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# Adiposity in children and adolescents: correlates and clinical consequences of fat stored in specific body depots

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## Summary

The 2011 Pennington Biomedical Research Center's Scientific Symposium focused on adiposity in children and adolescents. The symposium was attended by 15 speakers and other invited experts. The specific objectives of the symposium were to (i) integrate the latest published and unpublished findings on the laboratory and clinical assessment of depot-specific adiposity in children and adolescents, (ii) understand the variation in depot-specific adiposity and related health outcomes associated with age, sex, maturation, ethnicity and other factors and (iii) identify opportunities for incorporating new markers of abdominal obesity into clinical practice guidelines for obesity in children and adolescents. This symposium provided an overview of important new advances in the field and identified directions for future research. The long-term goal of the symposium is to aid in the early identification of children and adolescents who are at increased health risk because of obesity and obesity-related conditions.

**Keywords:** Abdominal obesity, brown fat, imaging, visceral fat.

## Introduction

Pediatric obesity has become one of the greatest public health challenges of the 21st century, and the identification of children who are at risk of health problems because of their obesity is a priority for modern health care. A major public health goal in the USA is to achieve health equity, eliminate disparities and improve the health of all groups by 2020 (1). A total of 51% and 64% of the ethnic gap in life expectancy between white and African-American men and women, respectively, can be explained by differ-

ences in mortality rates from diabetes, cardiovascular disease (CVD) and cancer, all of which are impacted by obesity (2). The degree to which these differences can be explained by sex and ethnic differences observed in childhood remains to be determined.

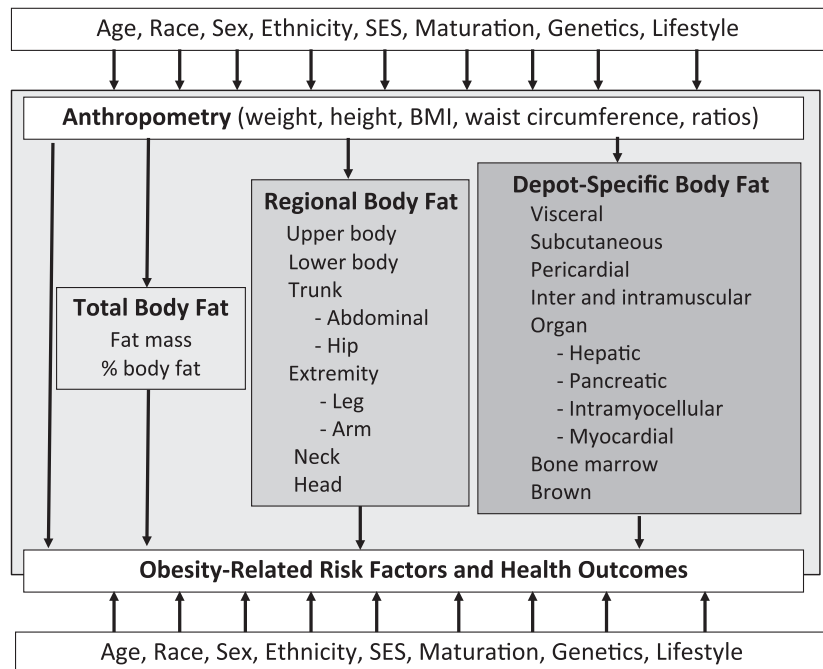
Studies among adults have shown that body fat stored in different depots (intra-abdominal, liver, etc.) may confer different health risks (3,4). Children also vary greatly in fat distribution, and it is evident that there are sex and ethnic differences in obesity prevalence (5). However, the degree to which there are

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**Figure 1** Conceptual model and main topics of discussion at the 2011 Pennington Biomedical Research Center symposium on adiposity in children and adolescents.



age, sex and ethnic differences in both the storage and health consequences of adipose tissue stored in different locations is not well understood in children and adolescents.

Studies incorporating advanced imaging techniques such as magnetic resonance imaging (MRI) to quantify depot-specific body fat in children are increasingly available. Abdominal fat measured by MRI is linked to metabolic and inflammatory complications in both male and female adolescents (6). Imaging technology will greatly enhance our ability to understand the health risks associated with body fat stored in different locations, and any differences that might be related to sex and ethnicity (7–10).

On 5–6 December 2011, the Pennington Biomedical Research Center convened a scientific symposium entitled 'Adiposity in Children and Adolescents: Correlates and Consequences of Fat Stored in Specific Body Depots' in Baton Rouge, LA, USA. The symposium was attended by 15 speakers and other invited experts. Figure 1 presents a model that illustrates the main topics discussed at the symposium. The specific objectives of the symposium were to (i) integrate the latest published and unpublished findings on the laboratory and clinical assessment of depot-specific adiposity in children and adolescents, (ii) understand the variation in depot-specific adiposity and related health outcomes associated with age, sex, maturation, ethnicity and other factors, and (iii) identify opportunities for incorporating new markers of abdominal obesity into clinical practice guidelines for obesity in children and adolescents. It is hoped

that a long-range outcome of the symposium will be to inform the development of clinical guidelines that will aid in the early identification of health risks in children so that corrective action may be taken early, thereby reducing the health burden associated with obesity.

## Frontiers in pediatric body composition imaging techniques

*In vivo* body composition analysis can be used in children and adolescents to assess growth and development as well as (i) related functions (e.g. metabolism), (ii) metabolic function and risks (e.g. insulin resistance-associated with childhood overweight) and (iii) monitoring in weight loss studies (11). As to developmental aspects, body composition analysis has revealed that the so-called adiposity rebound (i.e. an increase in body mass index [BMI] at age 5–7 years) is due to an age-dependent increase in fat-free mass (FFM) rather than fat mass (FM) (12). This suggests that preventive measures at time of the adiposity rebound may interfere with the normal development of FFM and may be of no advantage to children. With respect to understanding metabolic risks in children, visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT) as well as the ratio between VAT and total adipose tissue (TAT; both determined by whole-body MRI) is low in children compared to adults (13). Up to puberty, there is no sexual dimorphism in the VAT/

TAT ratio, which then markedly increases with age in males with only moderate increases in females. However, despite its low amounts there is an association between VAT and a biomarker of insulin resistance (i.e. the HOMA (Homeostatic model assessment) index) in children and adolescents (13,14). With respect to monitoring, TAT and VAT decrease with dietary-induced weight loss in overweight children, and these data resemble results obtained in obese adults (15). In both groups, the weight loss-associated decreases in VAT are closely related to baseline VAT, i.e. the higher VAT before weight loss, the higher the decrease in VAT with weight loss. These examples serve to highlight important applications of carefully phenotyping body composition in children.

