50*, 889–896.

Janssen, I., Shepard, D. S., Katzmarzyk, P. T., & Roubenoff, R. (2004). The healthcare costs of sarcopenia in the United States. *Journal of the American Geriatrics Society*, *52*, 80–85.

Kelly, T. L., Wilson, K. E., & Heymsfield, S. B. (2009). Dual energy X-Ray absorptiometry body composition reference values from NHANES. *PLoS ONE*, *4*, e7038.

Krakauer, N. Y., & Krakauer, J. C. (2012). A new body shape index predicts mortality hazard independently of body mass index. *PLoS ONE*, *7*, e39504.

Kuczmarski, R. J., Ogden, C. L., Guo, S. S., Grummer-Strawn, L. M., Flegal, K. M., Mei, Z., … Johnson, C. L. (2002). 2000 CDC growth charts for the United States: Methods and development. *Vital and Health Statistics*, *11*, 246.

Kuk, J. L., Saunders, T. J., Davidson, L. E., & Ross, R. (2009). Age-related changes in total and regional fat distribution. *Ageing Research Reviews*, *8*, 339–348.

Kussmann, M., Raymond, F., & Affolter, M. (2006). OMICS-driven biomarker discovery in nutrition and health. *Journal of Biotechnology*, *124*, 758–787.

Lang, T., Cauley, J. A., Tylavsky, F., Bauer, D., Cummings, S., & Harris, T. B. (2010). Computed tomographic measurements of thigh muscle cross-sectional area and attenuation coefficient predict hip fracture: The Health, Aging, and Body Composition Study. *Journal of Bone and Mineral Research*, *25*, 513–519.

Lauretani, F., Russo, C. R., Bandinelli, S., Bartali, B., Cavazzini, C., Di Iorio, A., … Ferrucci, L. (2003). Age-associated changes in skeletal muscles and their effect on mobility: An operational diagnosis of sarcopenia. *Journal of Applied Physiology*, *95*, 1851–1860.

Laurson, K., Eisenmann, J., & Welk, G. (2011). Development of youth percent body fat standards using receiver operating characteristic curves. *American Journal of Preventive Medicine*, *41*(Suppl. 2), S93–S99.

Leahy, S., Toomey, C., McCreesh, K., O'Neill, C., & Jakeman, P. (2012). Ultrasound measurement of subcutaneous adipose tissue thickness accurately predicts total and segmental body fat of young adults. *Ultrasound in Medicine & Biology*, *38*, 28–34.

Lee, S., Kuk, J. L., Davidson, L. E., Hudson, R., Kilpatrick, K., Graham, T. E., & Ross, R. (2005). Exercise without weight loss is an effective strategy for obesity reduction in obese individuals with and without Type 2 diabetes. *Journal of Applied Physiology*, *99*, 1220–1225.

Loos, R. J., & Bouchard, C. (2008). FTO: The first gene contributing to common forms of human obesity. *Obesity Reviews*, *9*, 246–250.

MacKelvie, K. J., Khan, K. M., & McKay, H. A. (2002). Is there a critical period for bone response to weight-bearing exercise in children and adolescents? *A systematic review. British Journal of Sports Medicine*, *36*, 250–257.

Malavolti, M., Mussi, C., Poli, M., Fantuzzi, A. L., Salvioli, G., Battistini, N., & Bedogni, G. (2003). Cross-calibration of eight-polar bioelectrical impedance analysis versus dual-energy X-ray absorptiometry for the assessment of total and appendicular body composition in healthy subjects aged 21–82 years. *Annals of Human Biology*, *30*, 380–391.

Manias, K., McCabe, D., & Bishop, N. (2006). Fractures and recurrent fractures in children; varying effects of environmental factors as well as bone size and mass. *Bone*, *39*, 652–657.

Muller, W., Horn, M., Furhapter-Rieger, A., Kainz, P., Kropfl, J. M., Ackland, T. R., … Ahammer, H. (2013). Body composition in sport: Interobserver reliability of a novel ultrasound measure of subcutaneous fat tissue. *British Journal of Sports Medicine*, *47*, 1036–1043.

Müller, W., & Maughan, R. J. (2013). The need for a novel approach to measure body composition: Is ultrasound an answer? *British Journal of Sports Medicine*, *47*, 1001–1002.

Nedergaard, J., & Cannon, B. (2010). The changed metabolic world with human brown adipose tissue: Therapeutic visions. *Cell Metabolism*, *11*, 268–272.

Neovius, M., Hemmingsson, E., Freyschuss, B., & Udden, J. (2006). Bioelectrical impedance underestimates total and truncal fatness in abdominally obese women. *Obesity*, *14*, 1731–1738.

Neovius, M., & Rasmussen, F. (2008). Evaluation of BMI-based classification of adolescent overweight and obesity: Choice of percentage body fat cut-offs exerts a large influence. The COMPASS study. *European Journal of Clinical Nutrition*, *62*, 1201–1207.

