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ORIGINAL ARTICLE

Body composition phenotypes in pathways to obesity and the metabolic syndrome

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Dynamic changes in body weight have long been recognized as important indicators of risk for debilitating diseases. While weight loss or impaired growth can lead to muscle wastage, as well as to susceptibility to infections and organ dysfunctions, the development of excess fat predisposes to type 2 diabetes and cardiovascular diseases, with insulin resistance as a central feature of the disease entities of the metabolic syndrome. Although widely used as the phenotypic expression of adiposity in population and gene-search studies, body mass index (BMI), that is, weight/height^2 (H^2), which was developed as an operational definition for classifying both obesity and malnutrition, has considerable limitations in delineating fat mass (FM) from fat-free mass (FFM), in particular at the individual level. After an examination of these limitations within the constraints of the BMI–FM% relationship, this paper reviews recent advances in concepts about health risks related to body composition phenotypes, which center upon (i) the partitioning of BMI into an FM index (FM/H^2) and an FFM index (FFM/H^2), (ii) the partitioning of FFM into organ mass and skeletal muscle mass, (iii) the anatomical partitioning of FM into hazardous fat and protective fat and (iv) the interplay between adipose tissue expandability and ectopic fat deposition within or around organs/tissues that constitute the lean body mass. These concepts about body composition phenotypes and health risks are reviewed in the light of race/ethnic variability in metabolic susceptibility to obesity and the metabolic syndrome.
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Introduction

Although malnutrition and obesity, as defined by body mass index (BMI), impose a substantial toll on life expectancy, it is clear that BMI has considerable limitations in the assessment of body composition and lack sensitivity for assessing disease risks, particularly in people who have normal or mildly elevated body weight. After an examination of these limitations within the constraints of the relationship between BMI and % body fat, this paper reviews recent advances in concepts about health risks related to body composition phenotypes that, as depicted in Figure 1, center on (i) the partitioning of BMI into a fat mass (FM) index (FM/H^2) and a fat-free-mass (FFM) index (FFM/H^2), (ii) the partitioning of FFM into organ mass and skeletal muscle mass, (iii) the partitioning of FM into hazardous fat and protective fat and (iv) the interplay between adipose tissue expandability and ectopic fat deposition within or around organs/tissues that constitute the lean body mass. These concepts about body composition phenotypes and health risks are reviewed in the light of race/ethnic variability in metabolic susceptibility to obesity and the metabolic syndrome.

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The history of BMI: an operational definition for obesity and malnutrition

Since the early 1970s, considerable effort has been made by international health organizations to design, perfect and implement nutritional surveillance pertaining to 'chronic energy deficiency' (CED), a term for which there was a lack of consensus about its meaning but which was used to indicate malnutrition resulting from inadequate household food supply. As CED was a loosely defined term for a major nutritional health hazard, an International Dietary Energy Consultancy Group (IDECG) task force was appointed in the late 1980s to come out with an operational definition for specifying the degree of CED in adults.[1] It proposed the use of BMI, the ratio of body weight to height^2, which Keys *et al.*,[2] while evaluating weight–height indexes as measures

of adiposity a decade earlier, found to have the highest correlations with % body fat as measured by skinfold and hydrodensitometry. Provisional cutoff points for low BMI were developed to define grades of CED in the same way as Garrow[3] was proposing higher levels of BMI to define grades of obesity, with different categories.

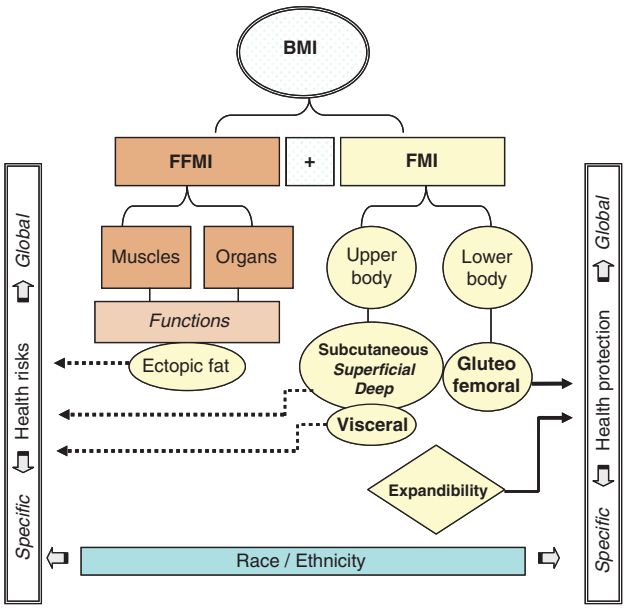

Figure 1 Concepts of body composition phenotypes depicting the partitioning of body mass index (BMI) into a fat-free-mass index (FFMI) and a fat mass index (FMI), followed by partitioning of FFMI and FMI into subcompartments, and their potential impact on heath across race and ethnicity.

The simplicity of this operational definition for classifying both malnutrition and obesity is encapsulated by the late Norgan[4] as follows: 'Body weight and height are two simple anthropometric measurements fundamental to the physical description of an individual or population. Both measurements possess the virtues of being precise (highly repeatable), accurate (close to the true value) and valid (representing what they are thought to represent). By themselves, they provide useful information on the mass and size of the human body, particularly the adiposity of the body. As different levels of fatness and energy stores in an individual or population are associated with different levels of morbidity and mortality, there is a need for a simple, non-invasive method for assessing fatness.' This need has been the impetus behind the use of BMI to monitor malnutrition and obesity, which, over the past few decades, have formed the basis of the World Health Organization BMI cutoff points[5] for classifying underweight, healthy weight, overweight and obese (Figure 2).

From the standpoint of cutoff points for underweight or 'thinness' thought to reflect different degrees of malnutrition, it was recognized that a measure of body fat is not so much that it provides a better index of energy stores but simply that the greater the proportion of fat in the body, the less likely it is for the individual to lose lean tissue,[6] a notion that, as shown in Figure 3, has been validated on data from

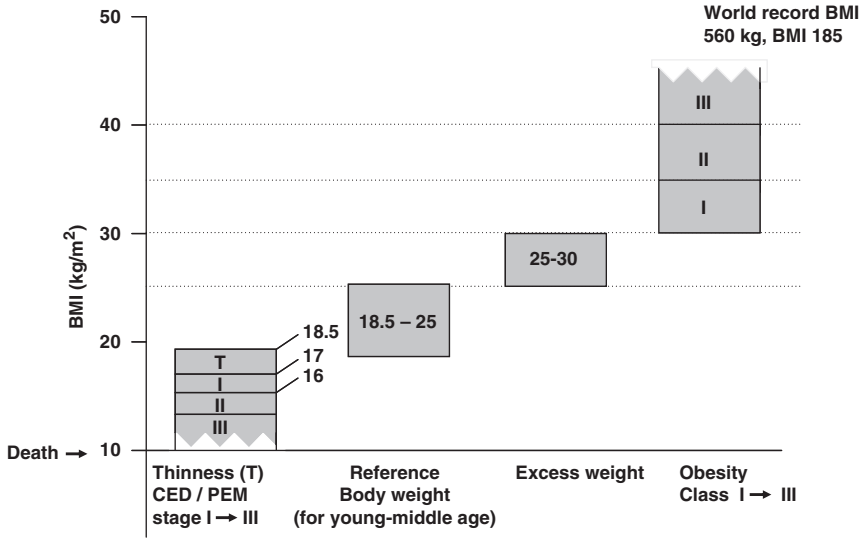

Figure 2 Classification and cutoff points for overweight and obesity versus thinness and malnutrition, according to the World Health Organization.[5] The reference zone for BMI is wide (18.5–25 kg m^{-2}), partly to account for differences in body build. On the obesity side (morbid/massive obesity), there is no further category defined above a BMI of 40 kg m^{-2}, which is less than twice the midrange 'normal' BMI. Yet, one of the highest BMI recorded (185 kg m^{-2}) is about eight times higher than the midrange reference BMI value. On the side of malnutrition, the BMI leading to death (about 9–12 kg m^{-2}, depending on sex, that is, 26–35 kg for 1.7 m height) is only half the midrange reference value! Note that the categories of BMI below 18.5 are very narrow, hence very sensitive to a few kg difference in body weight (1–1.5 units delta) as compared with those defining excess weight or obesity (5 units delta). At very low BMI values, a decrease in BMI primarily reflects the mobilization of FFM (which is critical for life), as at these levels, the fat mass is already very low. In contrast, at high BMI, the gain in body weight is primarily composed of adipose tissue, with little FFM added to the body. CED, chronic energy deficiency; PEM, protein-energy malnutrition.

