Body Composition Assessment in Pediatric Obesity:

Reliability, Validity, and Clinical Applications

by

Camila Estefani Orsso

A thesis submitted in partial fulfillment of the requirements for the degree of

Master of Science

in

Nutrition and Metabolism

Department of Agricultural, Food and Nutritional Science

University of Alberta

Abstract

Adipose tissue and skeletal muscle have unique metabolic roles. Despite body mass index for age and sex (BMI z-score) being historically widely used to evaluate and monitor health status in children with obesity, it does not depict adiposity and muscularity (or their changes) during growth or weight loss interventions. Thus, using body composition techniques to identify metabolic risk factors and evaluate the effectiveness of obesity interventions is a more meaningful approach.

The first goal of this research was to summarize the reliability and validity of laboratory and field techniques used for body composition assessment in children with overweight and obesity. A systematic review of 66 studies revealed that laboratory techniques, such as air-displacement plethysmography (ADP) and dual-energy X-ray absorptiometry (DXA), had high reliability to assess variables describing both adiposity (i.e. percent body fat [%BF], fat mass [FM]), and muscularity (i.e. fat-free mass [FFM]). Furthermore, small bias with clinically acceptable limits of agreement (≤5%) were found for %BF measured by ADP (bias range = -0.4% to 3.17%), DXA (bias range = 1.0% to 2.2%), and isotope dilution (bias range = -2.7% to 2.7%) compared to multicompartment models in Bland-Altman analyses. Regarding field techniques, ultrasound (US) was found as a reliable technique to assess skeletal muscle and adiposity (in visceral and subcutaneous depots) as well as a valid technique for %BF estimation (bias range = -0.4% to 0.1%, compared to DXA). On the other hand, skinfolds and BIA (also known as field techniques) showed large bias (ranging from -12.7% to -0.1% and -7.1% to 3.6%, respectively) with unacceptable limits of agreement for %BF estimation (>5%), whilst skinfolds presented with good reliability to measure thickness at different body sites. These findings suggest that laboratory techniques should not be replaced by field techniques, except for US, when assessing body composition in children with excess adiposity.

The second goal of this research was to evaluate the extent to which body composition parameters (i) varied across BMI z-score values and metabolic health status, and (ii) associated with metabolic risk factors in children with obesity. Whole-body and segmental body composition were assessed using ADP and US (at the midthigh level), respectively; the load-capacity index (LCI) was calculated as the ratio between adiposity and muscularity. Children with similar BMI z-scores had a large variability in body composition; e.g. males with BMI z-score between 3 to 4 SD had a variation of 42.9% in FM index (adjusted for height squared), 21.4% in FFM index, and 33.7% in LCI by ADP. Children with high LCI had greater concentrations of markers of insulin resistance (IR; i.e. homeostatic model assessment of IR [HOMA-IR]; $p = 0.041$) and low-grade inflammation (i.e. high-sensitivity c-reactive protein [hs-CRP]; $p<0.001$). Moreover, we found that HOMA-IR was positively associated with FFM index ($R^2 = 0.45$; $p = 0.002$) to a greater extent than FM index ($R^2 = 0.33$; $p = 0.028$), independent of sexual maturation. However, the associations were lost after adjusting for the effects of muscle echo intensity (mEI; a surrogate of ectopic fat in muscles; hence, muscle "quality"). In fact, mEI explained 43% of the variation in HOMA-IR ($p = 0.018$) and 49% of the variation in hs-CRP ($p = 0.004$).

The major finding of this research was that compared to children with obesity alone, those with obesity and metabolic dysfunction had lower muscle "quality" rather than lower muscle "quantity". As BMI z-score and two-compartment body composition models (e.g. ADP, DXA) cannot distinguish ectopic fat in muscles from whole-body adiposity, the US technique may have a greater clinical utility. However, future studies should evaluate the agreement between US and imaging techniques in depicting segmental body composition in pediatric obesity populations. These findings will contribute to advancing the field of pediatric body composition assessment,

design of trials investigating obesity intervention effectiveness, and improve care of children living with obesity.

Acknowledgements

Albert Einstein once said that "*The whole of science is nothing more than a refinement of everyday thinking*". In light of this quote, I would like to express my gratitude to all the people who have supported my daily progress in the graduate program.

First, I thank my supervisors Dr. Andrea M. Haqq and Dr. Carla M. Prado for creating a variety of learning opportunities that were imperative to develop my research skills. They were always open to hear my research ideas, discuss recent advances in the field, and guide my professional and personal decisions. Thank you for trusting in my abilities and allowing my creativity to flourish. I am also grateful for all the constructive feedback they both have provided. As such, I could not have obtained a better training as a Master student anywhere else.

I wish to express my appreciation to health care providers and patients from the Pediatric Centre for Weight and Health. This research would not have been possible without their involvement. My special thanks to Jessica Hamilton, Marcus O'Neill, Amanda Matkowski, Meagan Macleod, Laura Mercier, Lisa Tremblay for helping me with participant recruitment. I also thank to current and previous directors of the centre (Dr. Geoff Ball, Dr. Mohammad Ansarian, and Dr. Faria Ajamian) for allowing me to become part of their teams.

I cannot thank enough Lucila Triador, Reena Duke, Claire Trottier, Felicia Sim, and Susan Goruk for their continued technical support on this research. They have assisted me with ethics application, blood processing and analysis, body composition assessment, data collection, grant writing and reports, and proofreading. I cannot even list here all the activities they have helped me with.

I was very fortunate to have Dr. Joao Felipe Mota and Dr. Maria Ines Barreto Silva as my roommates. Thank you for spending time with me to discuss my research, and for teaching me how to critically evaluate the scientific evidence. Dr. Maria Ines Barreto Silva has also co-authored a manuscript with me and provided important input in my dissertation.

I am also thankful to Dr. Daniela A. Rubin, Dr. Catherine J. Field, Dr. Maria Cristina Gonzalez, and Dr. Steven B. Heymsfield for their tremendous support throughout my graduate program. Thank you for sharing your wealth of knowledge in nutrition and body composition research and collaborating as co-authors in publications. Thank you to Dr. Mohammadreza Pakseresht for providing me with statistical support and Dr. Margie H. Davenport for instructing me how to analyze the accelerometry data.

Thank you to my colleagues at the Haqq Lab: Dr. Maha Alsaif, Qiming Tan, Khushmol Dhaliwal, Shima Afhami, and Reihaneh Masoumi. It was also a pleasure working with students from the Prado Lab: Dr. Jingjie Xiao, Dr. Sarah Purcell, Dr. Leticia Cristina Radin Pereira, Camila Lemos Pinto Oliveira, Katherine Ford, Ana Paula Pagano, and Bruna Ramos da Silva. All these individuals had a role on shaping myself as a graduate student. They have also supported me in so many ways. My thank you extends to Jenneffer Rayane Braga Tibaes for her kindness and willingness to help at all the time.

My special thank you to my mom and dad for their unconditional support and love. Thank you to my sister for using her artistic skills to improve the quality of the recruitment material, figures, and videos that were developed throughout my graduate studies. A special note of gratitude to my wonderful husband, Ricardo Torquato Borges, who have always supported me in my endeavours and is helping me to become a stronger woman as I grow old.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

%BF: percent body fat

3-C: three-compartment model

4-C: four-compartment model

ADP: air-displacement plethysmography

AGA: appropriate size for gestational age

AMDR: Acceptable Macronutrient Distribution Ranges

AT: adipose tissue

BIA: bioelectrical impedance analysis

BMI: body mass index

BMI z- score: body mass index z-score

CI: confidence interval

cIMAT: carotid intima-media thickness

CRP: C-reactive protein

CT: computerized tomography

CV: coefficient of variation

DBP: diastolic blood pressure

DXA: dual-energy X-ray absorptiometry

FFM: fat-free mass

FFMI: fat-free mass index

FM: fat mass

FMI: fat mass index

HDL-C: high-density lipoprotein cholesterol

HGS: handgrip strength

HOMA-IR: homeostatic model assessment of insulin resistance

hs-CRP: high-sensitivity C-reactive protein

ICC: intraclass correlation coefficient

IDF: International Diabetes Federation

IGF-1: insulin-like growth factor 1

IL-6: interleukin-6

IMAT: intramuscular adipose tissue

IR: insulin resistance

LCI: load-capacity index

LDL-C: low-density lipoprotein cholesterol

LoA: limits of agreement

LST: lean soft tissue

mCSA: muscle cross-sectional area

mEI: muscle echo intensity

MetS: metabolic syndrome

MHO: metabolically healthy obesity

MRI: magnetic resonance imaging

MUO: metabolically unhealthy obesity

MVPA: moderate-to-vigorous physical activity

NHANES: National Health and Nutrition Examination Survey

OGTT: oral glucose tolerance test

OR: odds ratio

SAT: subcutaneous adipose tissue

SBP: systolic blood pressure

SEE: standard error of estimates

SGA: small-for-gestational age

TBK: total body potassium

TBW: total body water

TE: total error

TG: triglycerides

TGV: thoracic gas volume

TNF-α: tumor necrosis factor alpha

US: ultrasound

VAT: visceral adipose tissue

WC: waist circumference

WHR: waist-to-hip ratio

WHtR: waist-to-height ratio

Chapter 1 Introduction

1.1 Thesis Organization

This thesis has been prepared as a paper-format according to specifications by the Faculty of Graduate Studies and Research at the University of Alberta. Following the introduction, Chapter 2 is included as a literature review and Chapters 3 and 4 are included as individual manuscripts. A preface precedes Chapters 2, 3 and 4 with a brief description of the content.

1.2 Rationale

Prevalence rates of childhood obesity continue to rise worldwide (1). In Canada, analysis of survey data revealed that 27% of children and adolescents presented with either overweight or obesity in 2013, based on body mass index (BMI) classifications (2). Several studies have shown the associations between high BMI and metabolic dysfunction in children at the population level, including hypertension, insulin resistance (IR), and dyslipidemia (3). As adiposity during childhood tracks to adulthood, preventing and treating obesity and its related comorbidities at younger ages is the key focus in reducing obesity burden in adulthood (4). Yet the effectiveness of varied intervention approaches is limited, challenging their clinical implementation (5).

One flaw in many studies is the use of BMI as a primary outcome. Despite BMI being widely used as a surrogate measure of excess adiposity, it has several limitations that can lead to biased findings (6). Especially during childhood and adolescence, where individuals are experiencing maturational changes, BMI is not capable to capture modifications in the proportions of adiposity and muscularity (7). As these compartments have unique roles in the maintenance of homeostasis, body composition techniques thus present as more appropriate alternatives to evaluate the effectiveness of obesity interventions as well as to identify metabolic risk factors at the individual level (8). However, assessment of body composition in the pediatric population with obesity is challenged by many factors, including lean tissue hydration, body shape, and excess body weight (9). To progress in the area of obesity prevention and treatment, reliable and accurate body composition techniques must therefore be chosen. Evaluation of the current evidence on the reliability and validity of field techniques (e.g. bioelectrical impedance analysis [BIA], skinfolds, ultrasound [US]) and laboratory techniques (e.g. dual energy x-ray absorptiometry [DXA], air-displacement plethysmography [ADP], isotope dilution) would aid implementation of body composition assessment in research and clinical settings, facilitating the reliable report of intervention effects.

It is noteworthy that although skeletal muscle plays important functions in the body and metabolic regulation, this compartment is often overlooked (7). Furthermore, there is evidence that some children with obesity present with a healthy metabolic profile, or absence of metabolic risk factors (10). Given the contribution of adiposity (load) and muscularity (capacity) to physiological function, differences in body composition could determine the risk of metabolic dysfunction in childhood (8). Recent studies have confirmed that adults with both concurrent high adiposity and low muscularity have an increased risk of adverse health events (11-13), but there has been no detailed investigation on the metabolic risk associated with this phenotype in the pediatric population using accurate techniques. In addition, the use of an index that combine measures of adiposity and muscularity (i.e. metabolic load-capacity index [LCI]) may have a greater ability to predict metabolic dysfunction during childhood (8). Therefore, characterization of body composition in children with obesity and its association with metabolic risk factors using valid and reliable techniques are timely required.

1.3 Purpose

The overall purpose of this research was to characterize body composition and its assessment as well as to evaluate the associations of adiposity and muscularity with metabolic risk factors in children with obesity. Additionally, this research aimed to explore the use of the LCI to identify single and clustered metabolic risk factors.

1.4 Research Questions

In children with overweight and obesity:

1. Are current field and laboratory techniques reliable and valid for body composition assessment?

In children with obesity:

2. Does body composition differ within and between BMI z-score categories?
3. Does body composition differ between those with and without metabolic dysfunction?
4. Are body composition variables (including the LCI) better discriminators of metabolic health than BMI?
5. What is the clinical utility of readily available techniques, such as an US device, to assess body composition?

1.5 Specific Objectives and Hypothesis

1.5.1 Assessment of Body Composition in Childhood Overweight and Obesity: A Systematic Review of The Reliability and Validity of Common Techniques (Chapter 3)

Objective:

In children with overweight and obesity, I will:

1a. Describe the reliability and validity of field and laboratory techniques used for cross-sectional body composition assessment.

1b. Evaluate the degree of agreement between techniques used to monitor longitudinal changes in body composition.

Hypothesis:

1a. Compared to field techniques, laboratory techniques will present with a greater reliability and validity to assess body composition cross-sectionally and longitudinally in children with obesity.

1.5.2 The Relative Contribution of Adiposity and Muscularity to Metabolic Function in Children with Obesity (Chapter 4)

Objective:

In children with obesity, I will:

1a. Characterize body composition and evaluate the extent to which body composition varied among degrees of obesity (as defined by BMI for age and sex [BMI z-score]).

1b. Compare and contrast body composition including the LCI (assessed by ADP and US) between those with versus without metabolic dysfunction.

1c. Investigate associations between body composition parameters and metabolic markers.

1d. Investigate whether body composition variables, including the LCI (by ADP or US), are better discriminators of metabolic dysfunction in children with obesity, as compared to BMI z-score.