Nguyen, N. D., Pongchaiyakul, C., Center, J. R., Eisman, J. A., & Nguyen, T. V. (2005). Abdominal fat and hip fracture risk in the elderly: The Dubbo Osteoporosis Epidemiology Study. *BMC Musculoskeletal Disorders*, *6*, 11. doi:10.1186/1471-2474-6-11

O'Connell, J., Lynch, L., Cawood, T. J., Kwasnik, A., Nolan, N., Geoghegan, J., … O'Shea, D. (2010). The relationship of omental and subcutaneous adipocyte size to metabolic disease in severe obesity. *PLoS ONE*, *5*, e9997.

Petit, M. A., Beck, T. J., Hughes, J. M., Lin, H. M., Bentley, C., & Lloyd, T. (2008). Proximal femur mechanical adaptation to weight gain in late adolescence: A six-year longitudinal study. *Journal of Bone and Mineral Research*, *23*, 180–188.

Pineau, J. C., Filliard, J. R., & Bocquet, M. (2009). Ultrasound techniques applied to body fat measurement in male and female athletes. *Journal of Athletic Training*, *44*, 142–147.

Pineau, J. C., Guihard-Costa, A. M., & Bocquet, M. (2007). Validation of ultrasound techniques applied to body fat measurement. A comparison between ultrasound techniques, air displacement plethysmography and bioelectrical impedance vs. dual-energy X-ray absorptiometry. *Annals of Nutrition and Metabolism*, *51*, 421–427.

Pluijm, S. M., Visser, M., Smit, J. H., Popp-Snijders, C., Roos, J. C., & Lips, P. (2001). Determinants of bone mineral density in older men and women: Body composition as mediator. *Journal of Bone and Mineral Research*, *16*, 2142–2151.

Pollock, N. K., Bernard, P. J., Wenger, K., Misra, S., Gower, B. A., Allison, J. D., & … Davis, C. L. (2010). Lower bone mass in prepubertal overweight children with prediabetes. *Journal of Bone and Mineral Research*, *25*, 2760–2769.

Rahman, S., Lu, Y., Czernik, P. J., Rosen, C. J., Enerback, S., & Lecka-Czernik, B. (2013). Inducible brown adipose tissue, or beige fat, is anabolic for the skeleton. *Endocrinology*, *154*, 2687–2701.

Rankinen, T., & Bouchard, C. (2012). Gene-exercise interactions. *Progress in Molecular Biology and Translational Science*, *108*, 447–460.

Rankinen, T., Rice, T., Teran-Garcia, M., Rao, D. C., & Bouchard, C. (2010). FTO genotype is associated with exercise training-induced changes in body composition. *Obesity*, *18*, 322–326.

Rauch, F., Bailey, D. A., Baxter-Jones, A., Mirwald, R., & Faulkner, R. (2004). The 'muscle-bone unit' during the pubertal growth spurt. *Bone*, *34*, 771–775.

Rosenberg, I. H. (2011). Sarcopenia: Origins and clinical relevance. *Clinics in Geriatric Medicine*, *27*, 337–339.

Ross, R., & Bradshaw, A. J. (2009). The future of obesity reduction: Beyond weight loss. *Nature Reviews Endocrinology*, *5*, 319–325.

Ross, R., Dagnone, D., Jones, P. J., Smith, H., Paddags, A., Hudson, R., & Janssen, I. (2000). Reduction in obesity and related comorbid conditions after diet-induced weight loss or exercise-induced weight loss in men. A randomized, controlled trial. *Annals of Internal Medicine*, *133*, 92–103.

Ross, R., Janssen, I., Dawson, J., Kungl, A. M., Kuk, J. L., Wong, S. L., … Hudson, R. (2004). Exercise-induced reduction in obesity and insulin resistance in women: A randomized controlled trial. *Obesity Research*, *12*, 789–798.

Roubenoff, R., Heymsfield, S. B., Kehayias, J. J., Cannon, J. G., & Rosenberg, I. H. (1997). Standardization of nomenclature of body composition in weight loss. *American Journal of Clinical Nutrition*, *66*, 192–196.

Sayers, A., & Tobias, J. H. (2010). Fat mass exerts a greater effect on cortical bone mass in girls than boys. *Journal of Clinical Endocrinology and Metabolism*, *95*, 699–706.

Schoenau, E., Neu, C. M., Beck, B., Manz, F., & Rauch, F. (2002). Bone mineral content per muscle cross-sectional area as an index of the functional muscle-bone unit. *Journal of Bone and Mineral Research*, *17*, 1095–1101.

Shafer, K. J., Siders, W. A., Johnson, L. K., & Lukaski, H. C. (2009). Validity of segmental multiple-frequency bioelectrical impedance analysis to estimate body composition of adults across a range of body mass indexes. *Nutrition*, *25*, 25–32.