### Pediatric obesity: phenotyping by magnetic resonance methods

Magnetic resonance spectroscopy (MRS) and MRI are non-invasive methods that have been increasingly used to study human body composition and its related physiological and pathological conditions. MRS and water fat separation imaging can be used to quantify the fat content of liver, skeletal muscle, pancreas and other organs (16–18). Without concerns of radiation, MRI and MRS methods are ideal for characterizing key aspects of pediatric obesity including its phenotype, severity and treatment effects *in vivo*. Recent advances in MRI and MRS make it possible to quantify total body and regional adiposity, to map adipose tissue distribution and to evaluate ectopic fat in children. Adipose tissue is not a homogenous depot but rather distinct adipose tissue components with different metabolic activities. New knowledge has been gained with measurement of sub-regions of potentially metabolically different adipose tissue depots such as visceral adipose tissue (i.e. omental, mesenteric adipose tissue and extra-peritoneal adipose tissue), intermuscular adipose tissue and bone marrow adipose tissue (17,19).

Whole-body axial, coronal or three-dimensional images can be rapidly acquired on most clinical MRI scanners (20). The images can then be segmented into subcutaneous, visceral and intermuscular adipose in software packages by combining automatic algorithms and human judgment (21). Optimizing and improving accuracy of existing MRI measurement methods can unveil scientific truth that would otherwise be covered. Specific pediatric studies of errors related to slice gap and single-slice location have been carried out recently (10,22,23). These data allow investigators to design

the most cost-effective study based on subject population and adipose tissue depots of interest. However, single-slice imaging is not accurate in measuring VAT or SAT changes during weight loss in adults (24), and this may imply the possibility that single-slice imaging may not be an accurate measurement of VAT and SAT changes in longitudinal studies in children.

While most MRI methods were initially developed in adults, it is important to standardize the protocols and test for reproducibility in children for certain age groups when necessary (23). Protocol selection is based on factors such as subject age, cost, availability and post-processing complexity. Particular attention should be directed towards identification of landmarks in growth studies. Comparing to adult MRI, cardiac synchronization and respiratory gating are more important for pediatric MRI. Ultra-fast imaging methods have advantages in minimizing scanning time in children as long as signal-to-noise ratios are adequate. Effective motion artefact reduction technique will be extremely important for scanning children below 4 years old (25). Hardware improvements such as special coil design might be needed for adequate resolution of scans in young children especially for whole-body scan.

MRI and MRS, as promising non-invasive technology, are increasingly available for phenotyping pediatric adiposity and these technologies open new opportunities for metabolism and nutritional research. The future directions include (i) expanding the application of MRI methods developed in adults to the pediatric population; (ii) validating MRI methods for specific pediatric populations; (iii) developing new MRI methods, especially those that can be applied to young children; and (iv) using MRI as a reference method to validate other adiposity measurement technology (26,27).

### Phenotyping adiposity by MRI/MRS in neonates and infants

The development of chronic metabolic disorders such as insulin resistance and type 2 diabetes are closely linked to central obesity, with deposition of ectopic fat, including liver, skeletal muscle, myocardium and pancreas, being implicated in their pathophysiology. Furthermore, in recent years, we have seen an increasing number of studies showing the importance of early life events on the susceptibility of a subject to develop these life-threatening conditions. And with the advent of the epigenomic era, the need to unravel the mechanisms that underlie the impact of early life events on the development

of later-life diseases has accelerated. Although the mechanisms by which central obesity accumulates are not fully understood, the development and application of non-invasive methodology, together with advances in molecular biology, are beginning to shed light on this problem (28,29). In turn, this is leading to the development of a new research paradigm, where modulation of ectopic fat accumulation and adipocyte-derived factors play a pivotal role in the development of novel therapeutic strategies.

Humans are quite unique among terrestrial animals in being born with relatively large levels of adipose tissue. However, significant differences in adiposity are known to occur between newborns, with maternal BMI, ethnicity, gestational age and sex identified as potential modulatory factors (30–32). *In vivo* and post-mortem cross-sectional studies have further shown that total adiposity in neonates can also be modulated by nutritional intake, although again the extent and form has not been fully discerned. This is partly because of the methodologies utilized to assess body fat content, most of which do not allow differentiation of different body fat compartments (28). Cross-sectional studies have also shown that significant changes in body composition take place during infancy, with infants increasing their FM up to three times their original level in the first 4 months of life (29). Our understanding of the variation in body fat distribution observed in infants is, however, relatively sparse because of the lack of full body composition data in these cohorts, especially related to central obesity and ectopic fat depots.

MRI and MRS have been applied to quantitate body fat content and distribution in order to enhance our understanding of the key factors that may influence neonatal body adiposity (28,29). At Imperial College London, where well over 400 newborn infants and neonates have been scanned, researchers have reported that healthy newborn babies (term) can carry between 0.3–1.7 L of fat and that there is a strong positive correlation between birth weight and total FM ( $r=0.78$ ,  $P<0.0001$ ), but a much weaker correlation with VAT ( $r=0.14$ ,  $P<0.004$ ) and liver fat ( $r=0.17$ ,  $P<0.007$ ) (28–30,32). Significant sex differences in total FM (in absolute terms as well as a percentage of body weight) can be observed. As with adults, at birth, females showed elevated total FM, mainly subcutaneous fat. No significant differences in VAT and liver fat were observed between males and females (31). Significant ethnic differences were also observed, independent of sex. South Asian

newborns carry increased percentage body fat compared to Caucasian and Afro-Caribbean babies. Moreover, they showed a significant difference in fat distribution, with increased VAT (31). No differences in liver fat were observed between these three ethnic groups. In Caucasian babies, post-natal growth appeared to have no effect on relative percentage body fat, but there was a small yet significant reduction in the percentage VAT. Liver fat content, however, appeared to increase with post-natal growth. Interestingly, a positive correlation can be observed between percentage body fat and rate of growth, suggesting that accelerated growth may lead to increased body adiposity (29,30,32).

Maternal BMI was also shown to be an important contributor to the total and relative levels of body fat of the newborn, with strong positive correlation between maternal BMI and body and liver fat (33). Finally, some of the differences in body fat distribution observed in preterm babies (at term equivalent) can still be observed in the adult preterm, principally elevated liver fat. Clearly, the role of hepatic fat in the development of insulin resistance and type 2 diabetes in later life needs to be further validated in larger cohorts and the potential mechanism that underpins it elucidated.