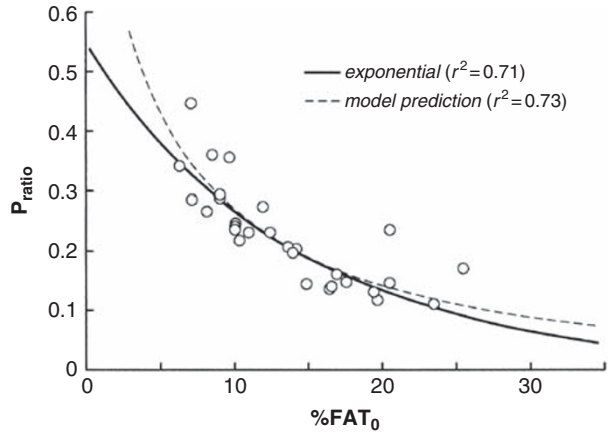

Figure 3 Exponential relationship between the fraction of energy lost as protein during semistarvation (P_{ratio}) and the initial percentage body fat (%FAT0) in healthy men ($n=32$) participating in the classic Minnesota experiment.[7] The data for initial body fat (range 6–25%) follow a normal distribution, with an almost threefold variability between the 10th percentile value (7.4%) and the 90th percentile value (20.5%), and with the 50th percentile (median) value being 13.7%. Comparison is made with the best fit of a model prediction of the partitioning characteristic (– – –, $r^2=0.73$) as a function of %FAT0 with the actual exponential relationship (——, $r^2=0.71$) observed between data for P_{ratio} of the Minnesota men and %FAT0. Note that both curves are almost superimposable when %FAT0 is greater than 5% (the lower limit of percentage body fat in a healthy population), and that both the predicted and actual relationships yield similar values for r^2, that is, 0.7. Adapted from the study by Dulloo and Jacquet.[8]

the Minnesota Experiment[7] on dynamic changes in body composition in normal-weight men undergoing experimental starvation.[8] As pointed out by Hull *et al.*,[9] in hospitalized individuals, recognition of malnutrition inferred from BMI is particularly important because nutritional status is related to longevity and mortality, influences the course of a disease and optimal treatment and affects the length of hospital stay. By comparing values of an individual patient with national norms, the health professional is able to assign a level of fatness, determine the level of risk for chronic disease and estimate mortality risk.

From the standpoint of BMI cutoff points for overweight and obesity, the greater the proportion of fat in the body the greater the risk for chronic diseases, in particular type 2 diabetes and cardiovascular diseases. Of the many epidemiological studies that have addressed the complex association between obesity, chronic diseases and survival, the most recent analysis of data from some 900 000 participants in 57 prospective studies on four continents confirms that obesity, as measured by BMI, is associated with increased total mortality in both men and women and in all age strata from 35 to 89 years.[10] This epic study also confirms the results of smaller studies, indicating that obesity shortens lifespan and that increased mortality due to high BMI is mainly from specific causes, such as ischemic heart disease, stroke, diabetes and liver disease. It also shows that people with BMI in the low–normal range (18.5–22.5 $kg\,m^{-2}$) have an increased risk of death (mainly due to respiratory diseases), compared with the risk in individuals with BMI between 27.5 and 30 $kg\,m^{-2}$, and hence underscores the protective role of fat stores during exposure to acute insults or to chronic wasting, resources that people with low–normal BMI do not have.

BMI as a surrogate measure of body composition

Despite the fact that numerous techniques are now available for estimating body composition, there is no single gold standard for measurements *in vivo*. All methods incorporate assumptions that do not apply in all individuals, and the more accurate models are derived by a combination of measurements, thereby reducing the importance of each assumption. However, because of their costs in terms of time and money, these methods are not practical in large epidemiological studies and for routine clinical use.[11] In these situations, BMI is often used and assumed to represent the degree of fatness. Although it remains the most widely applied phenotypic expression of human adiposity, its close scrutiny over the years has led to the consistent observation that correlations with adult adiposity are generally modest, and that other factors, such as age, race, shape and physical activity levels, confound the BMI–adiposity relationship. These confounding effects are elaborated below.

BMI and muscle mass

BMI does not distinguish between FM and lean (non-fat) mass or FFM, and the latter can also vary considerably between individuals of the same height. For example, body builders and competition athletes in other power and strength sports (boxing, shot put, wrestling and culturism) have a low proportion of fat in the body, but their BMI is often in the overweight/obese range because of their large lean (muscle) mass. Conversely, a deficit of BMI may be due to a deficit in FFM (sarcopenia) or due to a mobilization of adipose tissue or both combined. Furthermore, data suggest different health effects of FM and FFM. When only BMI is used as a criterion of nutritional status, these divergent relationships cannot be distinguished. For example, in elderly individuals not classified as obese, involuntary weight loss as FM was associated with decreased mortality, whereas weight loss as FFM was associated with increased mortality.[12] By applying advanced magnetic resonance imaging techniques, Heymsfield *et al.*[13] have recently shown that, after controlling first for adiposity, skeletal muscle mass is also a significant and independent determinant of BMI in a population-based sample. Variation in muscularity represents a confounding factor and thus provides a mechanistic basis for the previously observed nonspecificity of BMI as a phenotypic expression of adiposity. These quantitative observations have important implications when choosing adiposity measures in population and gene-search studies.

BMI–FM% relationship: linear or curvilinear?

There has been some controversy as to whether the relationship between BMI and % body fat (FM%) is linear or curvilinear. Webster *et al.*,[14] who undertook measurements of body composition in lean and obese women using the water dilution technique, argued from an analysis of their data and from theoretical considerations that the BMI–FM% relationship was curvilinear (or quadratic), with values tailing off at an FM% of 55–60% in women. In contrast, a study from the United States of America[15] found that the relationship was linear rather than quadratic. However, in this last study, the range of BMI values was limited as virtually all subjects had a BMI of $<35\,kg\,m^{-2}$. Two more recent findings addressing this issue on populations in the United States of America[16] and Europe[17] are in agreement with the early demonstration by Webster *et al.*[14] that the BMI–FM% relationship is curvilinear in both men and women, as shown in Figure 4. This nonlinear response is expected from the influence of individuals with BMI much above $35\,kg\,m^{-2}$. Note the large scatter of BMI in the BMI range classified as 'overweight': for a given BMI, the range in body fat can be almost twofold! The explanation for FM% tailing off at very high BMI remains a matter of conjecture. Could this effect reside in a disproportionately greater FFM relative to FM for BMI >35, perhaps resulting from the gravitational effect of carrying excessive adipose mass (and hence excess weight) on skeletal muscle mass? It is difficult to conceive that the composition of net weight added to a super morbid obese would have less fat (in %) than a less obese subject gaining a similar amount of weight! Another explanation would be methodological, as it could result from technical errors inherent in measuring body composition in excessively obese people. In general, the amount of variation in FM% that is explained by BMI when age is accounted for is

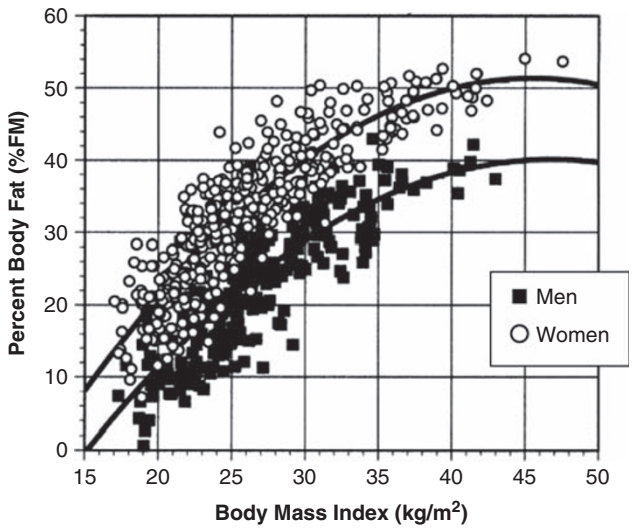

Figure 4 Nonlinear plot of the relationship between BMI and measured percentage body fat (FM%) by hydrodensitometry of the men and women from the Heritage Family Study data. Adapted from Jackson *et al.*[16]

$<60\%$ in men and women. Thus, the association between BMI and FM% is not strong, particularly in the desirable BMI range and when BMI is $<25\,kg\,m^{-2}$, as might be expected for the curvilinear relationship.[17] It should be emphasized, however, that body fat is measured with a much greater error than body weight and height. Consequently, this would weaken the relationship between the two variables and explain why any potential superiority of body composition measurements over BMI in predicting health risks is difficult to demonstrate. For example, in an investigation on a study population with a high prevalence of metabolic syndrome, Bosy-Westphal *et al.*[18] reported that measurement of body fat (as FM%) by air displacement plethysmography has no advantage over BMI and waist circumference in the prediction of obesity-related metabolic risk factors assessed as blood triglycerides, cholesterol, uric acid, C-reactive protein and insulin resistance by the homeostasis model assessment-insulin resistance model.

BMI–FM% relationship and race/ethnicity

Over the past two decades, it has become clear that the relationship between BMI and FM% differs among ethnic groups and populations. Differences in the BMI–FM% relationship compared with that in Caucasians have repeatedly been documented in Asians of many ethnicities (Chinese, Indians, Indonesians, Malays, Japanese), wherein FM% in men and women is found to be higher at a given BMI.[19–21] Asian Indians, in particular, consistently exhibit the greatest deviation from Caucasians with up to 5% higher body fat at any BMI value, as well as increased risks of type 2 diabetes and cardiovascular diseases at lower BMI. In several studies, differences in BMI–FM% relationship could be ascribed to differences in body build and/or frame size. It is well known that ethnic groups differ in frame size and in relative leg length (relative sitting height) and that this has an impact on BMI.[4] In addition to differences in trunk-to-leg-length ratio, slenderness and muscularity may also contribute to these racial differences in the BMI–FM% relationship.[5,13]

On the basis of these findings and the observed differences in the relation between BMI and disease risk, lower BMI cutoff points have been advocated to define overweight and obesity for specific ethnic groups. However, the expert committee of the World Health Organization has not redefined the cutoff points for specific Asian populations,[22] because available data do not necessarily indicate a clear BMI cutoff point for all Asian ethnic groups. For example, in contrast to Chinese adults in Singapore or New York, the BMI–FM% relationship in Chinese immigrants to Vancouver did not differ from that of White Canadians, nor did native Chinese in Beijing differ from Dutch adults.[20–22] Furthermore, there are also indications that the BMI–FM% relationship also differs among Caucasian groups.[19] These data may not necessarily be conflicting, as it is possible that the differences observed between studies result from different

methods of assessing body composition, which often rely on assumptions that are not validated in the population under study.