Slentz, C. A., Duscha, B. D., Johnson, J. L., Ketchum, K., Aiken, L. B., Samsa, G. P., … Kraus, W. E. (2004). Effects of the amount of exercise on body weight, body composition, and measures of central obesity: STRRIDE—a randomized controlled study. *Archives of Internal Medicine*, *164*, 31–39.

Slentz, C. A., Houmard, J. A., & Kraus, W. E. (2009). Exercise, abdominal obesity, skeletal muscle, and metabolic risk: Evidence for a dose response. *Obesity*, *17*(Suppl. 3), S27–S33.

Srikanthan, P., Hevener, A. L., & Karlamangla, A. S. (2010). Sarcopenia exacerbates obesity-associated insulin resistance and dysglycemia: Findings from the National Health and Nutrition Examination Survey III. *PLoS ONE*, *5*, e10805.

Srikanthan, P., & Karlamangla, A. S. (2011). Relative muscle mass is inversely associated with insulin resistance and prediabetes. Findings from the third National Health and Nutrition Examination Survey. *Journal of Clinical Endocrinology and Metabolism*, *96*, 2898–2903.

Steijaert, M., Deurenberg, P., Van Gaal, L., & De Leeuw, I. (1997). The use of multi-frequency impedance to determine total body water and extracellular water in obese and lean female individuals. *International Journal of Obesity and Related Metabolic Disorders*, *21*, 930–934.

Stolk, R. P., Wink, O., Zelissen, P. M., Meijer, R., van Gils, A. P., & Grobbee, D. E. (2001). Validity and reproducibility of ultrasonography for the measurement of intra-abdominal adipose tissue. *International Journal of Obesity and Related Metabolic Disorders*, *25*, 1346–1351.

Taylor, R., Jones, I., Williams, S., & Goulding, A. (2002). Body fat percentages measured by dual-energy X-ray absorptiometry corresponding to recently recommended body mass index cutoffs for overweight and obesity in children and adolescents aged 3–18 y. *American Journal of Clinical Nutrition*, *76*, 1416–1421.

Toomey, C., McCreesh, K., Leahy, S., & Jakeman, P. (2011). Technical considerations for accurate measurement of subcutaneous adipose tissue thickness using B-mode ultrasound. *Ultrasound*, *19*, 91–96.

Van Pelt, R. E., Evans, E. M., Schechtman, K. B., Ehsani, A. A., & Kohrt, W. M. (2002). Contributions of total and regional fat mass to risk for cardiovascular disease in older women. *American Journal of Physiology: Endocrinology and Metabolism*, *282*, 1023–1028.

Wagner, D. R. (2013). Ultrasound as a tool to assess body fat. *Journal of Obesity*, *2013*, 1–9. doi: 10.1155/2013/280713

Wajchenberg, B. L. (2000). Subcutaneous and visceral adipose tissue: Their relation to the metabolic syndrome. *Endocrine Reviews*, *21*, 697–738.

Wang, J., Thornton, J. C., Kolesnik, S., & Pierson, R. N. Jr. (2000). Anthropometry in body composition. An overview. *Annals of the New York Academy of Sciences*, *904*, 317–326.

Weiss, L. W., & Clark, F. C. (1985). The use of B-mode ultrasound for measuring subcutaneous fat thickness on the upper arms. *Research Quarterly for Exercise and Sport*, *56*, 77–81.

Wildman, R., Muntner, P., Reynolds, K., McGinn, A., Rajpathak, S., Wylie-Rosett, J., & Sowers, M. (2008). The obese without cardiometabolic risk factor clustering and the normal weight with cardiometabolic risk factor clustering: Prevalence and correlates of 2 phenotypes among the US population (NHANES 1999–2004). *Archives of Internal Medicine*, *168*, 1617–1624.

Williams, D., Teixeira, P. J., & Going, S. B. (2005). Exercise. In S. Heymsfield, Z. Wang, T. Lohman, & S. Going (Eds.), *Human body composition: Methods and findings II* (pp. 313–330). Champaign, IL: Human Kinetics.

Yerges-Armstrong, L. M., Miljkovic, I., Cauley, J. A., Sheu, Y., Gordon, C. L., Wheeler, V. W., … Zmuda, J. M. (2010). Adipose tissue and volumetric bone mineral density of older Afro-Caribbean men. *Journal of Bone and Mineral Research*, *25*, 2221–2228.

Zhao, L. J., Jiang, H., Papasian, C. J., Maulik, D., Drees, B., Hamilton, J., & Deng, H. W. (2008). Correlation of obesity and osteoporosis: Effect of fat mass on the determination of osteoporosis. *Journal of Bone and Mineral Research*, *23*, 17–29.

Zhu, S., Wang, Z., Shen, W., Heymsfield, S. B., & Heshka, S. (2003). Percentage body fat ranges associated with metabolic syndrome risk: Results based on the third National Health and Nutrition Examination Survey (1988–1994). *American Journal of Clinical Nutrition*, *78*, 228–235.