### Brown adipose tissue in children and teenagers

Positron emission and computed tomography (PET/CT) is the current preferred modality to image metabolically active brown adipose tissue (BAT). It has been used in adult cohorts; however, the number of BAT studies in children is limited. This is due to the risk of ionizing radiation and radionuclide tracer usage by PET/CT and the ethical restriction of performing such exams on healthy children. However, BAT has a higher prevalence in pediatric populations compared to adults. Young cohorts thus represent an ideal population to examine the physiology of human BAT. MRI represents the most promising modality to overcome the limitations of PET/CT. The development of sensitive MRI techniques to identify and quantify BAT without the use of exogenous agents is critically needed. We summarize here findings of BAT associations with muscle volume, puberty, adiposity and disease states from retrospective PET/CT data acquired at Children's Hospital Los Angeles (CHLA). We then briefly survey potential MRI-based signatures for assessing BAT *in vivo*.

BAT was believed to be present in all neonates and was thought to be lost after infancy. However,



significant amounts of metabolically active BAT have been observed in pediatric patients (34,35). Higher prevalence and greater amounts of BAT has also been observed in adolescence compared to childhood (36,37). At CHLA, it has been observed that <20% of studies in pre-pubertal girls or boys exhibited metabolically active BAT. In pubertal teenagers, however, the proportion is >75%. Greater changes in BAT volumes have also been documented during the later Tanner stages of puberty than during the early phases of sexual development. These changes were substantially higher in boys than in girls. Young patients with metabolically active BAT also have significantly greater muscle volume (about 50% greater neck and 33% greater gluteal) than patients of similar age and BMI with no metabolically active BAT (36). This finding was present in the axial and appendicular skeletons.

The depiction of metabolically active BAT by PET/CT is dependent on many physiologic and technical factors including age, sex, body composition, tracer dose, anesthesia, acquisition parameters, and season and temperature during examinations (38–43). However, no association has been noted between BAT depiction and the presence of metastases. In 62 studies involving 30 pediatric patients, approximately 10% of the exams at diagnosis exhibited metabolically active BAT, while a significantly higher proportion (80%) of follow-up exams after therapeutic treatment of metastases displayed BAT when there was no longer evidence of disease (44). In a longitudinal assessment of 30 pediatric oncology patients undergoing medical treatment, it has been investigated whether depiction of BAT on follow-up PET/CT scans was associated with changes (gains) in abdominal SAT and VAT volumes during the chemotherapy treatment period (45). It was found that patients who exhibited BAT at follow-up had significantly lower gains in weight, SAT and VAT, than those who were negative at baseline and remained negative for BAT depiction at follow-up.

The use of MRI and MRS to study BAT in rodents was previously investigated in the 1990s (46,47). Unlike PET/CT where the uptake of a tracer was needed to locate BAT, one common theme among the MR-based works was the use of only morphological differences between BAT and white adipose tissue (WAT) for identification and signal contrast. Specifically, the greater vascularity, mitochondria content and intracellular water of BAT have been exploited. Using chemical-shift water-fat MRI that can decompose lean (water-based) and fatty (lipid-based) signals, Hu *et al.* demonstrated in mice the

feasibility of BAT imaging based on the fat fraction metric (48). Whereas WAT is predominantly composed of lipids and is thus characterized by a fat fraction >90%, interscapular BAT was shown to occupy a much broader and lower fat fraction range. In another study, Branca *et al.* reported a spectroscopy technique utilizing intermolecular zero-quantum coherence (iZQC) transitions between water and fat protons to differentiate BAT from WAT in mice (49). The approach exploited the fact that in BAT, intracellular water and fat are in close physical vicinity to each other, and thus gives rise to distinctive iZQC signal peaks. On the contrary, in WAT, water and fat are separated by greater distances and thus such iZQC peaks were not observed. Furthermore, the authors demonstrated that the amplitude of the signal peaks were greater in thermogenically active young mice than in old or obese mice. In another study by Hamilton *et al.*, the authors utilized conventional high-resolution proton MRS to first confirm the finding that BAT has a lower fat fraction than WAT (50). The investigators then observed that the  $T_1$  relaxation time of the water component in BAT was significantly reduced by nearly twofold from that in WAT, and reported that BAT was more saturated than WAT, consistent with previous findings in adult humans (51).

Magnetic resonance is the most appropriate modality to address the shortcomings of PET/CT. It involves no ionizing radiation and requires no radio-nuclide tracer. It can be repeated multiple times with minimal risk in healthy volunteers and is applicable to large study populations, including children. MRI offers immense flexibility in signal contrast. Results from Hu, Branca and Hamilton represent new potential from the fact that none of the described MR-based signals of BAT depend on the tissue's metabolic functions, but rather its intrinsic cellular morphology. Validation and application of these methods to humans remains an area of future research. Many additional distinctive features of BAT are known but have not yet been explored by MRI and MRS. For example, BAT's immense vasculature lends itself to MRI perfusion techniques such as arterial-spin-labelling that can quantify local blood flow. MR techniques that are sensitive to fluctuating levels of oxy- and deoxy-haemoglobin in blood are being evaluated in BAT. Signal contrasts between BAT and WAT, such as diffusion, temperature and targeted molecular imaging of the mitochondria, have not been explored. Lastly, recent advances in fusion PET/MR also holds promise as a complementary tool for BAT imaging.

## Age, sex and ethnic variation in depot-specific adiposity

### Age- and maturity-associated variation in body fat distribution

Chronological age (CA) is an indicator of sidereal time whereas the body has its own clock that varies among and within individuals. Children increase in size and change in proportions and body composition with the passage of time. Maturation refers to progress towards the mature state, which varies among bodily systems. It is often viewed in terms of status (maturity status at a given CA), and timing (CA at which specific maturity events occur) (52).

Standard indicators of maturity status include skeletal age, which can be used from childhood through adolescence, and pubertal status, which is limited to the pubertal years. Both are considered invasive. Many current studies use self-assessments of pubertal status. Indicators of maturational timing include ages at peak height velocity (PHV) and at menarche. Both require longitudinal data for estimation in individuals. Recalled ages at menarche have major limitations with youth (52). Two non-invasive measures are increasingly being used. Percentage of predicted adult (mature) height attained at the time of study is an indicator of status (53). Predicted time before PHV (maturity offset) and in turn predicted age at PHV is an indicator of timing (54). Both non-invasive methods require cross-validation (55).

Fat distribution refers to regional variation in the accumulation of adipose tissue in the body. Initial focus was on global male (android) and female (gynoid) patterns of distribution and then contrasts of subcutaneous tissue on the trunk vs. the extremities. A common descriptor was the term pattern, android vs gynoid fat pattern or a truncal vs. extremity pattern. With advances in technology (CT, MRI), attention shifted to abdominal adiposity, specifically visceral vs subcutaneous. With widespread availability of dual-energy X-ray absorptiometry (DXA), trunk and extremity distribution of adipose tissue has received more attention (56,57).