As for comparisons between populations of Caucasians and those of African descent, no clear differences in the relation between BMI and FM% have been observed for African Americans versus Caucasian Americans, nor between Black and White South Africans.[20] By contrast, the BMI–FM% association was found to vary among populations whose ancestry originated from West Africa.[23] Despite a similar genetic background, African Americans had higher body fat at any given BMI than did Jamaicans, and both had higher levels than rural Nigerians.

These findings underscore the point that, although it is tempting to attribute all the differences in this relationship to factors inherent in the specific populations (genetic backgrounds influencing body build proportions and thereby affecting relative BMI), it is possible that environmental factors such as variation in diet and activity also contribute to the observed differences. As a population migrates to new environments and changes with regard to weight and height over generations, the relationship between BMI and FM% may also be affected.[20] It is unclear how these potential generational changes and ethnic-specific differences in the BMI–%FM relationship influence risk of chronic diseases, particularly type 2 diabetes. As Deurenberg[24] has argued, redefining (different) cutoff points for different ethnic groups should be based not only on the relationship between BMI and FM% but also on morbidity and mortality risks in relation to BMI. For the body composition component, this calls for international multicenter studies in which the method of measuring FM% is highly standardized and free of assumptions. Heavy water (Deuterium) dilution might be the most feasible alternative, as the method is easy to standardize, application is relatively easy even in field situations and samples can be sent for analyses to a specialized laboratory or analyzed locally using the cheaper benchtop Fourier transformed infrared approach, which is therefore more accessible in many developing countries than a mass spectrometer.

BMI partitioning: fat mass index and fat-free-mass index

An issue that has plagued nutritionists and body composition specialists is the expression of body composition data when interindividual comparisons are made: should comparisons be made in absolute value (kg) compared with relative value (% of body weight) or a normalized value for 'size' (that is, by height or height^2 such as in the BMI concept)? As FFM is related to height, it seems inappropriate, as is sometimes used in clinical practice, to assign, for any individual, a cutoff point of FFM in absolute value (kg) below which FFM is judged as 'low'. For example, a short individual would be penalized, as his absolute FFM is expected to be lower than that of a tall individual. Indeed, a healthy and well-nourished young man would have an FFM expressed in absolute terms in virtually the same way as that of a similarly aged but taller individual suffering from mild protein–energy malnutrition. Similarly, the use of FM% to describe the status of the body's fat stores can be misleading in cases of malnutrition or in disease states such as AIDS, in which individuals may be characterized by a normal %fat but suffer from wasting or reduced FFM. To overcome some of the pitfalls associated with merely expressing FM or FFM in absolute terms or as % of body weight, VanItallie *et al*.[25] have proposed the use of an FFM index (FFMI) and an FM index (FMI). This concept merits a reappraisal and appears to be of interest in the classification of underweight/'under-lean' patients and overweight/'over-fat' patients.

Calculation of FFM and FM indices: a simple partitioning of BMI

The FFM and FM indices are equivalent concepts to the BMI (as the denominator is the same), and result from the partitioning of BMI into two subcomponents using body composition, namely,

$$\text{BMI (kg/m}^2) = \text{FFMI (kg/m}^2) + \text{FMI (kg/m}^2),$$

$$\text{hence FFMI} = (\text{BMI} - \text{FMI}) \text{ and FMI} = (\text{BMI} - \text{FFMI})$$

Thus, FFMI and FMI use similar ratios for their calculation as does BMI, the only difference being that the numerator is composed of FFM or FM rather than body weight also in kg. Considering the equation above, an increase (or a decrease) in BMI could be accounted for by an increase (or a decrease) in either subcomponents (FFMI or FMI) or in both components. Note that, for a given BMI, if FFMI increases then FMI should mathematically decrease, as, at a constant BMI, there is a perfect inverse relationship between the two values.

FFM versus FM indexes: usefulness in obesity and leanness

By determining these indices, quantification of the amount of excess (or deficit) FFM and FM can be calculated for each individual. Thus, the calculation of FFMI will allow a clinician to identify a malnourished individual, whereas interpretation of BMI and FM% may fail to detect the presence of protein–energy malnutrition. Although BMI is a useful tool to compare body weights in individuals who differ in height, FFMI and FMI are useful for the comparison of body composition in individuals who differ in height. Some other potential advantages are listed below:

(i) The advantage of the combined use of these indexes is that one can judge whether the deficit or excess of body weight is selectively due to a change in FFM, FM or both combined. For example, an individual of 1.85 m and 100 kg, and hence having a BMI of 29.2 kg m^{-2}, would be judged as largely overweight and even borderline obese. This would be true if his FMI is higher than the

reference values and conversely if his FFMI is not simultaneously elevated.

(ii) Another advantage of FMI, as compared with the BMI concept, is that it amplifies the relative effect of aging on body fat. Expression of a change in relative body FM (%) alone fails to allow an appropriate comparison among subjects of different sizes. The high sensitivity of FMI (or conversely of FFMI) to a slight change in body fat stores (or conversely lean tissue mass), compared with the use of BMI or FM% as factors, makes it an index of potential interest for assessing static and dynamic nutritional status and energy reserve end points.

(iii) The use of FFMI may also provide insight into sarcopenic obesity, a major public health concern in the elderly population when a stable body weight and BMI may be masking an increase in total body fat and a decrease in FFM. Baumgartner *et al*.[26] defined sarcopenic obesity, associated with greater disability in elderly subjects, as a relative FFM lower than 73% (that is, a relative body fat $>27\%$) in men and an FFM $<62\%$ (that is, a body fat $>38\%$) in women. Sarcopenic obesity could well be defined on the basis of FFMI and FMI, that is, a low FFMI associated with high FMI, which may prove helpful for monitoring the development and progression of sarcopenia, leading to efforts to prevent disability and for the evaluation of rehabilitation programs following a fall or fracture. However, the diagnosis of sarcopenic obesity based on these two indices remains to be further defined.

(iv) The concept of FFMI could also be useful for calculating the relative muscle hypertrophy in bodybuilding and other sports, in which heavy muscular body build needs to be measured quantitatively to exclude false diagnosis of excess body fat based on single BMI measurements.

Overall, when combining FFMI with FMI, four extreme situations, shown in Figure 5, can be observed:

(a) low FFMI versus high FMI judged as sarcopenic obesity at different levels of BMI;
(b) low FFMI versus low FMI corresponding to CED (that is, low BMI);
(c) high FFMI versus low FMI as evidence of muscle hypertrophy (excess BMI without obesity);
(d) high FFMI versus high FMI, which suggests combined excess FFM and FM (such as in a *SUMO* somatotype with obese BMI).

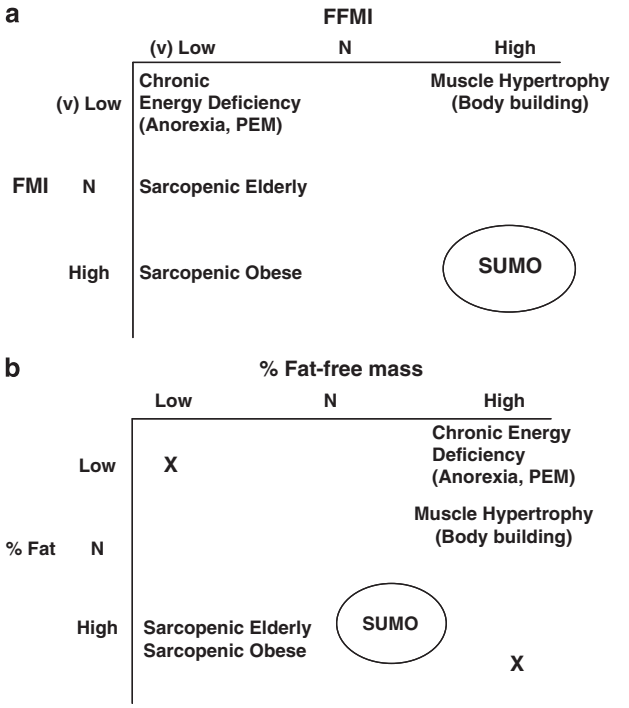

Figure 5 (**a**) Combinations in a latin square of the two components, FFMI ($kg\,m^{-2}$) versus FMI ($kg\,m^{-2}$). When these indexes are used in combination, the different conditions shown can be easily separated, defined and diagnosed. (**b**) Combinations in a latin square of the two components, % fat-free mass versus % fat mass. Note that both are mathematically inversely interrelated (x, impossible values). When the absolute mass of each subcomponent of the body is disregarded by presenting values in %, there is a cluster of conditions that render the interpretation of body composition very difficult. N, normal; PEM, protein–energy malnutrition; v, very.