Hypotheses:

1a. I hypothesize that body composition will differ across BMI z-score categories. Moreover, body composition values will vary considerably in children with similar degrees of obesity. Based on previous literature (7), ranges of fat mass index (FMI) and fat-free mass index (FFMI) will vary 40% and 20% within BMI z-score categories, respectively.

1b. Children with an unfavourable metabolic profile (i.e. IR, dyslipidemia, hypertension, metabolic syndrome, or metabolic unhealthy obesity) will have lower muscularity and, therefore, a higher metabolic LCI compared to those who are metabolically healthy.

1c. Higher adiposity and lower muscularity (whole-body by ADP and at midthigh by US) will be significantly associated with:

- elevated lipid values for low-density lipoprotein cholesterol (LDL-C) and triglycerides (TG)
- lower concentrations of high-density lipoprotein cholesterol (HDL-C)
- higher makers of systemic inflammation, as assessed by high sensitivity c-reactive protein [hs-CRP], interleukin-6 [IL-6], and tumor necrosis factor alpha [TNF-α] levels
- higher homeostasis model assessment of IR (HOMA-IR)
- higher blood pressure (systolic [SBP] and diastolic [DBP])
- lower muscular strength, as assessed by handgrip strength (HGS)

1d. Compared to BMI z-score, variables depicting adiposity and the LCI will have stronger direct associations with unfavourable metabolic profile. The associations between variables depicting muscularity will also be stronger than BMI, but in an opposite direction (i.e. negative associations).

1.6 References

1. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: A pooled analysis of 2416 population-based measurement studies in 128·9 million children, adolescents, and adults. Lancet. 2017;390(10113):2627–42.

2. Rodd C, Sharma AK. Recent trends in the prevalence of overweight and obesity among Canadian children. CMAJ. 2016;188(13):E313–20.

3. Friedemann C, Heneghan C, Mahtani K, Thompson M, Perera R, Ward AM. Cardiovascular disease risk in healthy children and its association with body mass index: Systematic review and meta-analysis. BMJ. 2012;345(7876):1–16.

4. Hao G, Wang X, Treiber FA, Harshfield G, Kapuku G, Su S. Body mass index trajectories in childhood is predictive of cardiovascular risk: Results from the 23-year longitudinal Georgia Stress and Heart study. Int J Obes. 2018;42(4):923–5.

5. Brown AW, Altman DG, Baranowski T, Bland JM, Dawson JA, Dhurandhar NV, et al. Childhood obesity intervention studies: A narrative review and guide for investigators, authors, editors, reviewers, journalists, and readers to guard against exaggerated effectiveness claims. Obes Rev. 2019;20(11):1523–41.
6. Vanderwall C, Eickhoff J, Randall Clark R, Carrel AL. BMI z-score in obese children is a poor predictor of adiposity changes over time. BMC Pediatr. 2018;18(1):1–6.
7. Wells JCK. Toward body composition reference data for infants, children, and adolescents. Adv Nutr. 2014;5(June):320S-329S.
8. Wells JCK. Using body composition assessment to evaluate the double burden of malnutrition. Ann Nutr Metab. 2019;75(2):103–8.
9. Williams JE, Wells JCK, Wilson CM, Haroun D, Lucas A, Fewtrell MS. Evaluation of Lunar Prodigy dual-energy X-ray absorptiometry for assessing body composition in healthy persons and patients by comparison with the criterion 4-component model. Am J Clin Nutr. 2006;83(5):1047–54.
10. Elmaogullari S, Demirel F, Hatipoglu N. Risk factors that affect metabolic health status in obese children. J Pediatr Endocrinol Metab. 2017;30(1):49–55.
11. Kang S-Y, Lim GE, Kim YK, Kim HW, Lee K, Park T-J, et al. Association between sarcopenic obesity and metabolic syndrome in postmenopausal women: A cross-sectional study based on the Korean National Health and Nutritional Examination Surveys from 2008 to 2011. J Bone Metab. 2017;24(1):9–14.
12. Van Aller C, Lara J, Stephan BCM, Donini LM, Heymsfield S, Katzmarzyk PT, et al. Sarcopenic obesity and overall mortality: Results from the application of novel models of body composition phenotypes to the National Health and Nutrition Examination Survey 1999–2004. Clin Nutr. 2018; 38(1):264-70
13. Cleasby ME, Jamieson PM, Atherton PJ. Insulin resistance and sarcopenia: Mechanistic links between common co-morbidities. J Endocrinol. 2016;229(2):R67–81.

Chapter 2 Literature Review

2.1 Preface

This chapter provides an overview of the determinants of adiposity and muscularity, implications of the high adiposity and low muscularity phenotypes on health outcomes, and body composition assessment in the pediatric population. Sections 2.5 to 2.8 have been adapted from published manuscripts in Clinical Nutrition (Orsso CE, Tibaes JRB, Oliveira CLP, Rubin DA, Field CJ, Heymsfield SB, Prado CM, Haqq AM. 2019; 38[5]:2002-15) and in Metabolism (Orsso CE, Tibaes JRB, Rubin DA, Field CJ, Heymsfield SB, Prado CM, Haqq AM 2019; Jul 23: 153949). Within each of these manuscripts, I performed the literature search, critically analyzed the literature, and drafted the initial version; all authors have contributed and approved the final manuscript.

The most accurate terminology to describe body composition evaluated by the reviewed studies were used here, which may vary from the original terminology presented by them. For clarify purposes, “adiposity” and “muscle mass” were used as generic terms to describe, respectively:

a adipose tissue (AT), percent body fat (%BF), or fat mass (FM)

b lean soft tissue (LST), fat-free mass (FFM), or skeletal muscle tissue.

Additionally, “visceral adipose tissue (VAT)” and “subcutaneous adipose tissue (SAT)” were used as generic terms to describe abdominal adiposity, independent of the body composition technique used by the reviewed studies.

2.2 Adipose Tissue Development and Its "Load" on Health

Adipose tissue is considered one of the largest organs in the body that provides protection and support for other organs and acts as an endocrine tissue (1). The mature AT is composed of adipocytes organized into lobules and other structures responsible for its expansion (e.g. preadipocytes and mesenchymal stem cells), metabolism (e.g. vascular muscle cells and immune cells), and structure (e.g. collagenous and elastic fibers) (2). Recent research has shown the existence of varied adipocyte subtypes, but only two of them (white and brown) have been extensively characterized in humans (1, 3). As these adipocytes reside in specific depots within the body, the AT containing white and brown adipocytes are termed white AT and brown AT, respectively.

White AT can be found in SAT, VAT, and ectopic depots (1); on the other hand, brown AT localization is age-dependent, with infants presenting brown AT within the interscapular and perirenal regions and adults exhibiting brown AT within the cervical, supraclavicular, axillary, and suprarenal regions (4). Although both AT types are important for body energy homeostasis, white AT stores and produces energy in form of triglycerides (TG) and brown AT utilize small lipid droplets for heat production (i.e. nonshivering thermogenesis) (1, 4). Furthermore, each AT type has a unique profile of cytokine secretion thus playing distinct roles in the regulation of metabolic diseases (1, 4). Here we focused on white AT (at the tissue level), as it is the largest component of total FM (at the molecular level); specifically, about 80% of AT is FM (5).

The development and expansion of AT, with consequent increases in total body fat, are dynamic processes that initiate in the second trimester of gestation and extend throughout life (6). These processes involve either enlargement of adipocyte cells by augmented lipid storage (termed hypertrophy) or increases in the number of adipocytes within a lobule through differentiated progenitor or mesenchymal cells (7). Sun et al. further classify the AT expansion into healthy and unhealthy processes (8). The first classification is related to the formation of new small adipocytes that are adequately vascularized and minimal inflammation in present. On the other hand, the unhealthy expansion is often observed in individuals with obesity under a persistent positive energy balance (8, 9). In these individuals, there is a rapid increase of pre-existing adipocyte size in the SAT due to greater lipid accumulation. With inadequate angiogenesis, the tissue is prone to hypoxia and adipocyte dysfunction. Because there is a limit for lipid storage in adipocytes, adipocyte hypertrophy is followed by hyperplasia, or leakage of lipids to other tissues

(e.g. liver and muscle), and consequent *de novo* lipogenesis and lipotoxity (8, 9). According to Sethi et al., the degree of toxicity will depend on the extent and duration of positive energy supply, effectiveness of lipid transport and storage mechanisms, and organ oxidative capacity (10). Another hypothesis is that persistent positive energy balance affects the secretion of adipokines (e.g. leptin, adiponectin, tumor necrosis factor alpha [TNF-α], interleukin-6 [IL-6]), with implications for glucose homeostasis and lipid metabolism and flux (10).

2.2.1 Intrauterine Adipose Tissue Accrual

Histological analysis of buccal fat pads from human fetuses revealed that intrauterine AT development occurs in five different stages, with overlapping stages 2 to 4 (11). The first stage, at 14 weeks, is marked by an outgrowth of loose connective tissue. Right after (stage 2 at 14.5 weeks), there is an early vascularization of the tissue. Stage 3 is characterized by the onset of mesenchymal cells growth at 19 weeks; although several studies have shown a mesoderm origin of these growth cells, recent investigation using mouse models suggests that mesenchymal cells associated with head AT formation originate from neural crest cells (12). The first adipocytes appear in stage 4, and at 28 weeks (stage 5) fat lobules are formed and can be distinguished from other structures. Despite the later development of adipocytes, findings from molecular body composition analysis estimated a lipid accretion rate of 7.8 g/day at earlier stages (24-28 weeks) and increases up to 19.8 g/day at 36-40 weeks (13).

There is a limited knowledge on intrauterine AT accrual in the third trimester of pregnancy due to the inability of current techniques to assess body composition (14). Using magnetic resonance imaging (MRI), one study reported increases of 2.5 mm in truncal AT thickness of fetuses from weeks 29 to 39-40 of gestational age (15). Body composition assessment of infants born preterm may therefore provide further information on AT development. For example, Lapillonne et al. compared body composition of appropriate size for gestational age (AGA) infants born at 32 to 41 weeks and found a 115% difference in FM ($p = 0.0001$) between these gestational ages (16).

2.2.2 Postnatal and Childhood Adipose Tissue Accrual

Soon after birth, newborns lose body weight due to changes in hydration of FFM, but not FM (17). Toro-Ramos et al. summarized the findings from several studies reporting infant body composition data and highlight the predominance of SAT rather than VAT in the first months of life (14). Fat mass development is marked by steep increases in this body compartment from birth

up to 6 months of age and a subsequent reduction in the rate of FM accrual in healthy term boys and girls, as assessed by multicompartment model (18). In fact, %BF accrual during infancy also differs between term and preterm newborns. Preterm infants at term corrected age (i.e. chronologic age adjusted for gestational age) had higher %BF (14.8±4.4% by air displacement plethysmography [ADP]) than term infants (8.6±3.71%, $p < 0.0001$) (19). Similar findings using ADP were reported by Ramel et al. in a longitudinal analysis; AGA preterm infants at term corrected age had higher %BF than term infants (17.8% vs. 15.2%, $p < 0.0001$), but these differences disappeared in measures obtained at 3 to 4 months (27.7% vs. 23.9%.; $p = 0.07$) (20).

There is evidence that adiposity at birth and first year of life determines adiposity levels in childhood and adulthood, albeit only a few studies have investigated longitudinal adiposity changes using body composition methods (21-24). As an example, Admassu et al. explored the associations between FM (assessed by ADP) at term birth and at 4 years of age in healthy Ethiopians (24). For every increase of 1 kg in FM at birth, there was a 1.17 kg/m^2 rise in FM index (FMI) at 4 years old. In addition, FM accrual in the first four months was positively associated with FMI at 4 years ($\beta = 0.30$; CI = 0.12, 0.47), after controlling for several sociodemographic and parental covariates (24). A 20-year longitudinal follow-up study investigated the associations of FM and trunk FM (by dual-energy X-ray absorptiometry [DXA]) in childhood and adolescence to FM in adulthood (25). Whole-body and trunk FM z-scores early in life were predictors of whole-body and trunk FM in young adulthood. These results highlight that children and adolescents with higher whole-body and trunk FM will possibly present with greater FM measures in adulthood.

Analysis of AT samples obtained from biopsies provides a better understanding on the associations between childhood and adulthood adiposity levels (26, 27). In a cross-sectional study, infants showed increases in cell size to an adult level from ages 6 months to one year, with reductions between one and two years (26). Researchers were able to stratify the analysis by weight categories only after age of two year, and it was noted that cell size was greater in children with obesity compared to children without obesity. However, there were no changes in size from two years old up to 16 years in children with obesity. In children of normal weight, adult levels for adipocyte size were reached at 11 to 13 years old. Regarding adipocyte cell number, increases were found throughout childhood and adolescence for children with obesity; but those children of normal weight had differences in cell number only after 10 years old (26). Spalding et al.

compared results from a study in childhood and adolescence with data obtained in adults (aged 20 years and older) and observed no further increases in the number of adipocytes during adulthood (28). Although adults with obesity showed a greater amount of AT cells than those of normal weight, the number of cells remained similar to that observed at younger ages (7). To prove that the number of cells set earlier in life is maintained even after weight loss, researchers examined whether there would be changes in the number of adipocytes after bariatric surgery; however, no differences were found pre- and post-surgery (28). More recently, research using in vivo analysis has shown that adipocyte cells can undergo a process called de novo adipogeneses (i.e. adipocyte turnover) contributing to obesity onset (29). Once adulthood is reached, there is also a pattern that is specific to weight status with regards to adipocyte turnover (death of adipocytes and generation of new cells). For example, although there seems to be no differences in the death rate of adipocytes across weight status, adults with obesity had 2.6 greater number of adipocytes generated per year than adults of normal weight (28).