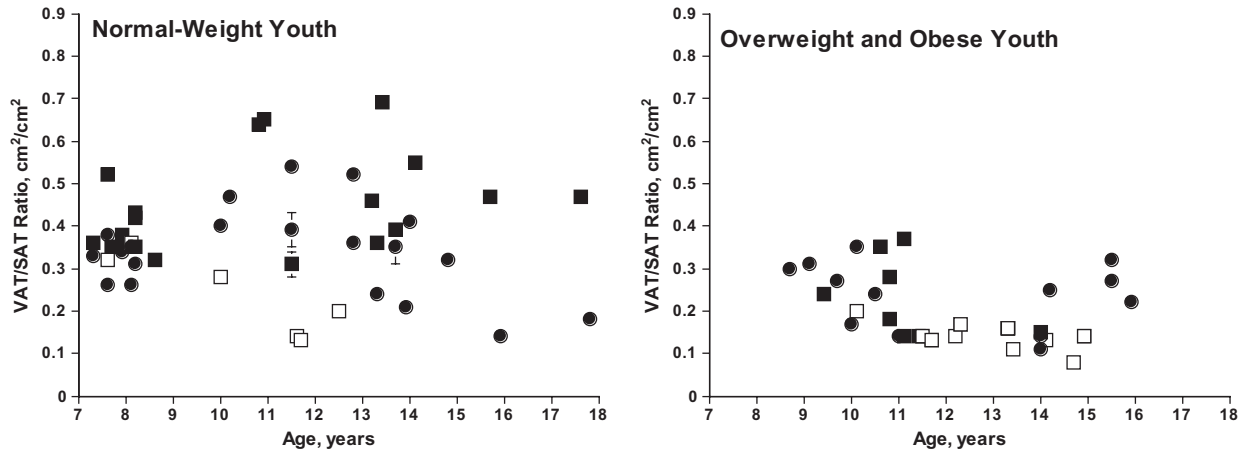
Available data on fat distribution during childhood and adolescence follow, in part, the development of technology and the increased emphasis on the metabolic complications of obesity. Subcutaneous fat distribution, as estimated with ratios of skin-folds measured on the trunk to those measured on the extremities, changes with age and differences between the sexes emerge during the growth spurt and sexual maturation (56,58,59). Ratios of trunk to extremity adiposity measured via DXA show a similar

trend (60,61). The ratio of abdominal VAT and SAT appears to show a similar trend, although data for normal-weight children and adolescents are less extensive than for overweight and obese youth. With increased emphasis on abdominal obesity and associated metabolic complications, waist circumference (WC) is increasingly used as an indicator of abdominal adiposity. It is often expressed relative to height (WC/Ht ratio). Allowing for discussion of the most appropriate level for measurement of WC in youth, data addressing age-, sex- and maturity-associated variation in the WC/Ht ratio and other anthropometric measurements are not yet extensive.

Fatness *per se* and relative fat distribution (ratio of trunk to extremity skin-folds) in late childhood and adolescence differ among individuals of contrasting maturity status. Children and adolescents advanced in maturity status compared to CA peers tend to be fatter and to have proportionally more subcutaneous fat on the trunk compared to the extremities (52,62). Some data indicate persistence of the trend into young adulthood and adulthood (63–66). Longitudinal studies of fat distribution are limited. Moreover, changes in individual skin-folds are variable during the growth spurt and specifically relative to the timing of PHV, more so in boys than in girls (58). Such variation may influence age-associated trends.

Pubertal status, clinically and/or self-assessed, is the most commonly used maturity indicator in studies dealing with maturity effects on fat distribution. Youth are typically grouped by stage of puberty and more often combined pubertal stages, so that several CAs are represented within a stage; the effect of CA *per se* is generally controlled statistically. Allowing for this limitation, major changes in fat distribution based on DXA occur during puberty, specifically late puberty (60,61). There is a need for studies that include sufficient numbers of children of the same CA who vary in stage of puberty.

Studies of abdominal visceral and subcutaneous adipose and fat distribution based on CT and MRI tend to have relatively small sample sizes compared to those using anthropometry. Samples are generally combined across age groups and in some instances combine males and females and/or youth of different ethnic groups. Stage of puberty is often described but not systematically analyzed and other maturity indicators are not used. Moreover, recent data with CT and MRI are seemingly more focused on obese youth. Ratios of cross-sectional areas of abdominal VAT to SAT were derived from 27 studies of normal-weight and overweight/obese youth (15 based on CT, 12 on MRI; 13 at umbilical level, 13 at L4-L5, one at minimum waist) (67–93) (Fig. 2). Among



**Figure 2** Abdominal visceral to subcutaneous fat ratios based on cross-sectional scans in samples of girls and boys from 27 published studies described in the text and reviewed by R.M. Malina at the 2011 Pennington Biomedical Research Center symposium on adiposity in children and adolescents. Filled squares = males; filled circles = females; open squares = sexes combined.

normal-weight youth, there is no clear trend with age and sex in relative fat distribution during childhood into early adolescence. Subsequently, males have, on average, proportionally more visceral adiposity in later adolescence. There does not appear to be a clear trend in overweight and obese youth, indicating that excess adiposity may attenuate age and maturity differences.

Advances in imaging technologies have permitted the quantification of ectopic fat deposition in the liver (non-alcoholic fatty liver disease, NAFLD), heart and other organs, and in skeletal muscle (intramyocellular fat). Such data for children and adolescents are quite rare thus far.

### Sexual dimorphism in body composition during childhood

Sexual dimorphism in body composition is apparent in both total adiposity and its regional distribution, as well as lean mass and physique. Several studies have now demonstrated that body composition dimorphism is apparent at birth, with the lower average birth weight of females attributable to lower lean mass (94,95). Females also appear to have greater adiposity and a more central fat distribution at birth (96). During development, sexual dimorphism in total body size, lean mass and adiposity remains modest during childhood but increases substantially from puberty onwards. Females enter puberty earlier than males, and achieve lower final stature and lean mass; however, they gain substantially greater peripheral adiposity over the same period (97). Males enter puberty later and achieve greater final stature

and lean mass, with less total but similar or higher central adiposity (97). These contrasting pubertal growth patterns lead to the well-established sexual dimorphism characteristic of all documented adult populations, with males having greater stature and upper body lean mass, and females having substantially greater total and peripheral but not central fat (98,99).