FFMI in different race/ethnic groups

The FFMI and FMI percentiles have been developed in European Caucasians aged 18–98 years.[27] Although no reference data exist for the FFMI in a diverse cohort, data have been published on how total body potassium differs by race.[28] Total body potassium, which is intracellular and found in lean tissues such as skeletal muscle, is used as a proxy to provide an estimate of FFM. For both genders, total body potassium values were highest in African Americans and the least in Asians.[28] In a recent study, using DEXA for assessing body composition, Hull *et al*.,[9] investigating whether FFMI differs in 1339 healthy adults (age 18–110 years) of different races and ethnicity (Caucasian vs African American, Hispanic and Asian), found that FFMI differed among the four ethnic groups for both genders (males > females), with FFMI greatest in African Americans and the least in Asians. These highlight racial disparities in body composition and suggest that identification of individuals by race will show greater susceptibility for disease related to loss of FFM. Further metabolic studies are needed to identify or clarify the interracial differences in FFMI in relation to health risk.

FFMI across adult age

The study by Hull *et al*.[9] also reported a curvilinear relationship between age and FFMI for both genders, and that there was a gender difference in the rate of change in FFMI with age. Declines in FFMI were found at an earlier age in male subjects, whereas decline in female subjects occurred in the late 40s. Schutz *et al*.[27] found that, in women, FFMI was 20%

lower than in men, but this difference did not fully persist with aging. It is unknown how the gender differences in the rate of decline in FFMI levels or the time point in the lifespan when the decline commences, predicts or relates to health outcomes or if the later decline in FFMI may help explain the greater longevity in female versus male subjects.

FFMI and FMI in children

In children, the calculation of FFMI and FMI relies on population growth reference standards expressed as BMI combined with concomitant body composition data measured with appropriate methodology in the same population. The pattern is highly dynamic as, at a certain age category (puberty), BMI increases in both gender, whereas % body fat decreases or stagnates in boys and increases in girls. Special charts that facilitate the interpretation of FFMI and FMI in children have been suggested.[29] The use of this index, which is promising but requires a valid assessment of body composition by the pediatrician, is increasingly under evaluation.[30–32]

Table 1 Advantages and shortcomings of FFMI and FMI

Advantages	*Shortcomings*
FMI is relatively independent of FFM	Need accurate body composition
Calculation is as simple as BMI	Affected by body build
In the dynamic change of BC (e.g., puberty), differentiate between gain in fat versus FFM	Ethnicity factor
Independent of age in adults (unlike BMI)	Body fat distribution?
Height squared (denominator) eliminates the association of the index with the numerator	Adequate for stunting men?

Abbreviations: BMI, body mass index; FFMI, fat-free-mass index; FMI, fat mass index; BC, body composition.

Perspective

Reference intervals of FMI versus FFMI, for adults, children and teenagers, can be used as indicative values for the evaluation of nutritional status (degree of overnutrition or undernutrition) of apparently healthy subjects. It can also provide complementary information to the classical expression of body composition reference values. FMI is able to identify individuals with elevated BMI but without excess FM. Conversely, FMI can identify subjects with 'normal' BMI but who are at potential risk because of elevated FM. The shortcomings and advantages of these two indices, the importance of which has been hampered by its apparent complexity, are outlined in Table 1. The importance of high FMI and low FFMI needs to be further explored in a dynamic way (in particular, in children), on the basis of longitudinal studies in order to determine at what levels these two variables, when used in combination, yield the lowest disability, low-risk factors and prolonged longevity.

Partitioning FFM into muscle mass and organ mass

FFM is the principal contributor to resting energy expenditure (REE), and total body FFM is commonly used as a proxy for metabolically active tissue for normalizing (adjusting) interindividual differences or within-individual changes in energy expenditure. It is, however, a heterogeneous compartment containing organ/tissues that possess a wide range of specific metabolic rates.[33] Skeletal muscle constitutes 40–50% of total body weight and accounts for only 20–30% of REE. This contrasts with the brain, liver, heart and kidneys, which collectively contribute to <6% of total body weight, but account for about 60–70% of REE in adults (Figure 6). Consequently, relatively subtle differences or changes in

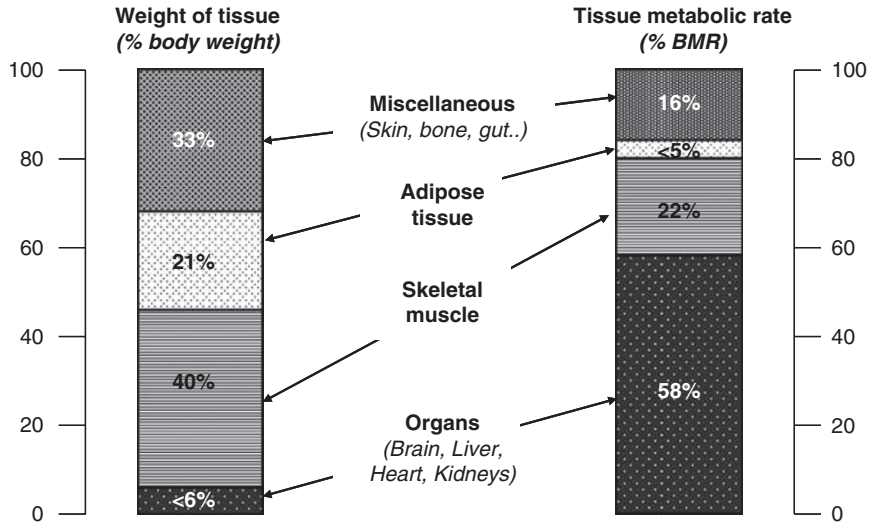

Figure 6 Contribution of organ/tissues to the basal metabolic rate (BMR) of a non-obese man; adapted from Elia.[33] Note that organs contribute to <6% of body weight but that their contribution to basal metabolic rate (BMR) is disproportionately high (>50% BMR).

organ masses and/or organ activity can have a significant impact on interindividual variability in energy expenditure, and may hence have relevance for metabolic predisposition to leanness or fatness. Over the past few years, the application of imaging techniques, such as computed tomography and magnetic resonance imaging, in quantification of the size of these tissues and organs *in vivo* has shown the potential of such an approach toward a better understanding of the contribution of these FFM subcomponents to the decline in REE with age[34] and in racial differences in REE.[35] It has been known for some time that, in comparison with White Americans, African Americans have significantly greater bone mass and skeletal muscle mass[36] and lower or similar FM[15] but a different fat distribution pattern.[15] Using magnetic resonance imaging, Gallagher *et al*.[35] have extended this list of body composition differences to include lower masses of the liver, kidney, spleen, heart and brain. The implication, therefore, is that African Americans may have a significantly smaller proportion of FFM with high metabolic rate organs than do Whites, which helps explain many previous reports of lower REE adjusted for FFM in African Americans than in Whites.[37] In the study by Gallagher *et al*.,[35] ~50% of the observed remaining difference in REE between African American and White men and women, after adjusting for age, fat and FFM, could be explained by differences in the mass of these organs. Because REE is ~65% of daily energy expenditure, the daily differences in REE observed in these studies (100–150 kcal), if not compensated for by a lower intake, may over a prolonged period of time be a contributing factor to the greater incidence of obesity in African-American than in White women. The mass of high metabolic rate organs and tissues is therefore a body composition phenotype that should be considered in future studies on interindividual variability in REE and in the assessment of metabolic susceptibility to obesity across various racial ethnic groups. However, tracking these organs requires expensive advanced body composition techniques.

Partitioning FM into hazardous fat and protective fat

During the past 60 years, research toward understanding how excess fat predisposes to chronic diseases has been dominated by concepts centered on the specific locations at which fat accumulates in the body. In the 1950s, Vague[38] proposed that excess fat stored in the trunk or android obesity could be metabolically more damaging than fat stored in the limbs (or gynoid obesity). Since then, a large number of cross-sectional and prospective studies have confirmed that individuals who have an upper body rather than a lower body distribution of fat have an elevated risk for type 2 diabetes and cardiovascular diseases.[39] These findings have served as the basis for classifying patients by measurement of waist circumference or waist-to-hip ratio, and for the recognition that abdominal (or central) obesity is a cardinal feature of the metabolic syndrome, with insulin resistance as a key link between abdominal fat and risks for chronic diseases.