Several studies in populations with varied ethnic origins have reported body composition reference data during childhood and adolescence. Using a longitudinal design, McConnell-Nzunga et al. investigated the %BF accrual (by DXA) in Canadians of Caucasian and Asian origins from ages 10 to 18 years (30). The authors found that those children in the highest %BF centiles (90^{th} and 97^{th}) had greater increases in %BF from 10 to 11 years, but a sharp reduction from 12 to 15 years. In a study in Caucasian children from Southern England, %BF peaked at age 11 years for those in the 50^{th} percentile; after this age, %BF decreased in boys but rose progressively up to 18 years in girls (31). Comparing %BF between sexes at age 18, girls had 60% more %BF than boys. A similar pattern of %BF accrual was observed in a recent study in Southern Brazilians; although a cross-sectional design was used to acquire data, girls in the 50^{th} percentile had higher %BF with advancing ages. It is interesting to note that the 50^{th} percentile had a flat shape in boys, but the 97^{th} showed a lower FM (kg) from 13 to 16 years, which was again higher with older ages (32). In summary, although these studies have assessed body composition in children and adolescents of distinct ethnic origins, adiposity accrual appears to follow a similar pattern across ethnicities. With the onset of puberty, adiposity levels decrease in boys along with FFM increases, while adiposity increases in girls.

Similar to whole-body adiposity accrual, the pattern of adiposity distribution is also sex dependent. A study in healthy white children (matched for age, height, and weight) showed that

prepubertal girls have a greater amount of total AT and SAT than prepubertal boys, but there were no differences for VAT ($p = 0.24$) (33). It was also noticed that while abdominal obesity plateau in girls at puberty, boys experience a steadily increase until adulthood (33). Another study analyzing VAT samples obtained from biopsies identified that prepubertal children with obesity presented with an increased expression of genes related to adipogenesis, lipid and amino acid metabolism, oxidative stress and extracellular matrix regulation, and inflammation compared to prepubertal children without obesity (34).

2.3 Determinants of Childhood Obesity

Several factors have been shown to determine obesity risk in the childhood population, including biological (e.g. sex, ethnicity, genetics), intrauterine exposures (e.g. maternal nutrition, exposure to chemicals), environmental factors (e.g. feeding practices, physical activity). This literature review provides a summary of the most recent evidence on the associations between these factors and adiposity measures.

2.3.1 Sexual Dimorphism

Sexual dimorphism in adiposity becomes more apparent in early puberty, with girls presenting with a greater tendency to increase FM, while boys tending to increase FFM. Another sex difference in body composition that initiates during the transition of adolescence to adulthood is adiposity distribution. Males tend to develop more android fat (i.e. fat accumulation in the abdominal region) and females a greater gynoide fat (i.e. fat accumulation in the hip region) (35). For instance, Taylor et al. compared FM in the trunk, waist, and hip lines (measured by DXA) between males and females at different pubertal stages (35). Sex differences in trunk fat appeared at late puberty (Tanner stages 4-5), with boys having 17% greater trunk fat than girls ($p < 0.001$). Regarding FM at the waistline, sexual dimorphisms were observed at all puberty stages (boys having greater fat than girls); on the other hand, girls had greater amount of fat at the hip than boys (35). Using MRI, a more accurate technique, Shen et al. compared SAT and VAT between sexes; results from regression analysis showed sexual dimorphism in SAT also after entering puberty, with girls having a larger SAT volume than boys (36). Differences in VAT between sexes were not significant during adolescence but became clearer with advancing age. In contrast to these findings, Kjellberg et at. reported that greater SAT volume in girls compared to boys was apparent even at prepuberty (mean age of 7.1 years) (37). An ecological explanation for this

sexual dimorphism is that with puberty, females need to store energy in SAT for the subsequent period of pregnancy and lactation (38).

Hormonal differences between boys and girls also explain the characteristic sexual dimorphism of whole-body adiposity and its distribution patterns at puberty (39). The levels of estrogen, a hormone responsible for suppressing appetite and increasing energy expenditure, are higher in females (39). Besides regulating energy metabolism, estrogen also increases sympathetic tone and down-regulates androgen receptors expression in SAT, favouring lipid accumulation in this fat depot in females (40). It is noteworthy that girls with obesity enter puberty at younger ages than girls with normal weight (41). The adipokines leptin and adiponectin may play a role in the inverse association between menarche onset and weight status by modulating the hypothalamic-pituitary-gonadal axis (42). Briefly, leptin activates the hypothalamus through secretion of the hormone kisspeptin to secrete gonadotropin releasing hormone. This hormone then activates the pituitary glad to produce follicle stimulating hormone and luteinising hormone, resulting in the secretion of estrogen by the ovaries and, consequently, menarche onset. On the other hand, adiponectin inhibits the secretion of gonadotropin releasing hormone and delayed puberty onset (42).

2.3.2 Race/Ethnicity

Obesity rates and body composition also differs across racial and ethnic groups. In the United States, for example, obesity prevalence was shown to be greater among American Indian and/or Native Alaskan (31.2%), Hispanic (22.0%), and non-Hispanic blacks (20.8%) children compared to White (15.9%) and Asian (12.8%) children (43). In Canada, regression analysis of national data including children aged 3 to 19 years revealed an odds ratio (OR) of 1.13 (95% confidence interval [CI], 1.02, 1.24) for being overweight or obese in non-White children, independent of biological and socioeconomic predictors (44).

Ethnic differences in body composition are evident since early life. In healthy male term infants aged 1 to 3 days old, %BF (by ADP) was 13%, 16%, and 20% lower in those of Caucasian origin compared to those of African-American, Asian, and Hispanic origins, respectively (45). Likewise, Caucasian girls had 10% less fat than African-American girls, but no differences were found for other racial groups. Data from childhood and adolescence reveal a shift towards individuals of Caucasian origins presenting with a greater adiposity. For example, Freedman et al. compared body composition (using DXA) between race/ethnicity in more than a

thousand children ages 5 to 18 years (46). Overall, White boys and girls had greater %BF than Black (3.5% and 2.6%, respectively) and Hispanic (0.5% and 0.5%, respectively) children with similar levels of age and body mass index [BMI] for age (all $p < 0.001$); White girls had 0.7% lower %BF than Asian girls ($p < 0.001$). Further stratified analysis by BMI categories revealed that White children with overweight had 2 to 3% higher %BF than Asian children, Black children, and Hispanic girls (46).

Differences between ethnic groups can be explained by genetics, hormonal and cultural factors (47, 48). After controlling for maternal pre-pregnant BMI, gestational weight gain, and breastfeeding, a study has shown that newborns of Hispanic and non-Hispanic Black mothers had a 2.72% greater and 1.93% lower %BF (by ADP at birth), respectively, than newborns of non-Hispanic White mothers (all $p < 0.001$) (48). Regarding hormonal influences, contradictory evidence exists; for example, one study reported higher leptin concentrations in African American girls aged 8 to 17 years compared to Caucasian girls (independent of age and FM) (49), but another study showed that leptin concentrations were not influenced by ethnicity (50). Additionally, cultural beliefs and perceptions of body image (e.g. increased adiposity being associated with a healthier status than leanness) and environmental influences (e.g. neighborhood crime and safety, recreation, societal stressors, influences on early feeding) may lead to a greater adiposity development during childhood (47). For example, a study following children from 2 years of age until their entrance into kindergarten revealed that the prevalence of risk factors associated to childhood obesity was greater among African American children, while the lowest prevalence was observed in Asians (51).

2.3.3 Genetics

Several studies have explored the role of genetics as a determinant of obesity, or excess adiposity. Using a twin study design (mean age of 9.9 years), Wardle et al. compared genetically identical (monozygotic) and fraternal (dizygotic) twin pairs and found that genetic inheritance explained 77% of high BMI (i.e. obesity) and 40% of high waist circumference (i.e. abdominal obesity) (52). Another study investigated the changes in anthropometrics and body composition after a two-week overfeeding dietary intervention in 12 pairs of young adult male monozygotic twins (mean age of 21 years) (53). Not surprisingly, changes in regional AT distribution and abdominal VAT (by computerized tomography [CT]) were similar within pairs, but highly variable between pairs (53). Furthermore, structural changes in genes including deletions,

variations, or mutations in proteins responsible for encoding proteins related to metabolism and appetite regulation can lead to genetic forms of obesity (54). These genetic variants can be inherited in an autosomal or x-linked pattern, and there are currently three classifications for genetic obesity: monogenic, syndromic, and polygenic obesity (54).

Monogenic non-syndromic obesity results from single-gene mutation associated with increased appetite (i.e. hyperphagia), early onset severe obesity, and endocrine dysfunction in some patients (55). Several single-gene mutations have been identified and the most common forms are associated with dysfunctions in the leptin (*LEP*) gene and its receptor (*LEPR*) or regulator (*SH2B* adaptor protein 1 [*SH2B1*]), proopiomelanocortin (*POMC*) gene, pro-protein convertase subtilisin/kexin type 1 (*PCSK1*) gene, melanocortin 4 receptor (*MC4R*), and neurotrophic tyrosine receptor type 2 (*NTRK2*). Clinical features specific to each form of non-syndromic obesity are reviewed in detail by Pigeyre et al. (55).

Syndromic obesity results from single- or multiple-gene mutations but differs from the other two by the characteristic cognitive delay, dysmorphic features, extreme hyperphagia, organ-specific abnormalities and other characteristics of hypothalamic dysfunction (56). The most common forms of syndromic obesity are Prader-Willi syndrome, Albright's hereditary osteodystrophy, Bardet-Biedl syndrome, Alstrom syndrome and others. Irizarry & Haqq provide a detailed description of clinical features of these genetic forms of obesity (56).

On the other hand, polygenic obesity is characterized by multiple gene dysfunction that results in obesity due to their interaction with the environment (57). Importantly, polygenes enclose one allele that is susceptible to higher and another to lower body weight. More than 100 polygenes associate with body weight regulation have been described as a result of the implementation of genome-wide association studies. Given that these studies are not hypothesis based, the discovery of new genes associated with obesity and weight trajectories are possible. For example, one prospective study evaluating Norwegian children from birth to eight years found strong positive associations between a single-nucleotide polymorphism (*rs2767486*) in the *LEPR/Leptin Receptor Overlapping Transcript (LEPROT)* locus and BMI at 6 months but no effects later in life or adulthood (58). A similar transient effect was observed near *LEP* (*rs104875*), which peaked at 1.5 years. Interestingly, the *FTO* gene (common gene described in adulthood obesity) was associated with BMI only after the age of 7 years. In addition, Alves et al. combined genomic and anthropometric data from five different prospective studies conduct in

European countries, including children from birth to 13 years (59). This study identified similar association of adiposity and the *LEPR/LEPROT* but at a distinct single-nucleotide polymorphism (*rs9436303*).

2.3.4 Fetal Programming

Fetal programming, first described as the "Barker hypothesis", refers to the idea that environmental and lifestyle factors during pregnancy may impact fetal growth and development over the long-term, resulting in permanent effects (60). The mother's nutritional status is one of the aspects already known to affect the programming of the body (61). Maternal health and prenatal exposure to toxins have been shown to contribute to obesity development during childhood and adolescence. Findings from a large study including 1,173 mother-child pairs (mostly Caucasians) demonstrated that maternal obesity during early-pregnancy was associated with a 0.63 standard deviation increase in BMI z-score ($p=0.006$) and a 11.5% increase in sum of skinfold thickness ($p <0.001$) in children at 6 years old (adjusted analysis for maternal covariates) (62). The authors also investigated factors predicting body adiposity at 6 years and found that smoking and sedentary behaviours (i.e. time spent watching television) in early pregnancy were positively associated with child's adiposity measures. On the other hand, inverse associations were observed between children's body adiposity measures and maternal sleep, alcohol consumption, and multivitamin use (62). The association between maternal glucose metabolism (assessed by oral glucose tolerance test [OGTT] and glycated haemoglobin) during pregnancy and children's %BF at 10 to 14 years were evaluated by Lowe Jr. et al (63). After adjusting for confounders (e.g. child's sexual maturation, adiposity, and maternal variables), the authors found that the OR for having high %BF (>85th percentile for age and sex; measured by ADP) during childhood and adolescence for maternal glucose markers ranged from 1.14 to 1.18, all $p <0.05$ (63). Other studies indicate that exposure to gestational diabetes during fetal growth may impact children's adiposity (64, 65).

Animal models have shown that maternal undernutrition and overnutrition affect the development of fetal AT (66). Compared to ewes fed to satiation, restriction of nutrients in the second trimester of pregnancy resulted in greater fetal adiposity at day 80 of gestation (67). This effect has been linked to an increased AT sensitivity and anabolic effects of insulin-like growth factor 1 (IGF-1) (67). Khanal et al. studied the effects of maternal diet during the last trimester and adiposity outcomes in offspring (68). Ewes born from ewes fed with different energy

requirements during late gestation (high, normal or low energy intake) were fed either normal or high-carbohydrate, high-fat diet after birth. At six months of age, corresponding to puberty, AT biopsies were performed, revealing that maternal over- and undernutrition, in addition to a high-carbohydrate, high-fat diet, contributed to hypertrophy in contrast of hyperplasia of AT (including SAT, mesenteric, and perirenal AT) (68).

In humans, maternal diet quality (assessed by the Healthy Eating Index-2015) during pregnancy and lactation was positively associated with infant %BF and FM (in kg, by ADP) at 6 months of age (69). To evaluate the implications of intrauterine growth restriction on adiposity development and metabolic risk in the first years of life, Sebastiani et al. assessed body composition using ADP in small-for-gestational age (SGA) and AGA infants at birth, ages 1 and 2 years (70). Compared to AGA infants, SGA infants had lower %BF at birth (which was normalized at 1 year old), thicker carotid intima-media thickness (cIMAT) at 1 and 2 years old, and greater pre-peritoneal fat at 2 years old. There were no differences in cardiovascular markers or cardiac morphometry. Another study in preterm infants comparing body composition by ADP of SGA and AGA at term, one, three and five months revealed that although %BF was lower in SGA at term, %BF was normalized in the SGA group at one month and similarities between the groups persisted until the last follow-up visit (at 5 months) (71).

Maternal exposure to endocrine disrupting chemicals, such as bisphenol A that is found in plastics, has been shown to affect fetal and infant development (72). Bisphenol A appears to cross the placenta and researchers have quantified human exposure in several body fluids, including breast milk, umbilical cord blood, and amniotic fluid. Although several animal studies confirm prenatal exposure to bisphenol A and its effects on health through the perozisome proliferator-activated receptors pathways (see Shafei et al., for a detailed description on the mechanism), epidemiological studies have not been conducted to investigate the implication of bisphenol A in adiposity development in humans (73).