Following similar method-specific work (100–106), new cross-sectional reference data for total and regional adiposity, obtained using the four component model, DXA, air displacement plethysmography, bioelectrical impedance analysis and anthropometry (body circumferences and skin-folds) have recently been obtained in a sample of 532 healthy individuals from the UK aged 4 to 23 years (107). These data are the basis for children's body composition growth charts, and enable age- and sex-specific standard deviation scores of total and regional adiposity to be calculated. The data also characterize in greater detail the age profile of adipose tissue deposition in each sex. Sex differences in arm and torso skin-fold thickness are not significant in this sample, indicating that the lower body is the primary site of adiposity dimorphism. This is supported by data on leg fat obtained by DXA.

Ethnic differences have been reported in the magnitude of sexual dimorphism for whole-body adiposity in adolescence (102), and for body shape in adults (108). A recent literature review of data from young adulthood indicates that sexual dimorphism in both lean mass and adiposity varies in relation to mid-sex adiposity (male–female average), suggesting that population energy availability influences the relative



allocation of energy to lean tissue vs adiposity in males vs females, and that body composition dimorphism has a plastic component (109).

Longitudinal studies likewise suggest that variable rates of tissue deposition in adolescence can be predicted by growth rates during infancy (110), suggesting that the magnitude of adiposity dimorphism is sensitive to experience during early life. Birth weight appears most consistently associated with subsequent lean mass rather than FM; however, the ratio of fat to lean mass in childhood was found to increase more strongly in relation to ponderal index (weight/length<sup>3</sup>) at birth in females compared to males (111). Similar findings are emerging from studies of infant growth but few data are currently available.

### Ethnic differences in body fat distribution

Despite the well-known links between obesity and metabolic diseases, and the increased rate of obesity and metabolic diseases among ethnic minority groups, the mechanisms of these observations remain elusive. Several putative explanations exist for why fat affects metabolic health and how this might vary across different ethnic groups. One such theory is based on the anatomic location of fat deposition and ectopic fat accumulation in critical organs like muscle and liver. Specifically, current literature suggests that visceral, liver and skeletal fat accumulation affect organ function and contributes to the development of insulin resistance, fatty liver and the metabolic syndrome. However, even in individuals matched for body fat and fat distribution, significant differences can exist in metabolic outcomes. In addition, ethnic differences in fat distribution and ectopic fat deposition do not fully explain ethnic disparities in metabolic diseases.

VAT has long been hypothesized to be one of the major factors linking obesity and disease risk. However, this hypothesis leads to an ethnic paradox (112) because African-Americans, who are at increased risk for obesity-related diseases, especially CVD, have lower VAT on average beginning early in life (80,81). More recent studies have also shown that ectopic fat deposition varies by ethnicity in the same way as VAT. Studies consistently show that Hispanics have a much higher prevalence of fatty liver disease than African-Americans, also beginning early in life (113,114). Part of this ethnic difference is driven by a genetic contribution from PNPLA3 (115), a single nucleotide polymorphism that is more prevalent in Hispanics than African-Americans (115), and

influences greater liver fat in Hispanics beginning early in life (116), in part driven by higher sugar consumption (117). Pancreatic fat fraction is also higher in Hispanics than African-Americans, and the magnitude of this difference increases with age (118). In young obese individuals, pancreatic fat is related to visceral and liver fat but does not appear to be related to insulin resistance or beta-cell function (118). Thus, collectively, these studies show that African-Americans have lower visceral and ectopic fat deposition than Hispanics. This finding is in conflict with the hypothesis that greater visceral and ectopic fat drive increased risk of metabolic diseases since both these ethnic groups tend to have similarly high risk of metabolic diseases despite the clear difference in fat pattern.

There is also some evidence to suggest that ethnic differences in body fat pattern and accumulation may result from fundamental differences in adipose tissue biology and that adipose tissue biology itself drives metabolic disease risk. The increase in body fat content with obesity can occur by either an increase in adipocyte cell size or number, or by the spillover of triglycerides to ectopic tissues. When adipocyte cell size increases with progressing obesity, it is an indication of the inability of adipocytes to expand in number to accommodate the extra triglyceride accumulation. Larger adipocytes have also been shown to be associated with more lipid deposition in visceral and hepatic tissues (not muscle), and this may contribute to insulin resistance (119). Furthermore, it is now also evident that adipose tissue can become infiltrated with macrophages (120,121) and this inflammatory profile drives metabolic risk. In a previous study among obese young minority adults (Hispanic and African-American), we found that approximately 40% of subjects had subcutaneous abdominal adipose tissue with crown-like structures, indicating inflammation, whereas approximately 60% of subjects had no signs of adipose tissue inflammation (122). Despite the two groups being identical for overall obesity and subcutaneous abdominal adipose tissue volume, those with inflamed adipose tissue had approximately 30% greater VAT and 41% greater liver fat; 53% greater fasting insulin and 23% lower beta-cell function; and 22% higher tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ). Given these observations, the disparities in metabolic diseases among obese minority individuals may be explained by the degree of chronic low-grade inflammation of adipose tissue. Therefore, targeting adipose tissue inflammation has become an important new strategy in treating the metabolic conditions typically associated with obesity.

## Health consequences of body fat stored in specific compartments

### Early life influences on infant body composition and later outcomes

It is well known that rapid infant growth is an early indicator of later obesity and elevated adiposity (123,124), but at the same time, robust post-natal weight gain is necessary to achieve appropriate developmental goals, particularly in preterm and small for gestational age infants (125). Our current understanding of optimal rates of infant growth that balance these competing risks is itself in its infancy. To date, infant growth has been measured using either body weight or weight relative to length. However, body weight and even relative weight are non-specific indicators and include rapidly changing proportions of fat and lean mass in early infancy. The Minnesota Infant Nutrition, Neurodevelopment, and Obesity study (MINNOWS) is aimed at examining (i) the relationship between maternal obesity and infant growth and body composition and the possible mediating factors including differences in breast milk content between 2 weeks and 3 months of age, and (ii) the relationship of infant adipose tissue and lean mass gains in preterm infants to their neurobehavioral development in later infancy and early childhood. Body composition is measured using air displacement plethysmography, and visual evoked potentials are used to assess memory formation and processing time. Maternal self-reported data on infant sleep and feeding are also collected.