Upper body fat

Whether specific anatomical compartments in the abdominal region confer greater risk for insulin resistance and its complications is, however, controversial. Many studies do in fact support the concept of a specific role for *intraabdominal* fat accumulation or *visceral obesity* in the link between abdominal obesity and insulin resistance. In particular, removal of visceral adipose tissue (VAT) by omentectomy results in decreased glucose and insulin levels in humans,[40] whereas removal of subcutaneous adipose tissue (SAT) by liposuction does not always result in an improvement in glucose and lipid metabolism.[41,42] The causative mechanism is attributed to the release of free fatty acids from VAT, which, by draining into the portal vein, exerts adverse effects on hepatic metabolism. However, there is no clear proof of such a causal link between VAT and insulin resistance. Both are in fact common correlates of abdominal SAT accumulation, which, on the basis of its considerably larger mass than VAT, could have a greater potential to contribute to insulin resistance through the release of free fatty acids into the systemic circulation.[43] Goodpaster *et al*.[44] showed that SAT was positively associated with insulin resistance in White Caucasians after adjusting for VAT. In addition, it has been reported that posterior or deep subcutaneous adipose tissue (DSAT) is more importantly associated with peripheral and hepatic insulin sensitivity than anterior or superficial subcutaneous adipose tissue (SSAT) in White Caucasian men,[45] and in other ethnic groups such as African Americans[46] and South Indians.[47] In addition, at any given FFM, men had more DSAT and less SSAT than women, regardless of ethnicity, a sexual dimorphism that mimics the pattern observed for VAT in relation to FM[48,49] and could also provide insights into the cardioprotective role of the SAT depot in women.[50] It would seem therefore that abdominal SAT can no longer be regarded as one single entity, but that there are two anatomically and functionally distinct compartments: the SSAT and the DSAT compartments, which are separated by a fascial plane and can be recognized by computed tomography scan or magnetic resonance imaging. There seems to be a gradient toward less organization and more vascularization of the adipose tissue depots proceeding from the outermost compartment, SSAT to DSAT and then to VAT;[51] this gradient in abdominal adipose tissue could be of potential importance in assessing the risk for the metabolic syndrome.

Ectopic fat

In humans and in most animal models, the development of obesity leads not only to increased fat depots in classical adipose tissue locations, such as in the SAT and VAT

compartments, but also to significant lipid deposits within and around other tissues and organs.[52] This phenomenon of ectopic fat deposition can impair tissue and organ function in two possible ways. First, lipid accumulation can occur in non-adipose cells and may lead to cell dysfunction or cell death, a phenomenon known as lipotoxicity. Intracellular lipid accumulations in endocrine pancreas, liver and skeletal muscle cells have all been described and contribute to the pathogenesis of impaired insulin secretion and insulin resistance.[53] Second, a substantial increase in the size of fat pads around key organs, although constituting a physical protection against external shock, could modify organ function either by simple physical compression or because peri-organ fat cells may secrete various locally functioning substances.[52] Increased epicardial fat pads associated with intramyocardial lipid deposition may lead to both systolic and diastolic dysfunctions, whereas accumulation of fat around blood vessels (perivascular fat) may affect vascular function in a paracrine manner, as perivascular fat cells secrete vascular relaxing factors, proatherogenic cytokines and smooth muscle cell growth factors.[54,55] High amounts of perivascular fat could also mechanically contribute to the increased vascular stiffness observed in obesity, whereas accumulation of fat within the renal sinus associated with the increased intraabdominal pressure of visceral obesity may compress the renal papilla, the renal vein and lymphatics vessels, altering intrarenal physical forces that favor sodium reabsorption and arterial hypertension.[52] Finally, the accumulation of adipose tissue surrounding skeletal muscle bundles, that is, intermuscular adipose tissue (IMAT), albeit in the thigh region, also has a strong association with insulin resistance.[56,57] IMAT may affect peripheral insulin dynamics by impairing muscle blood flow, reducing insulin diffusion capacity, increasing local concentrations of fatty acids or enhancing rates of lipolysis within skeletal muscle.[56] Taken together, ectopic fat storage in the lean tissue compartment may impair their functions, contributing to the increased prevalence of type 2 diabetes and cardiovascular diseases in obese subjects.

Lower body fat

In contrast to upper body obesity, wherein expansion of the abdominal DSAT and VAT depots has been repeatedly linked to an increased risk of dyslipidemia, dysglycemia and vascular disease, an enlarged gluteofemoral adipose tissue mass (as measured by thigh or hip circumference or leg adipose tissue mass) is associated with a favorable lipid and glucose profile, as well as with a decrease in cardiovascular and metabolic risk.[58] This fat depot is viewed as a protective 'metabolic sink' functioning as a buffer against the postprandial surge in circulatory fatty acids (fatty acid trapping), and hence protects other tissues from lipid overflow associated with ectopic lipotoxicity.[59] Indeed, femoral fat accumulation that is typical of female fat distribution pattern is associated with an increase in adipose tissue lipoprotein lipase activity, a key enzyme controlling the entry of fatty acids from the circulation into adipose tissue, whereas the activity of hormone-sensitive lipase, a key enzyme in lipolysis, is lower in the gluteal than in the abdominal fat depot.[58] Furthermore, the low amounts of gluteofemoral fat observed in pathogenic states, such as in partial lipodystrophy or in Cushing's syndrome, are associated with increased metabolic and cardiovascular risks.[58] This underscores the protective properties of gluteofemoral adipose tissue by the long-term entrapment of excess fatty acids, thus protecting from the adverse effects associated with ectopic fat deposition. Gluteofemoral adipose tissue could also contribute to a more protective adipokine profile by secreting more beneficial adipokines (leptin and adiponectin) and less proinflammatory cytokines compared with abdominal fat.

Adipose tissue expandability

During the development of obesity, adipose tissue expands by increasing the volume of preexisting adipocytes (adipose hypertrophy), by generating new small adipocytes through adipocyte proliferation/differentiation (adipose hyperplasia), or by both. A prevailing concept of the late twentieth century, namely, that preventing adipocyte differentiation might serve as a target for obesity, was strongly rebutted by Danforth,[60] who argued that 'Prevention of adipocyte differentiation is destined to exchange obesity for diabetes'. He put forward the hypothesis that type 2 diabetes is the result of the inability of the adipose organ to expand to accommodate excess energy, and that type 2 diabetes in the centrally obese individual, in spite of their unlikely phenotype, is a form of lipodystrophy. Since then, the utilization of both transgenic and knockout murine models has provided strong support for a central role for adipose tissue expandability in the mechanisms by which both adipose and nonadipose tissues could predispose to ectopic fat storage and the metabolic syndrome. According to Virtue and Vidal-Puig,[61] all individuals possess a maximum capacity for adipose expansion, which is determined by both genetic and environmental factors. Once the adipose tissue expansion limit is reached, adipose tissue ceases to store energy efficiently, and lipids begin to accumulate in other tissues, with such ectopic lipid accumulation in non-adipocyte cells resulting in lipotoxic insults that include insulin resistance, tissue damage and inflammation. Indeed, exposure to free fatty acid has been shown to activate inflammatory signaling, in particular the protein kinases JNK1 and IKK-β, in several cell types, including adipocytes, hepatocytes, myocytes, pancreatic islet and macrophages.[62] At the same time, hypertrophic adipocytes undergo necrotic cell death, and leukocytes infiltrate into the saturated adipose tissue. Therefore, obesity is associated with a chronic inflammatory state, generally referred to as 'metabolic inflammation'. It was indeed proposed that in the link between positive energy balance and metabolic syndrome, the critical factor that

triggers metabolic inflammation is not adiposity *per se* but a saturation of the lipid storage capacity of adipocytes.[62] Consistent with this contention are findings that obese subjects with few large adipocytes are more glucose intolerant and hyperinsulinemic than those having the same degree of obesity and many small fat cells.[63–65] In longitudinal studies, enlarged subcutaneous abdominal adipocyte size has been shown to be an independent predictor of type 2 diabetes, including in Pima Indians in Arizona[66] and more recently in a population-based Swedish (Caucasian) cohort.[67] Furthermore, gene expression profiling of human adipocytes of different sizes from the same adipose tissue sample has identified genes with markedly higher expression in large than in small adipocytes: the majority were immune related, with importance for cell structure, or with unknown function.[68] As adipocyte hypertrophy may impair adipose tissue function by inducing local inflammation, mechanical stress and altered metabolism, these genes may provide links between hypertrophic obesity and metabolic disorders.

Hypertrophic versus hyperplastic adiposity phenotypes

Thus, the risk for metabolic complications is increased not only by the amount and localization of adipose tissue but also by the size of adipocytes within the adipose tissue. Sex differences in body fat distribution and adipocyte metabolism suggest that the storage capacity and propensity for fat cell hypertrophy or fat cell hyperplasia may be regulated in a depot-specific manner, and that obese women are prone to accumulate fat in SAT rather than in VAT. In a study examining omental and subcutaneous fat depot in French obese women undergoing abdominal hysterectomies,[69] hyperplasia was indeed found to predominate in the SAT depot, whereas fat cell hypertrophy was observed both in omental VAT and SAT compartments. A higher storage capacity of the SAT compartment in women compared with men could theoretically prevent fat accumulation in the VAT compartment, and explain their lower prevalence of metabolic disturbances. For any adipose tissue depot, however, there is a large interindividual variation in adipocyte size among lean and obese individuals,[66,70] such that lean individuals can have larger adipocytes than obese individuals and vice versa. The mechanisms responsible for the development of these different forms of adipose morphology are largely unknown. However, in recent years, measurement of adipocyte turnover by analyzing the incorporation of atmospheric ^{14}C (derived from 1950s nuclear bomb tests) in genomic DNA has indicated that the turnover rate of adipocytes is high at all adult ages and across all BMI levels,[71] with approximately one-tenth of the total adipocyte pool being renewed every year by ongoing adipogenesis and adipocyte death. In a follow-up study,[72] a low adipocyte turnover could be associated with adipose hypertrophy, which is linked to low insulin sensitivity and high circulating insulin levels. Conversely, a high adipocyte turnover could be associated with the more benign adipose hyperplasia. These findings suggest that, in hypertrophic state, the body produces few adipocytes over time, requiring existing adipocytes to accumulate more lipids in comparison with the hyperplastic state.