2.3.5 Feeding Practices and Nutrition

Feeding practices during infancy and throughout childhood are also associated with excess adiposity. The benefits of breastfeeding to infant's health have been extensively described in the literature and includes, for example, improved immunity and cognitive development (74, 75). However, there is contradictory evidence on whether breastfeeding influences adiposity development. One study has shown positive associations between breastfeeding duration and

SAT (by ultrasound [US]), but not VAT at 3 and 6 months (76). Comparisons between breastfed and formula-fed healthy newborns from low-risk pregnancies revealed greater %BF (using ADP) at 3 and 6 months in those who were breastfed (77). In contrast, no differences in %BF or FM (also by ADP) were found between breastfed and formula-fed infants at 1, 4, and 7 months of age in another study (78). Indeed, nutrient content of human milk appears to influence AT development as negative associations between carbohydrate content in human milk and FM or %BF (by US) have been reported in infants aged 2, 5, 9, and/or 12 months (79). Thus, infants may respond differently to breastfeeding regarding AT development because nutrient content of human milk can affect this association.

In addition to breastfeeding, the time of complementary feeding introduction is also a determining factor for adiposity accrual early in life and during childhood. A prospective study has shown that children who were breastfed during infancy and had complementary feeding initiated earlier than 4 months had a greater likelihood of presenting with higher truncal fat (by DXA) in mid-childhood ($\beta = 0.33$ [95% CI, 0.01, 0.65]) and early adolescence ($\beta = 1.20$ [95% CI, 0.33, 2.06) than breastfed children who had complementary feeding initiated at 4 to 6 months (80). Similar associations were found in formula-fed children; complementary feeding earlier than 4 months was positively associated with truncal fat at mid-childhood ($\beta = 0.52$ [95% CI, 0.07, 0.97) and %BF at early adolescence ($\beta = 2.55$ [95% CI, 0.20, 4.91]). Interesting, 82% of the children who received complementary feeding at earlier than 4 months had infant cereals, whereas 30% had fruits, 22% were fed vegetables and 30% fruit juice (80).

Studies have also investigated the implications of dietary patterns with obesity. After following 325 children for four years (age period from 3.8 to 7.8 years old), Wosje et al. observed an association between higher fried-food intake and higher FM (using DXA) (81). Furthermore, a positive association between glycemic load at 9.6 years old and %BF (by DXA) at 11.7 years old was reported in children at risk of obesity (parents with obesity) (82). Prospective studies evaluating the associations between diet quality at baseline and FM (by DXA) at follow-up revealed mixed findings. In two studies, lower diet quality indices in early (6 and 12 months) (83) and mid-childhood (8 to 10 years) (84) were associated with greater FM at follow-up (at 6 years and 10 to 12 years old, respectively). Contrary to these results, Nguyen et al. reported that positive associations between diet quality and BMI were explained by greater FFM index and not

%BF or FMI. The different approaches used to calculate the diet quality index may partially justify the heterogeneous findings.

Appetite and eating behaviours also influence the development of childhood obesity, as regulation of food intake contributes to energy homeostasis. According to Boswell et al., appetite is related to physiological (homeostatic) and psycho-social needs (hedonic), and eating behaviours are the actions during eating events (85). In the absence of physiological energy needs, consumption of palatable food characterizes the hedonic eating and triggers the release of dopamine in the nucleus accumbens, leading to overeating and consequent obesity (86). Thus, hedonic eating is driven by the reward of food consumption and not metabolic need. Eating behaviours are influenced by many factors, including mothers' eating behaviours (87), stress (88), attention-deficit/hyperactivity disorder (89), and eating disorders (e.g. binge eating and lack of control overeating) (90).

2.3.6 Gut Microbiota

Gut microbiota composition during the first years of life are determined by several factors, such as mode of delivery, feeding practices, antibiotics use, and environmental exposures (91). The associations between these factors and risk of obesity development have been evaluated in humans (92-94). For example, infants born by caesarean delivery from mothers with overweight were five times more likely to present as overweight by one year old (93) and breastfed infants had a lower risk of becoming overweight at 12 months than formula-fed infants (95). Moreover, mechanistic studies using animal models have confirmed the causal role of gut microbiota in the obesity pathogenesis (96, 97). Please see Kincaid et al. for a comprehensive review of the literature discussing the most recent animal and human evidence on the interactions between gut microbiota, early life exposures, and obesity onset (97).

During childhood and adolescence, when the gut microbiota has been completely assembled, interactions between dietary components and gut microbiota can result in inflammation and metabolic abnormalities (98). A diet poor in fiber is particularly associated with suboptimal production of short chain fatty acids by the gut microbiota, limiting the beneficial secretion of anorexigenic hormones, anti-inflammatory cytokines, and mucin on the protective intestinal mucus layer (99-101). Furthermore, a high-fat diet has been shown to promote metabolic endotoxemia, leading to increases in AT, inflammation as well as diabetes (102). Regarding microbiota composition, children with obesity presented with a lower

abundance of the beneficial bacteria *Akkermansia muciniphila* (103) (known to promote barrier integrity) and enriched *Bacteroides eggerthii* (104) and *Bacteroides fragilis* (105) (positively associated with adiposity and inflammation).

2.3.7 Physical Activity

A recent report from Statistics Canada (years 2016-2017) revealed that 39% of Canadian children aged 5 to 17 years spent at least 60 minutes of moderate-to-vigorous physical activity (MVPA) per day (106). Furthermore, 53% of them met the recommendations for daily screen-time (maximum of 2 hours) (106). Although these recent findings have not yet been analyzed according to body weight categories, studies conducted using data from previous surveys have reported lower MVPA in boys with obesity (107) and greater time spent in sedentary behaviours (both sexes) (108) compared to children with normal weight. Interesting, higher physical activity intensity was associated with lower %BF by DXA in boys (but not in girls) aged 3 to 7 years (109), and time spent in physical activity negatively predicted VAT (using MRI) in 8-year-old children at risk for obesity (110).

Despite clear differences in physical activity behaviours between weight categories, it appears that physical activity and/or exercise do not have a direct effect on adiposity (111). Even when a 12-week high-intensity interval training was combined with dietary counselling, no changes in FM or %BF (by DXA) and abdominal VAT and SAT (by MRI) were observed in children with obesity aged 7 to 16 years old (111). As one of the proposed pathways for lipolysis is through the release of growth hormone, the authors suggested that the reduced growth hormone levels and catecholamine responses to acute exercise can be associated with a disadvantage in reduction of adiposity in children with obesity (111). Despite changes in body composition not being observed, the exercise intervention was shown to improve cardiorespiratory fitness. In the context of enhancing overall health, a recent meta-analysis demonstrated that physical exercise in children with obesity promoted a reduction in inflammation (i.e. lower IL-6 concentrations) and hormonal changes (i.e. reduced leptin and increased adiponectin concentrations) (112). Another explanation for the lack of positive exercise effects on adiposity resides in the constrained model of energy expenditure proposed by Pontzer (113). According to the author, the human body compensates the increases in energy expenditure through exercise by reducing the energy expended in non-physical activity metabolic activity; therefore, a negative energy balance that results in adiposity changes are unlikely to occur. More recent studies in the adult population

have shown that increases in dietary intake accompanied by exercise initiation is a mechanism often observed that contributes to compensation (114, 115).

2.4 Associations Between Body Fat and Health Outcomes During Childhood

2.4.1 Metabolic and Immune Function

2.4.1.1 Glucose Metabolism

The implications of adiposity on glucose metabolism have been extensively evaluated in the pediatric population. As birth weight and adiposity early in life track into childhood and adolescence, researchers have investigated the relationship between anthropometrics or body composition measures of adiposity at birth and insulin sensitivity later in life. For example, being born with low birth weight predicted higher risks of insulin resistance (IR) and impaired fasting glucose (OR = 1.54 [95% CI, 1.05, 2.24]; and OR = 1.94 [95% CI, 1.22, 3.10]; respectively) at ages 6 to 8 years, possibly because low birth weight is related to rapid increases in adiposity (116). However, mediation analysis did not find any effects of BMI or %BF (by bioelectrical impedance analysis, BIA) in these associations, but lower %BF mediated the protective effect of high birth weight on IR (OR of mediated effect = 0.96 [95% CI, 0.92, 0.98]). In contrast to these findings, a recent prospective study has shown that only those infants with a faster rate of weight gain (adjusted for length) from birth to 2 years had a greater %BF at 8 to 10 years old, which then mediated a lower insulin sensitivity (OGTT test) at 10 to 12 years old (117).

Studies using cross-sectional designs also evaluated the relationship between whole-body and/or abdominal adiposity and glucose metabolism markers. In a study of children and adolescents aged 7 to 15 years, higher FM assessed by DXA was moderately associated with higher HOMA-IR ($r = 0.447$; $p < 0.001$), independently of several covariates (i.e. race, sex, sexual maturation, height, and LST) (118). Particularly in prepubertal children, regression analyses adjusted for birth weight and maternal characteristics revealed a positive association between both MRI-measured SAT ($\beta = 2.96$; $p < 0.001$) and VAT ($\beta = 12.74$; $p = 0.001$) only in girls (37).

Stratified analysis according to different levels of glucose metabolic markers revealed mixed findings. For instance, Hubers et al. compared FM (by ADP) and SAT and VAT (by MRI) between HOMA-IR categories (low, normal, and high; adjusted for BMI) in pre- or intra-pubertal children and post-pubertal adolescents (119). The authors described differences between groups for FM in children but not in adolescents; furthermore, there were no differences in SAT and VAT depots between the three groups, independent of age categories. Likewise, Kim et al. did

not find any differences in %BF (by DXA) and VAT (by MRI or CT) between children and adolescents with overweight and obesity who had an early glucose peak (≤30 min) or late glucose peak (> 30 min) response to an OGTT test (120). These different responses have been previously associated with type 2 diabetes risk; adults with a late glucose peak had lower insulin sensitivity, impaired insulin secretion, and higher risk for prediabetes and type 2 diabetes than adults with an early peak (121). In the study by Kim et al, participants with late peak showed a higher free fatty acid area under the curve and worse β-cell function compared to early peak, suggesting IR of the lipid metabolism (120).

Using ^{1}H nuclear magnetic resonance spectroscopy, researchers compared the intramyocellular and extramyocellular lipid content of soleus muscle in adolescents with obesity or normal weight as well as the associations with insulin sensitivity (122). Adolescents with obesity presented with a greater content of both intramyocellular and extramyocellular lipid (all $p < 0.002$). After adjusting for %BF (by DXA) and SAT (by MRI), intramyocellular was negatively correlated with insulin sensitivity ($r = -0.73$; $p < 0.01$); however, adjusting for the effects of VAT removed the significance of associations between intramyocellular lipid and insulin sensitivity, suggesting an important role of VAT on type 2 diabetes risk (122). It is interesting to note that adolescents with obesity had lower rates of whole-body glucose uptake than adolescents with normal weight ($p < 0.01$). Adipose tissue IR, or the reduced ability of insulin to supress lipolysis and uptake glucose, was evaluated by Kim et al. in 205 pubertal and post-pubertal adolescents using a surrogate index (fasting insulin x fasting free fatty acid concentrations) (123). Compared to children with normal weight, children with obesity and normal glucose tolerance test had a 2.2-fold higher adipose IR index, and those with obesity and dysglycemia (either impaired glucose tolerance or type 2 diabetes) had a 4.6-fold higher index. Positive, moderate correlations were found between adipose IR and whole-body %BF and FM as well as AT distribution (VAT and SAT by CT or MRI) (123).

2.4.1.2 Lipid Metabolism

Abnormalities of lipid metabolism lead to an increased risk for development of premature cardiovascular dysfunction in children and adolescents (124). These abnormalities are often characterized by measuring components of the plasma/serum lipid profile, such as total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and TG concentrations (125). The associations of FM at birth and FM accretion in the

first three months of life to markers of lipid metabolism at 5 years were evaluated by Wibaek et al. in Ethiopian children (126). After adjusting for childhood FM and several other covariates, a 0.16 mmol/l (95% CI, 0.05, 0.26 mmol/l; p = 0.005) higher LDL-C was estimated at 5 years for every 100 g increase of FM at birth. Similar findings were observed for adiposity accrual in the first three months of life. In older children and adolescents of Chinese ethnicity (ages 6 to 18 years), those presenting with high %BF by DXA (defined as ≥75th for sex and age percentiles) had higher total cholesterol, LDL-C, and TG, but lower HDL-C compared to children with low %BF, independent of sex (all p <0.01) (127). Furthermore, positive but weak correlations between these lipid markers (except HDL-C) and abdominal adiposity (SAT and VAT) adjusted for participants' demographics, sexual maturation and smoking were described, with slightly stronger correlations in boys (r range = 0.23 to 0.39; p <0.001) than in girls (r range = 0.09 to 0.23; p <0.001) (128). Visceral AT and SAT correlated negatively with HDL-C in both boys (r range = -0.22 to -0.25) and girls (r=-0.18); all p <0.001. In children of younger age (median age = 5.1 years), there was a trend for negative, moderate correlation between HDL-C and epicardial AT thickness (Spearman's rho = -0.35; p=0.06) and between adiponectin and epicardial AT thickness (Spearman's rho = -0.44; p=0.016) (129). A stratified analysis by weight categories revealed that children with overweight and obesity had greater epicardial AT than children of normal weight (p = 0.002).

2.4.1.3 Hypertension and Cardiovascular Disease

High blood pressure is one of the modifiable risk factors associated with cardiovascular disease. As blood pressure tracks from childhood to adulthood, having high blood pressure during childhood may increase the risk of hypertension or cardiovascular disease later in life (130, 131). Sexual dimorphism in the associations between blood pressure and whole-body and abdominal adiposity was reported by Pausova et al. after children underwent a 52-minute cardiovascular protocol evaluating blood pressure across supine, standing, sitting, stress, and post-stress conditions (132). Overall, %BF was positively associated to systolic blood pressure (SBP) in girls and negatively in boys. On the other hand, VAT (by MRI) was positively associated with SBP during the sitting position only in boys, explaining 3.50 to 4.54% of the variations in SBP (p <0.001). In a study conducted in China, both VAT and SAT assessed by DXA were weakly, but positively associated with SBP and diastolic blood pressure (DBP) in boys (r range = 0.20 to 0.34) and girls (r range = 0.09 to 0.18) (128). Furthermore, moderate and positive associations

between FMI (by DXA) and SBP and DBP as well as TG were apparent in adolescents after puberty (r range = 0.31 to 0.42; $p < 0.05$), but not in pre- and intra-pubertal children (119).