Although previous work has shown that maternal obesity is associated with elevated neonatal adiposity (126) and later obesity (127,128), few studies have examined early post-natal FM and FFM changes in offspring of obese and non-obese mothers. Data from MINNOWS suggests that as maternal BMI increases, the rate of early infant growth declines: increases in weight, length, FM and FFM from 2 weeks to 3 months were all significantly lower in overweight and obese mothers than normal-weight mothers (129). These differences were not due to regression to the mean, as they were conditional on the starting value and adjusted for the correlation between the two time points. Decelerated growth in infants of diabetic mothers has been previously reported (130), and a small number of previous studies in non-diabetic women have also found that despite being heavier at birth, by 3 months of age, infants of obese and overweight mothers are either smaller, or are no different in size, compared to normal-weight mothers (131–133). Possible mecha-

nisms explaining this decelerated growth are under investigation, including differences in infant-feeding patterns and breast milk composition. Overweight mothers are less likely to initiate breastfeeding and cease breastfeeding earlier than normal-weight mothers (134,135). Because some studies (but not all) have shown formula-fed infants tend to have lower body weight up to 6 months of age than exclusively breast-fed infants, this may explain these results, although the findings remained significant after adjusting for infant-feeding type. Interestingly, we have recently found that maternal BMI is associated with breast milk leptin concentrations, which are in turn associated with decreased weight gain from birth to 1 month of age (136). In addition, higher concentrations of insulin, interleukin-6 and TNF- $\alpha$ , all of which would be expected to be elevated in the circulation of obese women, were associated with lower infant FM, FFM and weight gain from birth to 1 month (136).

Preterm infants have elevated adiposity when compared to term-equivalent counterparts at hospital discharge (137), but much less is known about nutritional determinants of preterm body composition and long term outcomes. We have shown that the greater relative adiposity of preterm infants at discharge is due to lower FFM, as compared to term infants at the same post-conceptual age (138). Air displacement plethysmography is a non-invasive method that holds potential for monitoring preterm infant body composition during the hospital stay to optimize nutrition and attain the American Academy of Pediatrics' goal of achieving preterm infant body composition similar to that of the foetus *in utero*. Using this method, some authors are currently gathering body composition reference data for infants 30–36 weeks gestation to aid in this endeavour (139). These reference charts will be helpful in assessing the degree of catch-up growth in FM and FFM during the hospital stay, as they relate to cognitive and other health outcomes. A retrospective analysis of very low birth weight preterm infants indicated that lower recumbent length after discharge independently predicted poorer Bayley Developmental Scale cognitive scores at 24 months, independent of infant weight (140). Current work is following up on this finding to assess the relationship between the rate of infant FM and FFM change and cognitive development using visual evoked potential data. Preliminary results suggest that speed of processing of visual stimuli measured at 4 months corrected age is faster among infants with greater gains in FFM after discharge than in infants with slower gains (141). Continued assessment of the benefits and risks

associated with rapid growth is particularly important for preterm infants, for whom early catch-up growth is the norm.

### Total and trunk fat in adolescence and future health outcomes

Although obesity in adulthood is a well-documented risk factor for both type 2 diabetes and CVD, it remains unclear whether a longer history of relative overweight, starting earlier in life, poses an additional risk. It has long been recognized that there are 'critical periods' during human development when exposure to specific environmental stimuli are required in order to elicit the normal development of particular anatomical structures or their normal functioning. Traditionally, cardiovascular and metabolic diseases have been considered to be the result of behavioural risk factors in adulthood interacting with genetic predisposition to disease. Recently, this paradigm has been questioned by findings that suggest (i) factors in prenatal and early post-natal life play an important role in the aetiology of disease, (ii) early age at adiposity rebound (the nadir of BMI and fat occurring ~6 years of age) affects adult obesity and (iii) the timing, magnitude and duration of adolescent growth and maturation are associated with critical body composition changes, including the normal acquisition of body fat and fat patterning. To address these questions, long-term longitudinal studies of childhood growth and development coupled with long-term follow-up in adulthood are required. In a study of the Israeli Army Medical Core, Tirosh *et al.* (142) found that elevated BMI in adolescence constituted a substantial risk factor for obesity-related disorders in midlife. While BMI is a useful tool in epidemiological studies, its inability to distinguish FM from FFM in individuals being tracked over time is problematic.

Two ongoing longitudinal studies in Saskatchewan are uniquely situated to address the relationship between adolescent development of fat and subsequent adult disease (143,144). The first study, the Saskatchewan Growth and Development Study (SGDS) (144), was initiated in 1963 with the recruitment of a pure longitudinal sample of 200 seven-year-old boys and later with a mixed longitudinal sample of one hundred 7–14-year-old girls. SGDS participants were evaluated on a number of physiological and growth parameters on a yearly basis between 1964 and 1973 and then again in 1980, 1999 and 2009. In 2009, participants were approximately 48 to 50 years of age; the age where clinical manifestations of CVD and type 2 diabetes are seen more frequently. This dataset thus provides a unique

opportunity to prospectively study the relationships among childhood body composition, physical activity and physical fitness development to health indicators in adulthood, specifically the development of factors underlying the metabolic syndrome. In 1991, a new longitudinal study of childhood growth was initiated, namely the University of Saskatchewan's Pediatric Bone Mineral Accrual Study (PBMAS) (143). Between 1991 and 1993, two hundred and fifty-nine 8–15-year-old boys and girls were recruited into a mixed longitudinal study investigating bone mineral accrual and other body composition development patterns. Subjects were annually assessed between 1991 and 1998 and then again from 2002 to 2011.

At PHV, 94% of the SGDS sample had BMI within a normal range; however, in adulthood (40 years) only 36% remained normal weight, the majority being overweight (145). When using adulthood (40 years) groupings of normal weight ( $\text{BMI} < 25 \text{ kg m}^{-2}$ ), overweight ( $\text{BMI} 25\text{--}29 \text{ kg m}^{-2}$ ) and obese ( $\text{BMI} \geq 30 \text{ kg m}^{-2}$ ) and plotting childhood BMI development by age, it was found that all adult weight status groups had average BMI's below the 85th BMI for age percentiles during childhood. However, age-grouped analysis of variance indicated that average BMIs of the SGDS obese adults were significantly ( $P < 0.05$ ) higher than the other groups from 7–16 years of age. A similar analysis was used to describe the trajectory of growth of total FM in the PBMAS participants. Average heights and body mass approximated the 50th percentile at all CAs in both sexes. The vast majority were classified as normal weight. Adult values (25 to 30 years) of BMI were used to construct weight groupings (normal and overweight). These adult weight groupings were then used to distinguish childhood growth patterns between groups. In males, it was found that the normal-weight adults had significantly less total body FM percentage from –4 to –2 years from PHV and +5 years after PHV ( $P < 0.05$ ). No differences were found between –1 year from PHV and 4 years post-PHV ( $P > 0.05$ ). In females, a different picture emerged with overweight adult female PBMAS participants demonstrating significantly greater FM percentages from –3 years from PHV to +7 years post-PHV ( $P < 0.05$ ). In another analysis, the PBMAS participants were classified as high and low risk for cardiometabolic risk in young adulthood (146). It was found that high-risk males and females were significantly heavier, had a greater BMI, FM percentage and trunk FM percentage in adulthood. FM percentage and trunk FM showed age-related inclines in both males and females following PHV. Visual inspection of the graphs suggested that individuals

at higher risk for metabolic syndrome at 26 had greater FM development (both total body and trunk) at all ages. Using random effects models, it was found that once biological age (years from PHV) and height effects were controlled, there were no significant independent effects of maturity category or metabolic syndrome risk group on FM development in males. However, there was a significant independent physical activity and dietary fat effect, in that increasing physical activity significantly reduced FM development ( $P < 0.05$ ) and dietary fat intake significantly increased FM independent of the other variables ( $P < 0.05$ ) during growth. Similar results were observed in female PBMAS participants.