Race/ethnicity and FM partitioning

The higher risks for type 2 diabetes and cardiovascular diseases in people of Aboriginal, Asian or African descents than in those of European descent have often been attributed to race–ethnic differences in body fat distribution.[73,74] There have been conflicting findings, however, as to the role of an enlarged VAT is these race–ethnic differences, with VAT being reported to be greater[75] or no different[76] in South Asians than in Caucasians, or increased VAT being found in women, but not in men, of Asian origin compared with Europeans.[77] Ethnicity-specific differences in VAT have also been reported between African Americans and Europeans, indicating that African-American men have smaller amounts of VAT, whereas African-American women have similar or smaller amounts than Europeans for a given body FM.[78–81] However, many of these reports suffer from small sample size, lack of gender distribution and often fail to adjust for ethnic differences in total body fat, thereby introducing an important confounding variable given that fat-specific depots (VAT and SAT) correlate with total body fat. Over the past few years, however, a number of comprehensive studies on race–ethnic differences in fat distribution and metabolic risks have been conducted in Europe, Canada and the United States of America. These are summarized below.

(i) Asians, in whom metabolic complications associated with obesity (dyslipidemia, insulin resistance and type 2 diabetes) are apparent at lower BMI and waist circumference, show a greater proportion of VAT for a given total body fat compared with Europeans.[82] In particular, in a study comparing body fat distribution in Chinese, Indians, Aboriginals and Caucasians of European descent living in Canada, it was shown that for a given amount of total body fat, the Chinese and South Asian participants had a greater amount of abdominal adipose tissue, particularly in the VAT depot than did the Caucasians.[83] In contrast, no differences were observed between the Canadian Aboriginal and Caucasian participants. These data are nonetheless consistent with a similar study in USA Aboriginals showing no difference in VAT between Pima Indians and Caucasians matched for BMI.[84]

(ii) Other studies have suggested that abdominal (SAT) depots, which are thicker in adult Asian Indians compared with European Caucasians, are a more important predictor of the metabolic syndrome in Asian Indians than VAT.[85,86] In a recent comprehensive investigation comparing South Asians and Europeans,

Kohli *et al*.[87] showed that body fat distribution, as measured by SSAT and DSAT, also differs according to ethnicity and gender. More importantly, at any given FFM, South Asians had more DSAT than did Europeans, regardless of sex, whereas there were no differences observed in SSAT. Sniderman *et al*.[88] have suggested that South Asians may have a less-developed SSAT compartment, and therefore, in situations of energy excess, South Asians would tend to accumulate greater amounts of adipose tissue in the DSAT compartment, in addition to VAT, compared with Europeans, and this would consequently predispose South Asians to developing early-onset complications that are associated with obesity. Consistent with these hypotheses are data from west India, which suggest that Asian Indians have a tendency for central obesity and have truncal subcutaneous adiposity from birth, in spite of having a lower birth weight compared with British neonates.[89]

(iii) In the largest study published to date that examined racial differences in abdominal fat depots, African-American men and women were found to have lower amounts of abdominal VAT for a given amount of total body fat than White Americans, and these differences increase with the amount of total body fat.[90] Furthermore, after adjustment for age, total body FM and other covariates, abdominal SAT was found to be higher in African-American men and women compared with White men and women, respectively. It appears that the increase in SAT in African Americans is specifically in SSAT, and not in DSAT, compared with Caucasian or Hispanic Americans.[91]

(iv) There is also emerging evidence that African Americans have less hepatic and intramyocellular lipid levels than Caucasians or Hispanic Americans.[91–93] Furthermore, intramyocellular lipid has been reported to be a significant determinant of insulin sensitivity among healthy, young European Americans, but not among African-American women.[94] At high levels of adiposity, however, African-American men, though not women, have greater quantities of total body intermuscular fat (IMAT) than do Asians or Whites after adjustment for differences in total adiposity and other covariates.[95] To what extent IMAT, which has been reported to be associated with diminished insulin sensitivity, contributes to the more diabetogenic profile and higher cardiovascular risks in African Americans as compared with Caucasians is currently unknown. These data do not prove, but suggest that IMAT may contribute to racial and gender differences in cardiovascular risks.

(v) Finally, in a study in young, lean, healthy but sedentary Asians and Caucasians living in the United States of America, Asian-Indian men showed a higher prevalence of insulin resistance, associated with a twofold higher hepatic lipid content relative to Caucasian men even after adjustment for insulin sensitivity.[96]

Table 2 Body composition phenotyping in men of different race/ethnicity

	Asian Indian vs Caucasians	*African Americans vs Caucasians*
Type 2 diabetes and cardiovascular risks	↑	↑
FFMI	↓	↑
Muscle mass	↓	↑
Bone mass	↓	↑
Organ mass (sum of the liver, heart, spleen, kidneys, brain)	**?**	↓
FMI		
Upper body		
Superficial SAT	↑	↑
Deep SAT	↑	—
VAT	↑	↓
Hepatic lipids	↑	↓
Lower body		
Gluteofemoral		
SAT	↓	↑
IMAT	↑	↑
Intramyocellular lipids (from leg muscle)	?	↓
Resting energy expenditure	?	↓

Abbreviations: FFMI, fat-free-mass index; FMI, fat mass index; IMAT, intermuscular adipose tissue; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue. ↑ = higher; ↓ = lower; — = no difference; ? = unknown.

From an analysis of the above discussions, it is clear that race/ethnicity is of central importance in determining the pathways that lead to obesity and metabolic diseases. As illustrated in Table 2, African-American and South Asian men are both more susceptible to obesity and metabolic complications than are White Caucasian men, but they exhibit marked differences, often in opposite directions, in several of the phenotypic expressions of body composition that may be considered hazardous or protective.

Conclusion

Although BMI will remain the best simple measure for tracking excess and deficit of body weight in various populations, the time is ripe to go beyond BMI to refine the assessment of both health risk and health protection factors (Figure 1). The partitioning of BMI into FMI (FM/H^2) and FFMI (FFM/H^2) seems to be useful for characterizing certain medical conditions (for example, sarcopenia and sarcopenic obesity), and may be important for defining health risk factors such as malnutrition. Tracking the metabolic susceptibility to obesity across various racial/ethnic groups may benefit from the functional partitioning of FFM itself into organ mass and skeletal muscle mass, in addition to the anatomical partitioning of body fat into

hazardous fat and protective fat. Obviously, the budget and technical expertise needed to assess these subcomponents will preclude any large-scale study at the epidemiological level, as well as in fieldwork.

Conflict of interest

The authors declare no conflict of interest.