Carotid intima-media thickness has been used as a marker of atherosclerosis development and prediction of cardiovascular events, although further standardisation in the assessment procedures is needed to ensure accuracy in the measures (133, 134). In Chilean children with hypertension (SBP and/or DBP $\geq 90^{th}$ percentile for sex, age, and height), cIMAT was positively associated with SBP ($r = 0.428$; $p < 0.001$), DBP ($r = 0.382$; $p = 0.004$), aldosterone-renin ratio ($r = 0.57$; $p < 0.0001$), and serum aldosterone ($r = 0.478$; $p < 0.0001$) (135). Nevertheless, %BF was not associated with cIMAT. Other studies further explored the associations between fat depots and cIMAT and significant findings were reported (136, 137). For example, perirenal AT measures by US was a predictor of cIMAT (overweight: $\beta = 0.250$; $p = 0.006$; $r^2 = 12.8\%$; obesity: $\beta = 0.254$; $p = 0.002$; $r^2 = 15.5\%$) in prepubertal children aged 5 to 12 years, independent of BMI, sex, age, and metabolic markers (136). In pubertal children and adolescents with obesity and metabolic syndrome (MetS; ages 9 to 18 years), epicardial AT thickness assessed by echocardiography was shown to be the only independent predictor of cIMAT ($\beta = 0.65$; $p < 0.001$) (137). Therefore, cIMAT appears to be increased in those children and adolescents with greater amount of more inflammatory fat compartments than with whole-body adiposity.

2.4.1.4 Clustered Metabolic Risk Factors and Inflammation

Given the clear evidence of clustering metabolic risk factors in children with obesity (138), studies have evaluated the implications of adiposity on metabolic health in children presenting with multiple metabolic risks factors (139, 140). In a cohort study of more than 6,500 children at age of 6 years, Gishti et al. found a greater association of %BF (by DXA) with clustering cardiovascular risk factors (OR = 3.01 [95% CI, 2.67, 3.39] per standard deviation of %BF) than with hypertension or hypercholesterolemia alone (139). Similar observations were found for android to gynoid FM ratio, preperitoneal AT area, and SAT area with clustering cardiovascular risk factors (OR range = 2.2 to 3.0). In a cross-sectional design, Taksali et al evaluated metabolic markers, total body composition (by DXA), and abdominal and intrahepatic fat (by MRI) in 118 adolescents with obesity (140). The authors stratified the sample into VAT tertiles; compared to the first tertile, those children in the highest tertile were 5.2 times more likely to present with MetS. Interestingly, children in the highest tertile had the lowest %BF and SAT, but higher liver enzymes as well as HOMA-IR, TG and lower insulin sensitivity (Matsuda

index). Participants from the same study were followed for about 19.2 months, and girls with the highest ratio of VAT/(SAT + VAT) at baseline presented with a 4.4-fold higher risk of impaired glucose tolerance and type 2 diabetes at follow-up (141). To investigate the mechanisms leading to unfavourable metabolic phenotype, Nouws et al. evaluated the turnover of lipids and adipocytes in the SAT and gluteal/femoral AT with different levels of VAT/(VAT + SAT) (142). A higher triglyceride turnover rate was observed, which was positively correlated with intrahepatic fat store but not de novo lipogenesis, in those girls with high VAT/(VAT + SAT) ratio.

Regarding inflammation, children with overweight or obesity (ages 5 to 18 years) presented with a higher concentration of inflammation markers, such as C-reactive protein (CRP), leukocytes, lymphocyte, erythrocyte, platelet, and transaminase levels (all $p < 0.04$) compared to children with normal weight (143). In pubertal adolescents with obesity aged 13 to 18 years, inflammation index (z-score for IL-6, TNF-α, and leptin) was positively associated with FM (by DXA) in boys ($\beta = 0.146$; $p = 0.015$) and girls ($\beta = 0.168$; $p = 0.032$), after adjusting the statistical analysis for age (144). Together, these findings confirm the presence of low-grade inflammation also in the pediatric population with excess adiposity.

2.4.2 Sleep Disordered Breathing

Sleep disordered breathing is a common obesity-related comorbidity. A recent study reviewing the medical records of children with obesity aged 8 to 16 years who had completed a polysomnography study in one of three pediatric sleep laboratories across Canada reported that 44% of them presented with obstructive sleep apnea and 90% described one or more sleep concerns (e.g. snoring, fatigue, mouth breathing) (145). The apnea hypopnea index is the most used approach to capture respiratory events during sleep, and studies have assessed the associations between this index and adiposity measures in the pediatric population. For example, Bhatia et al. found that higher apnea hypopnea index was associated with higher whole-body and trunk FM (using DXA) in boys with obesity and snoring aged 10 to 17 years ($r = 0.426$ and 0.401, respectively; $p < 0.05$); however, associations were neither significant for whole-body %BF measures in boys nor in girls possibly due to the small size ($n = 9$ females) (146). Another study evaluating VAT and SAT in single-slice MRI images at the level of the fourth lumbar vertebrae found that VAT was the only predictor of apnea hypopnea index in children in linear regression analysis ($r^2 = 0.556$; $p = 0.003$) compared to other possible predictors, such as age, sex

and BMI z-score (147). As the apnea hypopnea index does not provide a measure of obstructive sleep apnea severity (148), Bhatia et al. further investigated the association of oxygen desaturation and arousal indices (i.e. sleep fragmentation) to adiposity and found that the former was moderately associated with whole-body FM ($r = 0.490$; $p < 0.01$) and trunk FM ($r = 0.483$; $p < 0.01$) in males (146).

The mechanisms underlying the positive associations between obstructive sleep apnea and adiposity measures are not completely clear. Recent studies have suggested that functional, structural, and inflammatory factors contribute to sleep concerns in children and adolescents with overweight or obesity (146, 149, 150). Excess adiposity in the trunk was shown to affect the functional residual capacity of lungs leading to oxygen desaturation during sleep (151). In addition, adolescents with obesity and obstructive sleep apnea had anatomical alterations in MRI examination, including greater adenotonsillar tissue and narrower nasopharyngeal airway compared with adolescents without obstructive sleep apnea (150). Inflammation is another important factor, and Gaines et al. reported that the association between higher VAT (by DXA) and obstructive sleep apnea in adolescents with obesity was 82% and 42% explained by elevated CRP ($p = 0.01$) and IL-6 ($p = 0.03$) concentrations, respectively, in mediation analysis (152). To support the effects of systemic inflammation on sleep apnea, treatment with anti-inflammatory therapy reduced the symptoms severity in most children with mild obstructive sleep apnea (153). Given these associations with inflammatory markers, it is noteworthy that obstructive sleep apnea also represents a cardiovascular risk as changes in arterial stiffness have been associated with this syndrome in adolescents with obesity (154).

2.4.3 Bone

Peak bone mass occurs during adolescence and determines bone fragility and the risk of future osteoporotic fractures. Although genetics is the main contributing factor for healthy bones, nutrition, mechanical load, and chronic diseases (including obesity) also regulate the bone remodeling process (155). Sioen et al. conducted a systematic review to investigate specifically the associations between whole-body adiposity and bone parameters (i.e. bone mineral content, bone mineral density, and bone area) in the pediatric population (156). After analyzing 19 studies published up to November 2014, the authors concluded that previous research have reported mixed findings on the strength and direction of these associations due to methodologic

differences across studies, such as skeletal site being measured, sex, and age and maturation of children and adolescents.

More recent studies evaluated the associations of whole-body and abdominal adiposity with bone strength parameters, such as the strength-strain index. This index is a surrogate measure of the ability of a bone to resist bending or torsion, and it is estimated by peripheral quantitative CT. Using the strength-strain index in a longitudinal study of children between the ages of 11 to 19 years, Glass et al. found that higher VAT (by DXA) was associated with lower index at the radius (-0.06; $p = 0.001$) and tibia (-0.05, $p = 0.004$) in girls after adjusting for LST (157). The opposite was found in boys; only SAT and whole-body FM were negatively associated to strength-strain index at the radius ($r = -0.04$, $p = 0.004$; r -0.05, $p = 0.001$; respectively). Moreover, Hetherington-Rauth et al. reported weakly positive associations between FM using DXA and strength-strain index only at weight bearing sites (i.e. tibia and femur) but not at non-weight bearing sites (i.e. radius) in 9 to 12 years-old girls, after controlling for relevant covariates (i.e. maturation onset, height, and ethnicity) (158). These findings support two potential explanations for the negative associations between adiposity and bone, as highlighted by Duran et al (159). Although individuals with excess adiposity appear to have more lean mass than those with normal weight, the mechanical loading in bone that would favour bone deposition is reduced in children with obesity. Furthermore, the adipokines released by AT (especially VAT) can accelerate bone resorption by altering the sympathetic impulses to the bone (159).

The effects of high adiposity on the musculoskeletal system and gait biomechanics have also been explored. With a longitudinal study design, Meng et al. followed 327 children from the ages of 7-15 years to the ages of 31-41 years and observed that higher adiposity during childhood was associated with higher risk of patellar cartilage defects in adulthood (relative risk = 1.11 kg [95% CI, 1.01, 1.22] for FM) (160). The implications of having high %BF (by ADP) on gait biomechanics were investigated in 50 boys (ages 7 to 11 years; 40% with overweight or obesity) (161). Findings indicated that higher %BF was associated with an altered joint moment and range of joint angle in the lower limb during the gait, such as lower hip extension and greater external peak knee adduction. These biomechanical constraints are related to lower walking velocity and step distance as well as to osteoarthritis severity and progression during adulthood (161).

2.4.4 Physical Fitness

Physical fitness is considered an important determinant of overall health and cardiovascular diseases (162). Several studies have shown that children and adolescents with obesity presented with a poorer performance during cardiorespiratory and neuromuscular tests compared to their lean peers, independent of sex, age, and sexual maturation (163, 164). As an example of the association between adiposity and cardiorespiratory fitness, Lee et al. evaluated maximum oxygen uptake using the Bruce multistage treadmill protocol in White and African-American children aged 8 to 17 years and found that %BF assessed by DXA and abdominal adiposity (VAT and SAT using CT) were both negatively associated with cardiorespiratory fitness (r range = -0.43 to -0.72; $p < 0.05$) (163). Furthermore, multiple regression analysis revealed that both VAT and SAT were the strongest predictors of cardiorespiratory fitness (β = -1.332 and -1.894, respectively; all $p < 0.001$). Similar results were obtained in a Spanish study including adolescents aged 12.5 to 17.5 years; higher %BF and abdominal adiposity by DXA were associated with lower performance in the standing broad jump, Abalokov, 4x10-m shuttle run and 20-m shuttle run test in both boys and girls (164).

Regarding neuromuscular fitness, Haapala et al. described associations between higher %BF (by DXA) and poorer performance in neuromuscular tests, such as the sit-up test, flamingo balance test, and box and block test (165). Stratified analysis combining adiposity and physical activity levels revealed that children with higher %BF and lower levels of physical activity presented with the poorest results for neuromuscular performance tests compared to all the other groups. In another study, children aged 9 to 11 years old had physical activity measured by accelerometer and researchers compared body composition and cardiorespiratory fitness between those who achieved and those who did not meet the 60 minutes of MVPA (active vs. inactive) (166). Inactive children presented with greater %BF by DXA and lower peak oxygen uptake than active children ($p < 0.001$). Findings from these studies suggest that children with excess adiposity exhibit a poorer cognitive control and a perceptual-motor deficit.

2.4.5 Cognitive and Psychological Function

There is a growing body of literature that recognizes the implications of excess adiposity on cognitive and behaviour development during childhood and adolescence. In preterm infants born with AGA, a negative association between %BF gains (by ADP) from term to 4 months corrected age and working memory at 4 years old ($p = 0.01$) was found (167). The same study

described that higher %BF gains at later stages of life (from 4 months to 4 years) were associated with lower intelligence quotient and processing speed index at preschool age (4 years) in AGA term infants. Using different tests to evaluate cognitive functioning, Abera et al. reported that FM at birth measured by ADP was neither associated with global developmental nor with scores for language, fine and gross motor, or personal-social scores in unadjusted and adjusted analysis in Ethiopian children at 2 years old (168). However, further assessment of mental health outcomes in the same cohort at 5 years of age revealed a 5.69 points higher scores in the Strengths and Difficulties Questionnaire for each kilogram increase of FM at birth (adjusted for neonatal, postnatal, and parental characteristics), suggesting a greater risk of mental health problems in those individuals born with greater FM mass (169).

The associations between cognitive control and adiposity were also evaluated in older children (170). After adjusting for relevant covariates (i.e. demographics, anthropometrics, and physical fitness), higher %BF and abdominal FM (by DXA) were associated with lower scores for the Go/no-Go test (assessing the ability not to respond in inappropriate context) and reading and spelling domains of an academic achievement test (β range = -0.20 to -0.30; $p < 0.05$) in both boys and girls aged 7 to 9 years (170). Although Yau et al. did not assess body composition, the authors found that adolescents with obesity and type 2 diabetes had poorer performance in neuropsychological evaluation of intellectual functioning, verbal memory and psychomotor efficiency compared to adolescents with obesity without metabolic complications (171). Furthermore, structural analysis of the brain also revealed lower whole-brain and frontal white matter volumes and greater cerebrospinal fluid space in the whole-brain and frontal lobe of those adolescents with type 2 diabetes. These findings indicate that oxidative stress resultant from type 2 diabetes may contribute to brain damage (171).