These results from the SGDS and PBMAS studies indicate that children who became overweight or obese as adults were not identified as overweight or obese as children. This suggests that future research needs to identify when the critical period of weight gain occurs during the transition from adolescence to adulthood, rather than just using childhood derived cut points of childhood obesity. The results of the PBMAS studies of trunk and total body FM development suggest that young adults with high cardiometabolic risk, compared to low, have greater trunk FM as early as 8 years of age (4 years from PHV). Both results support the need for early lifestyle interventions for all children both normal and overweight.

### Metabolic implications of body fat loss consequent to bariatric surgery in obese adolescents

In 1999–2006, the US prevalence of extremely high BMI was estimated at 5.8% in 12–19-years-olds, equivalent to 2.34 million adolescents (147). National trend analysis from 1999 to 2008 indicates an increase in the prevalence of high BMI ( $\geq 97$ th percentile) among 6- to 19-year-old boys (148). Extremely obese adolescents are at high risk for serious comorbidities including premature death, heart disease, obstructive sleep apnoea, hypertension, dyslipidemia and type 2 diabetes (149). Adolescent obesity not only presents with serious medical and psychosocial conditions, but also strongly predisposes to adult obesity (150,151).

Bariatric surgery induces massive reductions in body weight and FM, which are associated with metabolic, energetic and hormonal adaptations (152). These adaptations involve multiple signals: pancreatic hormones impacting glucose homeostasis and insulin resistance (insulin); adipokines regulating energy balance (leptin, adiponectin, resistin);

gut hormones influencing satiety and hunger (GLP-1, PYY, ghrelin); and hypothalamic-pituitary-thyroid and -adrenal axes (153–155). These metabolic adaptations result in resolution or improvement in obesity-related comorbidities including type 2 diabetes, obstructive sleep apnoea, liver disease, pseudotumor cerebri, hypertension, hyperlipidemia and psychological disorders (154,156). The contribution of depot-specific fat losses induced by bariatric surgery has not been studied in adolescents, and the few studies in adults are conflicting (157–160).

Massive reductions in body weight and FM by Roux-en-Y gastric bypass (RYGB) surgery are associated with beneficial metabolic, energetic and endocrine adaptations in severely obese adolescents. Regardless of the initial BMI, the percent BMI change averaged 37% for BMI groups 40–54.9, 55–64.9 and 65+(161).

An ongoing study at Baylor College of Medicine is measuring energetic and metabolic responses to RYGB performed in extremely obese adolescents. Body composition measurements in severely obese individuals are challenging because of limitations in equipment capacities and assumptions underlying various models. In this study, deuterium dilution, air displacement plethysmography (BodPod) and the multicomponent Fuller and Siri models are being compared. It is unknown if the hydration and density of FFM differ in severely obese adolescents, and if the values change after surgery. Preliminary results based on the Siri model indicate that the mean hydration and density of FFM are 0.746 and 1.096, respectively, and do not differ before and after surgery.

Bariatric surgery is the most effective way to achieve significant, long-term weight loss, but not all adolescents qualify or opt for bariatric surgery. Research is needed to evaluate the body compositional changes and associated energetic and metabolic responses to surgical and non-surgical treatment strategies for extremely obese adolescents in order to provide effective options.

### Anthropometric markers of depot-specific adiposity and health

#### Anthropometric markers of abdominal body fat in children

As described above, body fat stored in specific depots such as the abdomen and in other tissues can be quantified precisely using imaging techniques such as MRI or CT. However, these methods are not always practical in clinical settings. Given the health



concerns associated with excess abdominal VAT, there is an interest in developing simple, non-invasive techniques to estimate VAT that can be applied in clinical and health surveillance settings.

Anthropometry, or the measurement of human body dimensions, has a long history in the field of human biology. Anthropometric dimensions and indices have the potential to provide important information on body composition in both adults and children. Common anthropometric markers that have been used to estimate total FM and VAT include subcutaneous skin-folds, BMI, sagittal diameter, WC and hip circumference.

Several studies have examined the association between anthropometric measurements and abdominal body fat in children and adolescents. Early studies found that subcutaneous skin-folds, particularly those on the trunk (abdominal, supra-iliac) were most highly correlated with VAT (162,163). More recent studies have focused on BMI and WC, and the results indicate that upwards of 60–65% of the variance in VAT can be explained by BMI or WC (164,165). Similar to results among adults (166,167), recent data from a cohort of 400 children and adolescents studied at the Pennington Biomedical Research Center indicate that both BMI and WC are more highly correlated (age adjusted  $r = 0.93$ – $0.95$ ) with total body fat and trunk fat (from DXA), than with VAT (age adjusted  $r = 0.72$ – $0.75$ ).

There are sex and ethnic differences in the relationships among BMI, WC and VAT in adults (168). For a given level of BMI or WC, men and white adults tend to have higher levels of VAT than women and African-American adults, respectively. Preliminary data from studies of children and adolescents indicate that these patterns are already present at younger ages (9). These results suggest that ethnic- or sex-specific thresholds for BMI and WC may be necessary to better define risk for abdominal obesity and associated health risks; however, more research is required to define the optimal levels across different sex and ethnicity groups. It is unclear whether the same level of health risk is conferred at the same BMI or WC in different ethnicities, and whether the same anatomic landmarks for the measurement of WC are suitable for all ethnic groups because of potential differences in the relative location of body fat, or differences in the architecture of the pelvis.