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References

1 James WP, Ferro-Luzzi A, Waterlow JC. Definition of chronic energy deficiency in adults. Report of a working party of the International Dietary Energy Consultative Group. *Eur J Clin Nutr* 1988; **42**: 969–981.
2 Keys A, Fidanza F, Karvonen MJ, Kimura N, Taylor HL. Indices of relative weight and obesity. *J Chronic Dis l* 972; **25**: 329–343.
3 Garrow JS. *Treat obesity seriously—a clinical manual*. Churchill Livingstone: London, 1981.
4 Norgan NG. Population differences in body composition in relation to body mass index. *Eur J Clin Nutr* 1994; **48** (Suppl 3): S10–S27.
5 World Health Organization. Obesity: preventing and managing the global epidemic. Report of a WHO Consultation (WHO Technical Report Series (894) 2000.
6 Elia M. Effect of starvation and very low calorie diets on protein–energy interrelationships in lean and obese subjects. In: Scrimshaw NS, Schurch B (eds). *Protein–Energy Interactions*. IDECG: Lausanne, Switzerland, 1991. pp 249–284.
7 Keys A, Brozek J, Henschel A, Mickelson O, Taylor HL. *The Biology of Human Starvation*. University of Minnesota Press: Minneapolis, MN, 1950.
8 Dulloo AG, Jacquet J. The control of partitioning between protein and fat during human starvation: its internal determinants and biological significance. *Br J Nutr* 1999; **82**: 339–356.
9 Hull HR, Thornton J, Wang J, Pierson Jr RN, Kaleem Z, Pi-Sunyer X *et al*. Fat-free mass index: changes and race/ethnic differences in adulthood. *Int J Obes* 2010. (e-pub ahead of print).
10 Whitlock G, Lewington S, Sherliker P, Clarke R, Emberson J, Halsey J, *et al*., Prospective Studies Collaboration. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. *Lancet* 2009; **373**: 1083–1096.
11 Snijder MB, van Dam RM, Visser M, Seidell JC. What aspects of body fat are particularly hazardous and how do we measure them? *Int J Epidemiol* 2006; **35**: 83–92.
12 Allison DB, Faith MS, Heo M, Kotler DP. Hypothesis concerning the U-shaped relation between body mass index and mortality. *Am J Epidemiol* 1997; **146**: 339–349.
13 Heymsfield SB, Scherzer R, Pietrobelli A, Lewis CE, Grunfeld C. Body mass index as a phenotypic expression of adiposity: quantitative contribution of muscularity in a population-based sample. *Int J Obes* 2009; **33**: 1363–1373.
14 Webster JJ, Hesp R, Garrow JS. The composition of excess weight in obese women estimated by body density, total body water and total body potassium. *Hum Nutr Clin Nutr* 1984; **38C**: 299–306.
15 Gallagher D, Visser M, Sepúlveda D, Pierson RN, Harris T, Heymsfield SB. How useful is body mass index for comparison of body fatness across age, sex, and ethnic groups? *Am J Epidemiol* 1996; **143**: 228–239.
16 Jackson AS, Stanforth PR, Gagnon J, Rankinen T, Leon AS, Rao DC *et al*. The effect of sex, age and race on estimating percentage body fat from body mass index: the Heritage Family Study. *Int J Obes* 2002; **26**: 789–796.
17 Meeuwsen S, Horgan GW, Elia M. The relationship between BMI and percent body fat, measured by bioelectrical impedance, in a large adult sample is curvilinear and influenced by age and sex. *Clin Nutr* 2010; **29**: 560–566.
18 Bosy-Westphal A, Geisler C, Onur S, Korth O, Selberg O, Schrezenmeir J *et al*. Value of body fat mass vs anthropometric obesity indices in the assessment of metabolic risk factors. *Int J Obes* 2006; **30**: 475–483.
19 Deurenberg P, Deurenberg-Yap M, Guricci S. Asians are different from Caucasians and from each other in their body mass index/body fat per cent relationship. *Obes Rev* 2002; **3**: 141–146.
20 Luke A. Ethnicity and the BMI-body fat relationship. *Br J Nutr* 2009; **102**: 485–487.
21 Wulan SN, Westerterp KR, Plasqui G. Ethnic differences in body composition and the associated metabolic profile: a comparative study between Asians and Caucasians. *Maturitas* 2010; **65**: 315–319.
22 WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *Lancet* 2004; **363**: 157–163.
23 Luke A, Durazo-Arvizu R, Rotimi C, Prewitt TE, Forrester T, Wilks R *et al*. Relation between body mass index and body fat in black population samples from Nigeria, Jamaica, and the United States. *Am J Epidemiol* 1997; **145**: 620–628.
24 Deurenberg P. Universal cut-off BMI points for obesity are not appropriate. *Br J Nutr* 2001; **85**: 135–136.
25 VanItallie TB, Yang MU, Heymsfield SB, Funk RC, Boileau RA. Height-normalized indices of the body's fat-free mass and fat mass: potentially useful indicators of nutritional status. *Am J Clin Nutr* 1990; **52**: 953–959.
26 Baumgartner RN, Koehler KM, Gallagher D, Romero L, Heymsfield SB, Ross RR *et al*. Epidemiology of sarcopenia among the elderly in New Mexico. *Am J Epidemiol* 1998; **147**: 755–763.
27 Schutz Y, Kyle UU, Pichard C. Fat-free mass index and fat mass index percentiles in Caucasians aged 18-98 y. *Int J Obes* 2002; **26**: 953–960.
28 He Q, Heo M, Heshka S, Wang J, Pierson Jr RN, Albu J *et al*. Total body potassium differs by sex and race across the adult age span. *Am J Clin Nutr* 2003; **78**: 72–77.
29 Wells JC. A Hattori chart analysis of body mass index in infants and children. *Int J Obes* 2000; **24**: 325–329.
30 Nakao T, Komiya S. Reference norms for a fat-free mass index and fat mass index in the Japanese child population. *J Physiol Anthropol Appl Human Sci* 2003; **22**: 293–298.
31 Demerath EW, Schubert CM, Maynard LM, Sun SS, Chumlea WC, Pickoff A *et al*. Do changes in body mass index percentile reflect changes in body composition in children? Data from the Fels Longitudinal Study. *Pediatrics* 2006; **117**: 487–495.
32 Eissa MA, Dai S, Mihalopoulos NL, Day RS, Harrist RB, Labarthe DR. Trajectories of fat mass index, fat free-mass index, and waist circumference in children: Project HeartBeat. *Am J Prev Med* 2009; **37** (Suppl 1): S34–S39.
33 Elia M. Organ and tissue contribution to metabolic rate. In: Kinney JM, Tucker HN (eds). *Energy metabolism: tissue determinants and cellular corollaries*. Raven Press Ltd: New York, NY, 1992. pp 61–79.
34 He Q, Heshka S, Albu J, Boxt L, Krasnow N, Elia M *et al*. Smaller organ mass with greater age, except for heart. *J Appl Physiol* 2009; **106**: 1780–1784.
35 Gallagher D, Albu J, He Q, Heshka S, Boxt L, Krasnow N *et al*. Small organs with a high metabolic rate explain lower resting

energy expenditure in African American than in white adults. *Am J Clin Nutr* 2006; **83**: 1062–1067.
36 Ortiz O, Russell M, Daley TL, Baumgartner RN, Waki M, Lichtman S *et al*. Differences in skeletal muscle and bone mineral mass between black and white females and their relevance to estimates of body composition. *Am J Clin Nutr* 1992; **55**: 8–13.
37 Weyer C, Snitker S, Bogardus C, Ravussin E. Energy metabolism in African Americans: potential risk factors for obesity. *Am J Clin Nutr* 1999; **70**: 13–20.
38 Vague J. The degree of masculine differentiation of obesities: a factor determining predisposition to diabetes, atherosclerosis, gout and uric calculous disease. *Am J Clin Nutr* 1956; **4**: 20–34.
39 Després JP, Arsenault BJ, Côté M, Cartier A, Lemieux I. Abdominal obesity: the cholesterol of the 21st century? *Can J Cardiol* 2008; **24** (Suppl D): 7D–12D.
40 Thörne A, Lönnqvist F, Apelman J, Hellers G, Arner P. A pilot study of long-term effects of a novel obesity treatment: omentectomy in connection with adjustable gastric banding. *Int J Obes* 2002; **26**: 193–199.
41 Klein S, Fontana L, Young VL, Coggan AR, Kilo C, Patterson BW *et al*. Absence of an effect of liposuction on insulin action and risk factors for coronary heart disease. *N Engl J Med* 2004; **350**: 2549–2557.
42 Giugliano G, Nicoletti G, Grella E, Giugliano F, Esposito K, Scuderi N *et al*. Effect of liposuction on insulin resistance and vascular inflammatory markers in obese women. *Br J Plast Surg* 2004; **57**: 190–194.
43 Frayn KN. Visceral fat and insulin resistance—causative or correlative. *Br J Nutr* 2000; **83** (Suppl 1): S71–S77.
44 Goodpaster BH, Thaete FL, Simoneau JA, Kelley DE. Subcutaneous abdominal fat and thigh muscle composition predict insulin sensitivity independently of visceral fat. *Diabetes* 1997; **46**: 1579–1585.
45 Misra A, Garg A, Abate N, Peshock RM, Stray-Gundersen J, Grundy SM. Relationship of anterior and posterior subcutaneous abdominal fat to insulin sensitivity in nondiabetic men. *Obes Res* 1997; **5**: 93–99.
46 Tulloch-Reid MK, Hanson RL, Sebring NG, Reynolds JC, Premkumar A, Genovese DJ *et al*. Both subcutaneous and visceral adipose tissue correlate highly with insulin resistance in African Americans. *Obes Res* 2004; **12**: 1352–1359.
47 Goel K, Misra A, Vikram NK, Poddar P, Gupta N. Subcutaneous abdominal adipose tissue is associated with the metabolic syndrome in Asian Indians independent of intra-abdominal and total body fat. *Heart* 2010; **96**: 579–583.
48 Lear SA, Humphries KH, Kohli S, Chockalingam A, Frohlich JJ, Birmingham CL. Visceral adipose tissue accumulation differs according to ethnic background: results of the Multicultural Community Health Assessment Trial (M-CHAT). *Am J Clin Nutr* 2007; **86**: 353–359.
49 Smith SR, Lovejoy JC, Greenway F, Ryan D, deJonge L, de la Bretonne J *et al*. Contributions of total body fat, abdominal subcutaneous adipose tissue compartments, and visceral adipose tissue to the metabolic complications of obesity. *Metabolism* 2001; **50**: 425–435.
50 Okura T, Nakata Y, Yamabuki K, Tanaka K. Regional body composition changes exhibit opposing effects on coronary heart disease risk factors. *Arterioscler Thromb Vasc Biol* 2004; **24**: 923–929.
51 Markman B, Barton Jr FE. Anatomy of the subcutaneous tissue of the trunk and lower extremity. *Plast Reconstr Surg* 1987; **80**: 248–254.
52 Montani JP, Carroll JF, Dwyer TM, Antic V, Yang Z, Dulloo AG. Ectopic fat storage in heart, blood vessels and kidneys in the pathogenesis of cardiovascular diseases. *Int J Obes* 2004; **28** (Suppl 4): S58–S65.
53 Unger RH. Weapons of lean body mass destruction: the role of ectopic lipids in the metabolic syndrome. *Endocrinology* 2003; **144**: 5159–5165.
54 Barandier C, Montani JP, Yang Z. Mature adipocytes and perivascular adipose tissue stimulate vascular smooth muscle cell proliferation: effects of aging and obesity. *Am J Physiol Heart Circ Physiol* 2005; **289**: H1807–H1813.
55 Thalmann S, Meier CA. Local adipose tissue depots as cardiovascular risk factors. *Cardiovasc Res* 2007; **75**: 690–701.
56 Goodpaster BH, Thaete FL, Kelley DE. Thigh adipose tissue distribution is associated with insulin resistance in obesity and in type 2 diabetes mellitus. *Am J Clin Nutr* 2000; **71**: 885–892.
57 Gallagher D, Kuznia P, Heshka S, Albu J, Heymsfield SB, Goodpaster B *et al*. Adipose tissue in muscle: a novel depot similar in size to visceral adipose tissue. *Am J Clin Nutr* 2005; **81**: 903–910.
58 Manolopoulos KN, Karpe F, Frayn KN. Gluteofemoral body fat as a determinant of metabolic health. *Int J Obes* 2010; **34**: 949–959.
59 Frayn KN. Adipose tissue as a buffer for daily lipid flux. *Diabetologia* 2002; **45**: 1201–1210.
60 Danforth Jr E. Failure of adipocyte differentiation causes type II diabetes mellitus? *Nat Genet* 2000; **26**: 13.
61 Virtue S, Vidal-Puig A. Adipose tissue expandability, lipotoxicity and the metabolic syndrome–an allostatic perspective. *Biochim Biophys Acta* 2010; **1801**: 338–349.
62 Solinas G, Karin M. JNK1 and IKKbeta: molecular links between obesity and metabolic dysfunction. *FASEB J* 2010; **24**: 2596–2611.
63 Stern JS, Batchelor BR, Hollander N, Cohn CK, Hirsch J. Adipose-cell size and immunoreactive insulin levels in obese and normal-weight adults. *Lancet* 1972; **2**: 948–951.
64 Weyer C, Foley JE, Bogardus C, Tataranni PA, Pratley RE. Enlarged subcutaneous abdominal adipocyte size, but not obesity itself, predicts type II diabetes independent of insulin resistance. *Diabetologia* 2000; **43**: 1498–1506.
65 Hirsch J, Knittle JL. Cellularity of obese and nonobese human adipose tissue. *Fed Proc* 1970; **29**: 1516–1521.
66 Weyer C, Foley JE, Bogardus C, Tataranni PA, Pratley RE. Enlarged subcutaneous abdominal adipocyte size, but not obesity itself, predicts type II diabetes independent of insulin resistance. *Diabetologia* 2000; **43**: 1498–1506.
67 Lonn M, Mehlig K, Bengtsson C, Lissner L. Adipocyte size predicts incidence of type 2 diabetes in women (Swedish). *FASEB J* 2010; **24**: 326–331.
68 Jernås M, Palming J, Sjöholm K, Jennische E, Svensson PA, Gabrielsson BG *et al*. Separation of human adipocytes by size: hypertrophic fat cells display distinct gene expression. *FASEB J* 2006; **20**: 1540–1542.
69 Drolet R, Richard C, Sniderman AD, Mailloux J, Fortier M, Huot C *et al*. Hypertrophy and hyperplasia of abdominal adipose tissues in women. *Int J Obes* 2008; **32**: 283–291.
70 Tchoukalova YD, Koutsari C, Karpyak MV, Votruba SB, Wendland E, Jensen MD. Subcutaneous adipocyte size and body fat distribution. *Am J Clin Nutr* 2008; **87**: 56–63.
71 Spalding KL, Arner E, Westermark PO, Bernard S, Buchholz BA, Bergmann O *et al*. Dynamics of fat cell turnover in humans. *Nature* 2008; **453**: 783–787.
72 Arner E, Westermark PO, Spalding KL, Britton T, Rydén M, Frisén J *et al*. Adipocyte turnover: relevance to human adipose tissue morphology. *Diabetes* 2010; **59**: 105–109.
73 Gill T. Epidemiology and health impact of obesity: an Asia Pacific perspective. *Asia Pac J Clin Nutr* 2006; **15** (Suppl): 3–14.
74 Kurian AK, Cardarelli KM. Racial and ethnic differences in cardiovascular disease risk factors: a systematic review. *Ethn Dis* 2007; **17**: 143–152.
75 Raji A, Seely EW, Arky RA, Simonson DC. Body fat distribution and insulin resistance in healthy Asian Indians and Caucasians. *J Clin Endocrinol Metab* 2001; **86**: 5366–5371.
76 Chowdhury B, Lantz H, Sjostrom L. Computed tomography-determined body composition in relation to cardiovascular risk factors in Indian and matched Swedish males. *Metabolism* 1996; **45**: 634–644.