Studies evaluating the effects of physical exercise on cognitive function reveled improvements in cognitive performance (172, 173). For example, Raine et al. found that reduced VAT (by DXA at the fourth lumbar vertebrae) after a 9-month physical activity intervention (MVPA for 2-hour/day, 5 days/week) was associated with improved inhibitory control in children with obesity (172). Another exercise intervention study assessed the effects of 40-minutes daily aerobic activities for eight months on brain white matter integrity (specifically the uncinated fasciculus by MRI) and improvements in integrity with exercise were found in children with overweight (173).

It has also been suggested that low-grade systemic inflammation may play a role on the effects of excess adiposity on depression symptoms (174). Using the Children's Depression Inventory in Hispanic/Latino children and adolescents aged 8 to 16 years, Nguyen-Rodriguez et al. reported that depression symptoms were positively associated with high-sensitivity CRP (hs-CRP; $\beta = 0.10$; $p = 0.037$), after adjusting the analysis for sociodemographic covariates (174). Although %BF was positively associated with hs-CRP, the indirect effects of %BF on the association between depression symptoms and hs-CRP was significant only in females (indirect effect = 0.001 [95% CI, 0.0007, 0.0140]).

Another relevant factor that may lead to psychological distress in children with obesity is weight-based teasing (175, 176). A recent systematic review reported that weight-based teasing is frequent among children, with girls presenting more repeated experiences than boys (frequency range 14 to 45% in girls and 10 to 35% in boys) (175). Furthermore, the authors noticed a positive association between weight-based teasing and symptoms of depression across included studies. In addition to these findings, a prospective study evaluated the associations between weight-based teasing and FM (by DXA) from childhood to adolescence/young adulthood (mean follow-up 8.5 years) in individuals with overweight or obesity and normal weight with family history of obesity (176). Children who experienced high levels of weight-based teasing had a 91% greater FM gain per year than those who did not experience weight-based teasing. Future studies should evaluate the weight bias internalization, or awareness of social weight stigma incorporated to oneself, to better explain these findings (176, 177).

2.5 Skeletal Muscle Development and Its "Capacity" on Health

Adequate skeletal muscle quantity and "quality" are essential for the maintenance of optimal health throughout life (178). Besides its contractile function, skeletal muscle is an important determinant of glucose metabolism (179). Approximately one quarter of all ingested glucose is taken up or stored as glycogen by skeletal muscle to use as an energy source (180). Additionally, skeletal muscle stores amino acids and lipids in the form of muscle triglycerides to produce energy during periods of starvation (181), and its metabolism is also a determinant of resting energy expenditure (182). Given these metabolic roles, the skeletal muscle has been characterized as a tissue with high metabolic capacity (183), directly influencing the development of metabolic diseases (184-186).

Skeletal muscle is a tissue capable of modifying its structure and metabolic properties. Despite its plasticity, the number of muscle fibers are partially set before birth during the embryonic and fetal stages of development (between weeks 6-8 and 8-18 of pregnancy, respectively) (187-189). After birth, muscle fibers grow mainly in size and to a much lesser degree in number (190); therefore, defects in muscle development that occurred during pregnancy due to environmental and genetic factors may be perpetuated throughout adult life (191, 192). Several postnatal factors also affect skeletal muscle development, such as dietary protein (193), physical activity (194), chronic diseases (195), and obesity (196). These factors can generate a phenotype defined as "sarcopenia", which is characterized by low muscle mass and strength and poor physical performance (197). In this section, we discuss factors affecting pre- and postnatal skeletal muscle development.

2.5.1 Fetal Programming

Evidence from animal models demonstrate that nutrient restriction during pregnancy, especially protein, impairs skeletal muscle development of the fetus (198, 199). On the other hand, gestational overnutrition and obesity also appear to affect muscle mass of fetus in a negative way. According to Tong et al., myogenesis was downregulated in fetus from sheep with obesity, and this effect was correlated with a pro-inflammatory state (200).

In humans, the lack or surplus of nutrient supply during the prenatal period affects skeletal muscle development of the fetus. Studies comparing skeletal muscle mass and strength of individuals born SGA with those of AGA have shown that nutritional deprivation during pregnancy may negatively impact muscle development (201-203). Individuals born SGA had lower LST at birth, reduced muscular growth from two months to eight years of age (202), and lower handgrip strength (HGS) at 30 years of age compared to those born AGA (203). Older adults (204) in the lowest quintile of birth weight, compared to the highest quintile, had decreased peripheral skeletal muscle cross-sectional area (mCSA) at 70 years of age. Additionally, a recent meta-analysis found a positive association between birth weight and muscle strength, and this association was maintained across the life cycle (205). In babies born to mothers with obesity, mesenchymal stem cells were found to have a preferential increase in adipogenesis potential rather than skeletal muscle anabolism as compared to babies born to healthy weight mothers (206).

2.5.2 Genetic and Chronic Diseases

Genetic diseases affect skeletal muscle development (207), with muscular dystrophy being the most commonly encountered group of myogenic disorders in pediatrics (208, 209). Muscular dystrophy is characterized by genetic defects of enzymes or proteins with structural, contractile or multifunctional properties, that leads to progressive and generalized muscle weakness, damage and wasting (208, 209). As a consequence of this disorder, most of the patients face serious problems with locomotion, breathing and feeding, which ultimately leads to premature death (208). More than 50 forms and sub-forms of muscular dystrophies have been recognized, with Duchenne muscular dystrophy being the most prevalent pediatric myopathy (1/5,000 boys) (210). A cure still does not exist, and treatment is aimed at delaying disease progression and relieving symptoms (208). Despite not recognized as a genetic disorder of the skeletal muscle system, children with Prader-Willi syndrome have a body composition phenotype also characterized by low muscle mass (combined with high FM). Similar to muscular dystrophies, there is no cure for Prader-Willi syndrome (211); however, treatment options comprised of medications (e.g. growth hormone), diet and physical activity can help manage its complications (212, 213).

Children with chronic diseases also experience alterations in muscle mass and strength, and the extent of muscle loss can be affected by disease severity and treatment (195, 214-216). Studies in children with acute lymphoblastic leukemia, a common form of cancer during childhood, reveal substantial reductions in appendicular LST (as measured by DXA) (214) and psoas mCSA (by CT) (215) after induction therapy. High doses of steroids during induction therapy cause myofibrillary atrophy due to degradation of myosin heavy chain and decrease in myosin synthesis (217). Deficits in muscle mass appear to persist after cancer treatment; for instance, a study in long-term cancer survivors demonstrated that 50% of those aged ≤18 years had low muscle mass even after ten years of diagnosis (218).

Other common chronic diseases affecting skeletal muscles during childhood are inflammatory bowel diseases (216), chronic kidney and liver diseases (219), and type 1 diabetes (220). In inflammatory bowel disease, for example, the prevalence of low muscle mass is relatively high; a recent systematic review reported that about 94% and 48% of pediatric patients with Crohn's disease and ulcerative colitis presented deficits in muscle mass, respectively (221). The deficits in muscle mass and strength observed in children with inflammatory bowel disease

can be attributed to several factors, including steroid therapy, protein malabsorption, inflammatory cytokines, and possibly vitamin D deficiency (216, 222). Specifically, inflammatory cytokines (e.g. TNF-α and IL-6) inhibit protein synthesis, mitochondrial biogenesis, and expression of the anabolic IGF-1 (223). Besides disease-induced inflammation and steroid therapy, prolonged inactivity and lack of adequate nutrition may also negatively affect muscle mass development in children with chronic diseases (214, 216, 224).

2.5.3 Hormones

Growth hormone, IGF-1, and sex-steroids, such as testosterone and estradiol, play essential roles in skeletal muscle development during infancy, childhood and adolescence (225). Although the exact mechanisms of interaction between growth hormone/IGF-1 and sex-steroids remain unclear, these hormones act synergistically, stimulating muscle protein synthesis and reducing its oxidation rate while leading to a positive protein balance and, consequently, muscle accretion (225). Before the onset of puberty in healthy boys and girls, muscle mass and FFM increase slowly and proportionally to body growth (225-227); however, during the pubertal growth spurt, growth hormone and sex steroids undergo a dramatic activation, which rapidly increases the percentage of muscle mass (228). Hormonal changes also affect skeletal muscle in a sex-dependent manner (225); boys synthesize more muscle mass for a longer duration when compared with girls during this stage of life (229). Despite studies in animals and human tissues have confirmed the implications of thyroid hormone on myogenesis, muscle fiber type differentiation, and glucose uptake by skeletal muscle (230), there is a lack of research evaluating whether abnormal concentrations of thyroid hormone affects muscle mass in children. To our knowledge, only one cohort study showed an inverse association between LST and free thyroxine, but not with thyroid-stimulating hormone (227).

Considering the impact hormones have on skeletal muscle development, hormonal deficiencies negatively influence individual's health status, especially during growth (225). Research has demonstrated that growth hormone and sex steroid deficiencies impair the development of LST as measured by DXA (231). The crux of therapy for these conditions revolves around hormone replacement, which has been shown to increase skeletal muscle mass (232, 233). In adolescents with growth hormone deficiency, discontinuation of hormone replacement reduced LST by 2 kg over a two-year period (234). Findings from clinical trials demonstrate that growth hormone replacement therapy (0.67 to 1 mg/m^2 per day) in Prader-Willi

syndrome increased muscle thickness by US in infants (212) and LST by DXA in adolescents (235). Furthermore, in boys with delayed puberty, three months of testosterone replacement therapy significantly increased FFM (measured by BIA) and height velocity (236). Another study confirmed the results previously mentioned and also demonstrated an average sparing of protein breakdown of 1.2 g/day/kg of FFM in adolescents with delayed puberty undergoing hormone replacement therapy (237).

2.5.4 Dietary Protein

There is a body of evidence associating protein intake and body composition phenotypes in children. Because muscle anabolism occurs when protein synthesis exceeds its breakdown rate, dietary protein is paramount for optimal muscle development (238). Indeed, a recent study including 3,991 children aged 8 years found an association between higher protein intake and higher FFM measured by DXA (239); similar associations were also described in adolescents with normal (240, 241) and high FM (242). Compared to late childhood, dietary protein requirements on a body weight basis are higher in the first years of life due to variations in growth rate (243). According to the World Health Organization, the average requirement of protein in healthy children range from 1.12 g/kg/day to 0.75 g/kg/day at 6 months and 10 years, respectively (244). To optimize weight gain, linear growth, and neurodevelopment in malnourished infants, an even greater intake of protein is required but no consensus has been reached on the optimal amount (244, 245). In very low birth weight infants, for example, a protein intake of 4.2g/kg/day promoted FFM (measured using BIA) accretion compared to a standard pre-term formula providing 3.7 g/kg/day of protein (193). Such high protein intake can be obtained by adding nutritional supplements in the preterm formula or feeding the infant with increased volume of the formula (193).

On the other hand, one study revealed that a higher protein intake was associated with increased FM (246) and risk of obesity in early childhood (247). Divergent from adults (248), protein intake above the amount needed for maintenance and growth appears to stimulate adipogenesis and inhibit lipolysis in children (249, 250). Known as the “early protein hypothesis”, scientists believe that the positive association between protein intake and FM might be related to hormonal responses because higher intakes of protein stimulate the production of insulin and IGF-1, which are responsible for differentiating preadipocytes into adipocytes (247, 249-251). According to this hypothesis, children who are genetically predisposed to obesity (252)

and the ones who experienced catch-up growth in early childhood (253) might be more affected. Not only protein quantity, but also its source influence muscle mass development in the pediatric population. For example, consumption of animal protein (especially red meat) was related to higher FFM measured by BIA at puberty (240) and using skinfolds in young adulthood (241) as compared to plant-based protein. This positive association could potentially be explained by the fact that animal protein provides all essential amino acids necessary to stimulate protein synthesis and plant-based protein does not (254). Additionally, animal protein has a greater content of leucine, which is a key amino acid in stimulating post-prandial anabolism (254). Despite these facts, a large population-based cohort of children aged 8 years, the *Generation R* study, described a stronger association between vegetable protein sources and FFM by DXA, as compared to animal protein sources (239). A German cohort study including children aged 5 to 6 years also supports this contradictory finding (255). Although the associations between plant-based protein and muscle mass remain unexplained and both studies adjusted the analysis for total energy intake, other dietary and lifestyle factors related to this dietary pattern may have also influenced muscle development but were not accounted in these studies. For example, children consuming more vegetables tend to be more active due to healthier family lifestyle (256). Large-scale, well-designed, randomized controlled trials are needed to clarify these associations.

Taken together, data from the studies discussed above suggest that dietary protein impacts muscle mass development. In addition, infants, children and adolescents may respond differently to the quality of the protein.

2.5.5 Physical Activity and Exercise

The majority of studies are finding that children and adolescents are currently not meeting the recommendations for physical activity due to potential barriers including limited access to playing spaces, poor motivation, reduced time for physical activity in school, and increased screen time (257, 258). This growing physical inactivity epidemic might directly impair optimal muscle development during childhood. Physical activity and exercise, especially long-term resistance training, play a role on skeletal muscle development by increasing the size and number of muscle fibers, recruitment of motor units, and promoting metabolic adaptations (259, 260). Although some of the metabolic and hormonal responses to long-term exercise in the pediatric population differ from adults (259), children and adolescents most likely increase muscle mass through similar mechanisms to adults when skeletal muscle is subjected to a mechanical stimulus

(261, 262). Briefly, the mechanical stimulus triggers a signalling cascade which results in satellite cells migration to the area and donation of myonuclei triggering protein synthesis and, consequently, increases in mCSA (known as hypertrophy) (263). For a detailed description of the mechanisms through which exercise promotes hypertrophy, see Watson & Baar (263).

Gains in muscle mass, however, do not necessarily translate into improvements in muscle strength or vice-versa (264). Several studies point out that resistance training in prepubertal children increases muscular strength without the same degree of muscular hypertrophy as in adults, and they suggest that this phenomenon might be due to greater neuromuscular adaptations (262, 264). Additionally, low concentrations of growth hormone and sex hormones may also contribute to reduced muscle mass accretion in younger children as cellular growth and proliferation are supported by these hormones. Despite gains in muscle mass do not directly associate with gains in muscle strength, improvements in both muscle mass and strength often occur together in postpubertal adolescents (233). A recent published study in older adolescents with obesity revealed that 22 weeks of resistance training or combined training (resistance plus aerobic training), but not aerobic exercise, resulted in 0.9 kg and 0.4 kg accretion in skeletal muscle mass, respectively (265). Moreover, muscle strength was greater in the resistance training group than in controls who did not exercise and in the combined training group compared to the aerobic training group (265). Thus, in children and adolescents, resistance training is important to ensure optimal muscle mass accrual.