### Anthropometric indicators of metabolic risk in children

The healthcare impact of obesity is largely due to the metabolic consequences associated with excess

FM. An association between obesity and morbidity has been clearly demonstrated in children too. The most common metabolic disorders associated with childhood obesity are hypertension, insulin resistance and impaired glucose tolerance, NAFLD and an atherogenic blood lipid profile. Three other characteristics of childhood obesity, i.e. tracking of overweight into adulthood, the risk of premature mortality in adulthood and the relatively modest efficacy of treatment, further support the need of enforcing prevention procedures for obesity early in life.

Diagnosis of childhood obesity is typically based on anthropometry. BMI is the most used index for categorizing children into normal weight, overweight or obese groups. Subcutaneous skin-folds are also used for excluding false positive/negative diagnosis of obesity. A strong relationship has been demonstrated between BMI and FM (measured by DXA) (169), as well as between BMI and WC, suggesting that both BMI and WC may be considered good indices of fatness in children. Anthropometric indices, in particular BMI and WC, which have the important advantages of simplicity of measure, acceptable accuracy and very low cost, may be useful in the clinic for selecting children with the highest chance of having CVD factors (170–172).

Several studies have reported an association between CVD risk factors and WC as well as WC/Ht ratio, in both children and adolescents (173–176), and both WC and W/Ht ratio have shown significant associations with VAT (164,165,177). This finding may be explained by the evidence that VAT is associated with metabolic disturbances more than SAT. Nevertheless, the role of ectopic fat accumulation seems to be still more important than that of VAT in explaining insulin resistance and, by implication, metabolic disturbances associated with obesity, at least in the youngest children (178,179). The most important ectopic accumulation of fat in terms of metabolic as well as clinical impact is fatty liver. NAFLD is the most common disease of the liver in children and has a high prevalence in obese children. Recent data suggest that WC/Ht is a useful predictor of NAFLD with good sensitivity and specificity, especially when some biochemical variables are included in the equation (180).

The use of WC/Ht as an anthropometric index for selecting children having a higher chance of CVD risk factors is more interesting in overweight subjects than in obese ones (181) since detection is more difficult in this adiposity range. In fact, from a clinical point of view, blood tests for fasting blood glucose, lipid profile and alanine transaminase are usually performed in already obese children so that the



diagnosis of metabolic complications of obesity may be easily obtained. On the contrary, there is no recommendation to perform the above mentioned blood tests in all overweight children. Therefore, availability of indices useful to select the subsample of overweight children with the highest risk to have CVD risk factors, so to apply the diagnostic procedure in these children, seems potentially helpful.

The utility of anthropometry to identify children with dyslipidemia has been investigated in studies of urban children from Buenos Aires (BA) and Koya children, an American Indian population who live in the mountains in San Antonio de los Cobres (SAC) northwest Argentina. A previous study showed that BMI, WC and WC/Ht ratio were specifically associated with dyslipidemia in BA children (182). However, when dyslipidemia was defined by criteria of the National Cholesterol Education Program and American Heart Association, the results indicated that BMI was a significant predictor for high triglycerides and low high-density lipoprotein-c (HDL-C) in BA children but not in SAC children. The areas under the receiver operator characteristic (ROC) curves (AUC) in predicting high triglycerides were BMI = 0.65 (95% confidence interval [CI] 0.52–0.77;  $P = 0.02$ ) in BA children, and BMI = 0.55 (95% CI 0.48–0.62;  $P = 0.15$ ) in SAC children. The AUC in predicting low HDL-C were BMI = 0.61 (95% CI 0.50–0.71;  $P = 0.04$ ) in BA children and BMI = 0.52 (95% CI 0.45–0.59;  $P = 0.5$ ) in SAC children. Similar results were obtained when BMI was replaced by WC and WC/Ht ratio. The results suggest that these anthropometric measures are not acceptable predictors for dyslipidemia among Koya Indian children. Future research in other ethnic groups is required to determine the universality of the associations between anthropometry and metabolic risk that have been identified in many samples of children to date.

In conclusion, WC, WC/Ht ratio and BMI are, at present, the anthropometric indices most promising for predicting metabolic risk in children. WC/Ht seems to be particularly suitable for identifying overweight children at higher metabolic risk.

## Critical questions in the field and future directions

The 2011 Pennington Biomedical Research Center Scientific Symposium provided a forum to present the latest research on pediatric obesity and its clinical consequences. In addition to understanding the current status of the field, several important directions for future research emerged from the discussion, as follows:

- There is an urgent need to standardize imaging protocols for population surveillance as well as clinical use. It is difficult to compare results across studies that have used different protocols (i.e. different anatomic landmarks, single-slice vs. multi-slice, MRI vs. CT, etc.), even though the studies may have used the same scanning instrumentation and protocol.
- Further research is required to understand the best anatomic approach for the measurement of abdominal adiposity (i.e. single-slice vs. multi-slice, number of slices, etc.) in children of different ethnicities, different age groups and different maturational stages.
- More research is required to understand the long-term health implications of excess VAT and ectopic fat (in liver, muscle, pancreas, etc.) during childhood and how this may translate into adult health risks.
- Comprehensive longitudinal body composition phenotyping of children in early life (at birth/infancy, etc.) is necessary to understand the full life course of depot-specific body fat and future health implications.
- Extensive research is required to understand the relationships between body composition and nutrition and physical activity, and the extent to which these associations modify the relationship between body composition and disease risk.
- Body composition measurements should be encouraged as a fundamental assessment of growth and maturation, metabolic functions and risks, as well as for monitoring the effects of weight loss interventions.
- Studies of maturity-associated variation in the development of body fat and depot-specific adiposity are needed to appropriately examine age, sex, and ethnic differences across the pediatric age range.
- More research is required on children and adolescents across a range of adiposity, particularly underweight, normal weight and severely obese, as current studies predominantly focus on overweight and obese adolescents.
- Investigations of bariatric surgery and pharmaceutical interventions are needed in children and adolescents to assess their efficacy in lowering total body fat, visceral adiposity, ectopic fat and their ensuing cardiometabolic health risks.
- Research is needed in the measurement of sub-regions of adipose tissue and fat depots including hepatic fat, BAT, VAT (i.e. omental, mesenteric, extra-peritoneal), intermuscular adipose tissue, pericardial adipose tissue and bone marrow adipose tissue.
- Research is needed to investigate the paradox of ethnic disparities in chronic disease not reflecting

ethnic differences in VAT or hepatic fat. These associations appear to begin in childhood and adolescence.

- There is an urgent need for suitable national and international reference data and standards developed from detailed assessments of body composition (e.g. from DXA and MRI/MRS) to better define obesity and provide a comparison to disease states.

## Conflicts of Interest Statement

The authors report no conflicts of interest in relation to this work.

## Author contributions

All authors were involved in writing the paper and had final approval of the submitted and published versions.

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