77 Park YW, Allison DB, Heymsfield SB, Gallagher D. Larger amounts of visceral adipose tissue in Asian Americans. *Obes Res* 2001; **9**: 381–387.
78 Hill JO, Sidney S, Lewis CE, Tolan K, Scherzinger AL, Stamm ER. Racial differences in amounts of visceral adipose tissue in young adults: the CARDIA (Coronary Artery Risk Development in Young Adults) study. *Am J Clin Nutr* 1999; **69**: 381–387.
79 Hoffman DJ, Wang Z, Gallagher D, Heymsfield SB. Comparison of visceral adipose tissue mass in adult African Americans and whites. *Obes Res* 2005; **13**: 66–74.
80 Despres JP, Couillard C, Gagnon J, Bergeron J, Leon AS, Rao DC *et al*. Race, visceral adipose tissue, plasma lipids, and lipoprotein lipase activity in men and women: the Health, Risk Factors, Exercise Training, and Genetics (HERITAGE) family study. *Arterioscler Thromb Vasc Biol* 2000; **20**: 1932–1938.
81 Lovejoy JC, Smith SR, Rood JC. Comparison of regional fat distribution and health risk factors in middle-aged white and African American women: the Healthy Transitions Study. *Obes Res* 2001; **9**: 10–16.
82 Misra A, Khurana L. Obesity-related non-communicable diseases: South Asians vs White Caucasians. *Int J Obes (Lond)* 2010. (e-pub ahead of print).
83 Lear SA, Humphries KH, Kohli S, Chockalingam A, Frohlich JJ, Birmingham CL. Visceral adipose tissue accumulation differs according to ethnic background: result of the Multicultural Community Health Assessment Trial (M-CHAT). *Am J Clin Nutr* 2007; **86**: 353–359.
84 Gautier JF, Milner MR, Elam E, Chen K, Ravussin E, Pratley RE. Visceral adipose tissue is not increased in Pima Indians compared with equally obese Caucasians and is not related to insulin action or secretion. *Diabetologia* 1999; **42**: 28–34.
85 Goel K, Misra A, Vikram NK, Poddar P, Gupta N. Subcutaneous abdominal adipose tissue is associated with the metabolic syndrome in Asian Indians independent of intra-abdominal and total body fat. *Heart* 2010; **96**: 579–583.
86 Misra A, Khurana L. Obesity and the metabolic syndrome in developing countries. *J Clin Endocrinol Metab* 2008; **93** (Suppl 1): S9–S30.
87 Kohli S, Sniderman AD, Tchernof A, Lear SA. Ethnic-Specific Differences in Abdominal Subcutaneous Adipose Tissue Compartments. *Obesity (Silver Spring* 2010. (e-pub ahead of print).
88 Sniderman AD, Bhopal R, Prabhakaran D, Sarrafzadegan N, Tchernof A. Why might South Asians be so susceptible to central obesity and its atherogenic consequences? The adipose tissue overflow hypothesis. *Int J Epidemiol* 2007; **36**: 220–225.
89 Yajnik CS, Lubree HG, Rege SS, Naik SS, Deshpande JA, Deshpande SS *et al*. Adiposity and hyperinsulinemia in Indians are present at birth. *J Clin Endocrinol Metab* 2002; **87**: 5575–5580.
90 Katzmarzyk PT, Bray GA, Greenway FL, Johnson WD, Newton Jr RL, Ravussin E *et al*. Racial differences in abdominal depot-specific adiposity in white and African American adults. *Am J Clin Nutr* 2010; **91**: 7–15.
91 Liska D, Dufour S, Zern TL, Taksali S, Calí AM, Dziura J *et al*. Interethnic differences in muscle, liver and abdominal fat partitioning in obese adolescents. *PLoS One* 2007; **2**: e569.
92 Smith LM, Yao-Borengasser A, Starks T, Tripputi M, Kern PA, Rasouli N. Insulin resistance in African-American and Caucasian women: differences in lipotoxicity, adipokines, and gene expression in adipose tissue and muscle. *J Clin Endocrinol Metab* 2010; **95**: 4441–4448.
93 Guerrero R, Vega GL, Grundy SM, Browning JD. Ethnic differences in hepatic steatosis: an insulin resistance paradox? *Hepatology* 2009; **49**: 791–801.
94 Lawrence JC, Newcomer BR, Buchthal SD, Sirikul B, Oster RA, Hunter GR *et al*. Relationship of intramyocellular lipid to insulin sensitivity may differ with ethnicity in healthy girls and women. *Obesity (Silver Spring* 2010. (e-pub ahead of print).
95 Yim JE, Heshka S, Albu JB, Heymsfield S, Gallagher D. Femoral-gluteal subcutaneous and intermuscular adipose tissues have independent and opposing relationships with CVD risk. *J Appl Physiol* 2008; **104**: 700–707.
96 Petersen KF, Dufour S, Feng J, Befroy D, Dziura J, Dalla Man C *et al*. Increased prevalence of insulin resistance and nonalcoholic fatty liver disease in Asian-Indian men. *Proc Natl Acad Sci (USA)* 2006; **103**: 18273–18277.