2.5.6 Obesity

The prevalence of childhood obesity has increased substantially around the world (266). Research has shown that obesity contributes to low muscle mass and weakness (267); children and adolescents with obesity exhibit low relative strength to body mass (268), impaired muscular fitness (269), and reduced neuromuscular activation capacity (270) when compared to their non-obese counterparts. A recent meta-analysis indeed described a negative correlation between muscle fitness and adiposity, with a pooled effect size of $r = -0.29$ (95% CI, -0.44, -0.12; $p = 0.001$) in in children aged 4 to 19 years old (271). The reduced muscle fitness and mobility in individuals with obesity can be partially explained by the excessive energy intake and body weight load, which leads to higher energy costs for body movement and increased fatigue rates (269, 272).

Neural activation of muscle also appears to be reduced in children with overweight or obesity. One of the first studies investigating the implications of FM on neural activation capacity in the pediatric population demonstrated lower quadriceps femoris muscle activation in boys with obesity as compared to lean peers matched for age, pubertal stage, FFM (estimated by skinfolds) and height (270). However, it is not clear whether this initial study controlled for physical activity levels, which could have attenuated the differences as children with obesity may have a greater neuromuscular stimulus on weight-supporting muscles when performing physical activity. To further understand the implications of FM on muscle activation by controlling for the body weight confounder, Miller and colleagues evaluated the first dorsal interosseous, a small muscle of the hand, during isometric actions in children aged 8-10 years (273). The researchers indeed found that overweight children had smaller motor units than children with healthy weight (273), contributing to reduced contractile capacity.

Although the underlying mechanisms by which obesity affects skeletal muscle in children remain largely unexamined, ectopic lipid accumulation in skeletal muscle along with a state of chronic low-grade systemic inflammation also contributes to muscle impairment (196, 274, 275). Chronic positive energy balance leads to excessive fat accumulation in AT and between skeletal muscle fibers or surrounding muscle (276). The stress imposed by fat accumulation initiates a systemic inflammatory response characterized by infiltration of immune cells into the skeletal muscle tissue and increased secretion and activation of pro-inflammatory cytokines by myocytes and adipocytes (196). As a consequence of the chronic exposure to pro-inflammatory cytokines, satellite cell function appears to be affected, as well as myoblast proliferation and differentiation, negatively impacting skeletal muscle maintenance and regeneration (275).

2.6 Associations Between Skeletal Muscle and Health Outcomes

Previous studies have established that low muscle mass and strength contribute to adverse health outcomes in childhood (185, 186, 277-281). Here, we discuss this evidence by highlighting the implications of low muscle mass and strength on metabolic homeostasis, bone health, and neurodevelopment.

2.6.1 Metabolic Function

Through a comprehensive search of the literature, we identified fifteen articles that investigated whether having low muscle mass is associated with increased risk of metabolic dysregulation in the pediatric population (**Table 2.1**). Findings are critically evaluated below.

2.6.1.1 Glucose Metabolism

Skeletal muscle is the primary site for insulin-stimulated glucose uptake, contributing directly to the maintenance of glucose homeostasis (282). When sensitivity to the effects of insulin is reduced, circulating glucose concentrations increase and chronic conditions such as type 2 diabetes likely manifest (283). To date, eight studies evaluated the relationship between measures of muscle mass and fasting glucose or insulin sensitivity in the pediatric population (185, 277, 278, 284-288).

Regarding the concentration of circulating glucose, one cross-sectional survey including 1,420 participants described a more than three times increase in the likelihood of having hyperglycaemia in Korean boys and girls with a body composition phenotype of low muscle mass (277). In this study, participants were defined as having low muscle mass if appendicular LST (sum of the LST masses for the arms and legs divided by height squared) adjusted for body weight was below the lower quintile of the studied population (277). Using a similar weight-adjusted index, Hou et al. also reported inverse associations between muscle mass and fasting glucose concentrations in Hong Kong Chinese boys (β = -0.017 [95% CI, -0.027, -0.008]) and girls (β = -0.018 [95% CI, -0.034, -0.002]) (285). In contrast, results from another cross-sectional survey (the US National Health and Nutrition Examination Survey; NHANES) with a greater sample size (n =3,004) indicated a positive, but weak correlation of fasting glucose with whole-body LST (by DXA), divided by squared height in boys (r = 0.149) (287). Caution however is needed when interpreting studies with large sample sizes; significance (i.e. p-value) of small-magnitude associations could be biased by such a large sample size (289). Furthermore, the contradictory findings above can be partially attributed to the methodological differences in the assessment of muscle mass. While on one hand adjusting muscle mass for body weight reduces differences in the mass of non-skeletal muscle tissues (such as fat, organ and bone), on the other hand it introduces statistical problems as muscle mass is part of both numerator and denominator (i.e. muscle mass is a fraction of body weight) (290).

A greater number of studies investigated the associations between muscle mass and insulin sensitivity (185, 278, 284-288). Data from more than seven thousand children and adolescents indicated a 68% reduction in the likelihood of hyperinsulinemia for each quartile increase in LST by DXA (OR = 0.32 [95% CI, 0.26, 0.40], p<0.001), independent of age, sex and race/ethnicity (185). Using cross-sectional data from a prospective cohort study, Hou et al. also

reported inverse associations between LST (measured using DXA) and the homeostatic model assessment of IR (HOMA-IR) in boys (β = -0.203 [95% CI, -0.245, -0.161]) and girls (β = -0.111 [95% CI, -0.172, -0.049]) (285). The association between these measures remained significant (β = -0.178 [95% CI, -0.213, -0.143]) when adjustments were made to control for sex, birth weight, mother's place of birth, parental education, and physical activity levels (285). Moreover, a cross-sectional study of 215 adolescents found that the likelihood of having hyperinsulinemia increased by a factor of 0.92 (OR [95%CI, 0.86, 0.99], p = 0.03) when weight adjusted FFM (measured by ADP) was included in the model (288). However, a cross-sectional study assessing FFM by BIA in 1,089 European individuals of similar age described opposite results (284). This latter study found positive associations between age- and sex-specific measures of FFM and HOMA-IR in boys (r = 0.335) and in girls (r = 0.215), all $p<0.001$ (284); but limitations inherent to the body technique employed may have contributed to inaccurate measurements of FFM. Bioelectrical impedance analysis, as discussed in section 2.5.1, is highly sensitive to hydration status requiring individuals to be in a euhydrated state (291), a standardized clinical condition hardly obtained in large-scale observational studies.

In a smaller study, nested in a clinical trial, forty male adolescents with obesity had their muscle mass assessed using MRI and insulin sensitivity by the hyperinsulinemic-euglycemic clamp technique; participants also underwent an OGTT test (286). Although MRI provides a more accurate and direct measure of the skeletal muscle tissue and fat infiltration within muscles (292), findings from the study revealed no associations between total skeletal muscle tissue, insulin sensitivity, or any OGTT parameters. By contrast, increased intramuscular AT was associated with decreased insulin sensitivity (r = -0.53) and increased OGTT-insulin area under the curve (r = 0.31) (286). Briefly, intramuscular AT depots release fatty acids and cytokines that impair the signaling mechanisms of insulin on muscles, contributing to the development of IR (293).

From these findings, it is unclear whether those children and adolescents with lower muscle mass have a decreased responsiveness to the actions of insulin. On one hand, large studies controlling for relevant biological and lifestyle covariates found inverse associations between muscle mass and indirect measures of IR (185, 285). However, other studies provide evidence of positive associations between these variables (284, 287, 288). Nonetheless, it should be noted that these studies employed surrogate indices to assess insulin sensitivity. Despite the advantages of

fasting insulin and HOMA-IR over direct measures (such as higher practicality, lower invasiveness, and lower costs), these tests are limited in the assessment of whole-body insulin sensitivity, especially in pediatrics (294); and a more adequate and widely accepted measure (reference standard) is the glucose clamp method (295). Of the studies reviewed here, only one attempted to use logarithmic transformation of HOMA-IR (278), an approach that corrects the skewed distribution of fasting insulin, providing a stronger correlation of this index with the glucose clamp (295). In this study of prepubertal children, however, FFM by BIA was neither significantly associated with log (HOMA-IR) nor fasting glucose concentrations ($p > 0.05$) (278). As evidence using the reference body composition technique was limited to boys with obesity and results were not controlled for body fat, further studies are required to confirm whether low muscle mass is linked to impaired glucose metabolism in pediatrics.

2.6.1.2 Lipid Profile

The associations between components of the lipid profile and measures of muscle mass were investigated in five of the reviewed studies (185, 277, 278, 284, 287). Data from two cross-sectional surveys suggest that having low muscle mass is associated with an increased risk of an unfavorable lipid profile although not controlling for the effects of body fat (185, 277). In one study, for each quartile increase in the relative LST by DXA there was a decrease in the odds of having clinically high total cholesterol (OR = 0.74 [95%, CI 0.70, 0.79]), high LDL-C (OR = 0.67 [95% CI, 0.61, 0.75]), and low HDL-C (OR = 0.55 [95% CI, 0.49, 0.61]), all $p<0.001$, independently of age, sex, and race/ethnicity (185). After controlling for the effects of multiple factors (i.e. age, sex, energy and protein intake, alcohol consumption, equivalent income, and resistance exercise), but not body fat, Korean children and adolescents with low muscle mass were nearly two times more likely to exhibit abnormally high fasting TG and low HDL-C (277). As physical activity and dietary intake are known factors to play a role on muscle mass and metabolic conditions (296-298), it may be crucial to control for these variables when evaluating the effects of muscle mass on lipid profile. Although these confounders were assessed using feasible methods given the study design (resistance exercise was captured using self-reported questionnaire and dietary intake using the 24-hour food record) (277), they have inherent limitations (299-301). An alternative to reduce the bias of self-report dietary intake data, caused by factors such as memory-recall, is to correct the amount of dietary components per 1000 kcal (301); however, this approach was not adopted by the authors (277). Future studies using direct

measures of physical activity and more stringent approaches of dietary data analysis are needed to confirm whether the inverse relationship between muscle mass and circulating lipids exist independently of these important confounders.

In contrast to these findings, two other large studies demonstrated that low FFM by BIA (284) or LST divided by squared height (using DXA) (287) were associated with improved lipid metabolism in adolescents. Age- and sex- specific measures of muscle mass were positively associated with TG levels in boys of both studies ($r = 0.173$-0.278) (284, 287) and in girls of one study ($r = 0.123$) (284), and inversely correlated with HDL-C ($r = -0.310$ and $r = -0.233$, for boys and girls, respectively) (287). After further adjustment for FM, only the relationship with HDL-C remained significant (OR = 1.5 [95% CI, 1.2, 1.9), suggesting that associations between LST divided by squared height and TG is partially mediated by FM (287). In fact, adiposity is a predictor of TG concentrations in overweight children and adolescents (302). Obesity can result in a low-grade chronic inflammation state characterized by increased production of pro-inflammatory cytokines (274). These cytokines are known to not only impair the regenerative capacities of skeletal muscle, but also contribute to dyslipidemia and IR. Interestingly, opposing results were found by Murphy et al. in prepubertal children (mean age = 5.9 years old) (278). Unadjusted analysis revealed slightly greater positive association between FFM (as measured by BIA) and TG in girls only ($r = 0.21$), but adjustments for FM led to moderate and inverse correlation of these variables in boys ($r = -0.41$) and removed the significance in girls ($p > 0.05$). Since these studies evaluated boys and girls at different pubertal stages, comparing results between studies is challenging. In fact, compared to more advanced pubertal stages, boys in early puberty appear to have higher systemic concentrations of total and LDL-C and girls in early puberty have higher HDL-C concentrations; however, no differences were observed in TG concentrations (303).

Another factor that may influence the association between muscle mass and lipid profile is race/ethnicity. According to a study conducted in children (aged 9 to 10 years old) living in England, there was a marked ethnic difference in blood lipids independent of sex, age, socioeconomic status, and physical activity (304). Children of Black African origin had lower mean systemic concentrations of total and LDL-C and triglyceride than White Europeans; compared to white Europeans, South Asians had similar total and LDL-C concentrations, but lower HDL-C and higher TG (304). Despite these known ethnic differences in lipid profile, none

of the studies discussed above (284, 287) (with heterogeneous study samples from the US and European countries) have adjusted the analyses for this potential confounding factor.

Thus, studies suggesting a role of muscle mass in preventing abnormalities in lipid metabolism were flawed due to failure to control for the influence of body fat. On the other hand, studies controlling for adiposity reported inconsistent findings as they evaluated children with diverse ethnic origins and pubertal stages, limiting our understanding of the implications of low muscle mass on lipid metabolism.

2.6.1.3 Blood Pressure

Given the importance in understanding the determinants of blood pressure in order to prevent future cardiovascular complications, most of the reviewed studies (10 out of 15) evaluated the associations between muscle mass and components of blood pressure (185, 277, 278, 284, 287, 305-309).

Regarding each component of blood pressure alone, muscle mass was moderately positively associated with SBP in unadjusted ($r = 0.27$-0.60) (278, 284, 287, 306, 307) and adjusted analyses ($r = 0.29$-0.41) (305, 308, 309) in both boys and girls. Indeed, there was a difference of nearly 8 mm Hg (95% CI 6.78-9.13, $p<0.001$) in SBP between children of young age (mean 9.9 years) in the highest and lowest quintiles of LST as measured by DXA (305). On the other hand, a large cross-sectional survey including more than seven thousand children and adolescents described a 32% decrease in the odds of having high SBP for each quartile increase in LST by DXA (OR = 0.68; 95% CI 0.64-0.74; $p<0.001$), independently of age, sex, and race/ethnicity (185). In this study, children and adolescents with values of SBP above the fourth quartile for each age group and sex were defined as having abnormally high blood pressure. Using data-driven cut-points to stratify individuals at a higher risk for disease is, however, problematic as it requires validation of the cut point which was not determined by the authors (310).

Only four studies found weak to moderate positive correlations of DBP to measures of muscle mass (305-308) ($r = 0.14$-0.50). It is important to note that results from one of these studies (307) are questionable because it employed the bipolar impedance technique, also known as foot-to-foot BIA, in children with overweight and obesity (more than 51% of the study sample). This technique only measures FFM across the lower legs, and as children with overweight and obesity may have a different body composition distribution, hence its use is not

recommended in the pediatric obesity population (311). After controlling for several confounding factors (e.g. sex, age, height, and puberty stage), DBP remained significantly associated to muscle mass in one study in adolescents (r = 0.32) (308), but not in children (305). Therefore, the contradictory results may be explained by the lack of assessment and adjustment for pubertal status in some studies. Although age gives an idea about sexual maturation, two children of the same sex and age could be in different developmental stages. As hormonal changes occurring during puberty are directly associated with increases in muscle mass (225), adolescents in a more advanced pubertal stage could have greater amounts of muscle mass than their peers. Specifically, there is a marked activation of the growth hormone/IGF-1 axis and synthesis of the sex steroids, which increases the rate of myofibrillar protein production and reduces the rate of protein breakdown resulting in muscle mass accretion (225). Thus, caution is needed when interpreting observational studies involving participants across a wide age range.

Two cross-sectional surveys evaluated the likelihood of having elevated blood pressure in the pediatric population based on measures of LST by DXA (277, 287). Whereas in one study, Korean children and adolescents with low muscle mass had a greater odds of having high blood pressure (OR = 1.93 [95% CI, 1.33, 2.80) (277), in another study conducted in the US having high LST divided by squared height was related to a higher odds of high blood pressure (OR = 1.8 [95% CI, 1.1, 2.9) (287). These studies, however, classified elevated blood pressure differently, making them difficult to compare. The first study defined children as having high blood pressure if systolic or DBP were greater than the 90th percentile for age, sex, and height, or they were using of blood-pressure lowering medication or were previous diagnosed as hypertensive (277). In the second study, individuals with elevated blood pressure were those with SBP ≥130 mm Hg or DBP ≥85 mm Hg (287). According to the most recent American Academy of Pediatrics Clinical Practice Guidelines, children older than 13 years with SBP ranging from 120 to 129, but DBP <80 mm Hg, are categorized as elevated blood pressure (312); thus, some children in the second study possibly were misclassified as the study used a higher cut point for blood pressure, leading perhaps to a weaker association between LST and hypertension. Also, as the first study enrolled Asians and the second had more diverse ethnic groups (71.9% were non-Hispanic White, 16% were non-Hispanic Black, and 12.1% were Mexican American), ethnic differences between the studies hinders comparison of findings. Results from a study conducted in the US, for example, demonstrated that non-Hispanic Black boys had on average 2 mm Hg

higher DBP than Asians boys and non-Hispanic Black girls had on average 3 mm Hg SBP than non-Hispanic Whites; however, there were no ethnic differences for SBP and DBP within each pubertal stage (313).

Comparisons between the reviewed studies are limited by differences in the methodology used to evaluate muscle mass, failure to control for key confounders, lack of consistent definition of high blood pressure among the pediatric population, as well as varied ethnic origins. Despite this, most studies described a positive relationship between muscle mass and blood pressure, within the reference range. The exact explanation for this positive relationship remains to be established, but it has been suggested that muscle mass has a potential direct effect on blood pressure by increasing cardiac output (306). Compared to other tissues, skeletal muscle has a higher metabolic demand requiring nearly 25% of all cardiac output in resting conditions, which markedly increases during exercise (314). Therefore, having high muscle mass could increase cardiac output and, consequently, blood pressure; but this increase would be still within the reference range for blood pressure in children without any metabolic complications. Perhaps a body composition phenotype of high muscle mass would be detrimental only for those children with concurrent metabolic risk factors or congenital heart defects. Although not yet shown, we speculate that a negative association between muscle mass and blood pressure could also indicate abnormalities in the cardiovascular system.

2.6.1.4 Clustered Metabolic Risk Factors

Two of the reviewed studies evaluated the associations between muscle mass and composite metabolic risk scores calculated using statistical models concurrently accounting for multiple risk factors. According to Andersen et al., composite risk scores are useful in pediatric studies because variations in individual risk factors can be compensated (296), with higher scores indicating a worse metabolic profile. Although these studies calculated composite scores slightly differently, positive association with measures of muscle mass were reported in boys (284) and girls (284, 315) with healthy body weights. Specifically, Gracia-Marco created a composite score based on the levels of SBP, cardiovascular fitness ($VO_{2\ max}$), HOMA-IR, CRP, total cholesterol to HDL-C ratio, and TG (284); in this study, FFM obtained using BIA explained nearly 18% of variation in the composite score in boys and 17% in girls (all $p < 0.001$). Furthermore, Cheng & Wiklund accounted only for blood pressure, HOMA-IR, HDL-C, and TG (315); increases in mCSA as measured by peripheral quantitative computerized tomography ($r = 0.32$) and LST of

the legs by DXA (r = 0.11) from prepuberty to early adulthood were associated with increased composite risk score in girls. As discussed above, the inclusion of blood pressure in the composite score partially explains the positive associations between muscle mass and clustered metabolic risk factors found by these studies. The reported associations disappeared after adjusting for FM in one study (315) but remained in the other study with FFM explaining nearly 57% of the variation in the composite score in girls (284).

Another approach to account for a combination of multiple related risk factors for metabolic and cardiovascular disease is to classify children as having or not having MetS. Despite the lack of definitive criteria for establishment of MetS in the pediatric population (316), three reviewed studies investigated the implications of muscle mass on this condition. In two cross-sectional surveys (277, 287), MetS was defined as the presence of three or more of the following factors: abdominal obesity, hyperglycemia, high TG, low HDL-C and hypertension. Using this criterion, prevalence of MetS was found to be greater in children and adolescents with low muscle mass (14.8%) than those without low muscle mass as assessed by DXA (2.4%), $p<0.001$ (277). Additionally, multiple logistic regressions adjusted for several confounding variables, but not FM, revealed an odd of 5.28 (95%, CI 2.76, 10.13) for the presence of MetS in children with low muscle mass (277). In children and adolescents of similar age, Weber et al. found that the 74th percentile of LST divided by squared height using DXA was the best discriminator of MetS; however, multivariate regression including measures of FM in the model removed the associations between muscle mass and MetS (287). In the third study (317), where cross-sectional data of a prospective cohort study in older adolescents (aged 16 to 17 years, all postpubertal stage) were evaluated, MetS was defined as the presence of abdominal obesity and two of the following: high fasting glucose, high TG, low HDL-C, and hypertension. According to the authors, there was a greater likelihood of MetS in boys with relative sarcopenia (OR = 21.2 [95% CI, 4.18, 107.5; $p <0.001$) than in girls with relative sarcopenia (OR = 3.61 [95% CI, 1.10, 11.9; $p <0.05$), independently of biological, anthropometric and lifestyle factors. In this study, relative sarcopenia was defined as weight adjusted FFM below the 25th percentile in boys and girls. Taken together, these studies support the concept that low muscle mass is characteristic of a more detrimental metabolic condition in which several risk factors, including obesity, are clustered together.

2.6.2 Bone Development

During childhood and adolescence, skeletal muscle development is accompanied by concurrent changes in bone tissue. Observational studies consistently show positive associations between skeletal muscle mass, strength and bone parameters in healthy children of both sexes (156, 280, 281). These associations can be explained by the mechanostat theory, which describes the adaptation of bone mass and geometry to the physiological loads imposed by muscle forces (318, 319); therefore, muscle mass and strength are considered important predictors of bone strength (320). Considering the close relationship between bone and muscle, scientists proposed the term "functional muscle-bone unit" to reinforce that muscle function must be taken into consideration when bone parameters are analysed (319, 321, 322). As bone and muscle function synergistically and "peak" bone mass during growth partially determines osteoporosis risk in adulthood and old age (320), "peak" muscle mass in adolescence may also contribute to later development of sarcopenia and osteoporosis.

A recent systematic review including observational and longitudinal studies investigated the association of muscle mass and bone parameters in children and adolescents (156). The majority of the reviewed studies found positive associations between muscle mass and bone mineral content, bone mineral density and bone area (156). A cross-sectional study evaluating 254 girls aged 16 to 20 years, for example, observed a strong correlation between LST, bone mineral content, and bone mineral density (all measured by DXA); moreover, 30% of the variability observed in bone mineral density was predicted by LST (323). Similarly, a longitudinal study on 370 children of both sexes aged 8 to 18 years found a positive association between LST (assessed using DXA), and bone mineral content and bone area (by peripheral quantitative CT) (324). In younger children, data from the Quebec Adipose and Lifestyle Investigation in Youth using the DXA technique revealed that a 1 kg increase in LST was associated with 28.4 g increase in whole-body bone mineral content, 19.9 cm^2 in bone area, and 0.007 g/cm^2 in bone mineral density (325).

The literature has also consistently shown a positive relationship between muscle strength and bone parameters in pediatric populations. A cross-sectional study evaluating children of both sexes observed significant positive correlations between HGS and bone mass at hip, spine and whole body; moreover, the authors reported HGS as an independent predictor of bone mass (326). In young athletes, HGS was a determinant factors of radial bone mineral density (327). A

recent study evaluating 1,427 adolescent students of both sexes aged 11 to 18 years demonstrated that HGS was associated with the bone mineral density and content. Moreover, a cross-sectional analysis of girls aged 13 to 15 years showed a strong association between HGS and bone mineral density (328). In support of the association between muscle strength and bone health, the Institute of Medicine has recommended the HGS test to be used as part of school-based fitness testing to monitor adequate levels of muscle strength for optimal bone health (329). To this end, cut-points for HGS were recently developed in order to facilitate the implementation of the use of HGS in assessment of bone health in youth (330).

Taken together, these studies suggest that optimal development of muscle mass and strength during childhood and adolescence is vital not only for bone growth and overall health but also for preventing osteoporosis and sarcopenia later in life.

2.6.3 Neurodevelopment

Cognitive development is a continuous process influenced by genetics and environmental factors. Pre- and postnatal environmental conditions are known to contribute to birth weight and cause long-term effects on brain development and cognition (331), impacting academic performance and later productivity in adulthood (332). Although birth weight has been identified as a strong predictor of child neurodevelopment (333, 334), children in the same birth weight range can have different neurodevelopmental progress; this suggests that there are other factors playing a role on neurodevelopment (333). Considering that body composition is highly variable in children with the same body weight (335, 336), researchers have investigated the impact of different body compartments on neurodevelopment in pediatrics.

In low birth weight infants, weekly assessment of body composition using ADP revealed that increased FFM gain during hospitalization was associated with improved neurodevelopment at 12 months, corrected for prematurity (337). Another study in preterm infants using the same body composition technique demonstrated that FFM reflects protein accretion and is a useful index of growth of the brain (338). In addition to this finding, the authors observed a greater absolute value of FFM associated with faster neuronal processing (338). Furthermore, a prospective cohort study measured the body composition of 227 Ethiopian children within 48 hours of birth also using ADP (168). Two years later, child development was assessed and the authors reported that FFM, but not FM, at birth predicted better global and language development at 2 years of age, independent of potential prenatal, postnatal and parental confounders (168).

Using data from the same birth cohort of Ethiopian children, researchers examined more recently how changes in body composition during early infancy are related to developmental progression from 1 to 5 years of age (339). Interestingly, it was demonstrated that fetal FFM accretion was associated with developmental progression, but not postnatal FFM accretion (339). For each kg increase in FFM at birth, global development progression increased 1.8 points from 1 to 5 years of age (339).

In contrast, Scheurer et al. found that body composition changes (also assessed by ADP) continue to induce neurodevelopmental benefit beyond infancy (167). In a prospective, observational design, a cohort of preterm infants was followed from infancy through preschool age (167). The authors observed that greater FFM gains from infancy to preschool age were associated with improved overall cognition and processing speed task performance (167). Furthermore, the skeletal muscle tissue indeed releases myokines that are able to cross the blood brain barrier (known as the muscle-brain crosstalk), promoting neurogenesis and synaptic plasticity to maintain cognitive function (340). Thus, these studies together support that optimal muscle growth is linked to cognitive development; further research is required to confirm whether muscle mass assessment could be used as a surrogate method to identify children at risk for abnormal neurodevelopment or as a novel target for those with existing cognitive deficits.

2.7 Sarcopenic Obesity in Pediatrics

As reviewed above, either obesity or low muscle mass alone poses metabolic challenges in the pediatric population. However, recent evidence suggests that a body composition phenotype combining both high FM and low muscle mass (also known as sarcopenic obesity in adults) is associated with higher health risks than either compartment alone (341, 342). To elucidate the relative contribution of these body components to physiological function, the model of metabolic load-capacity has been used in the adult population (343). Metabolic load was previously defined as the extent of an adverse effect on the organism caused by FM, and metabolic capacity as the ability of the organism to act against this effect through the use of muscle mass; thus, the ratio of FM to muscle mass represents the metabolic load-capacity index (LCI).

Although sarcopenic obesity and its related morbidities have not been investigated in detail in the pediatric population, excess FM with low muscle mass likely emerges in childhood given factors already discussed in this review (e.g. fetal programming, physical inactivity,

overnutrition, and inflammation) leading to compromised metabolic health before adulthood. One study indeed highlighted that obese adolescents with concurrent low muscle mass and high FM had higher MetS z-score, TG, IR and SBP compared to adolescents with either obesity or low muscle mass alone (344). On the other hand, it is also not clear whether children with metabolic healthy obesity (or absence of metabolic risk factors) (345) present with a lower ratio of FM to FFM than children with metabolic unhealthy obesity. Future prospective studies must be conducted to evaluate the predictive value of the metabolic LCI in prediction of cardiometabolic risks.

2.8 Body Composition Techniques for the Assessment of Muscle Mass in Pediatrics

As summarized in **Table 2.2** diverse body composition techniques (e.g. ADP, BIA, DXA, CT, MRI, US, and potassium counter) are current available in both research and clinical settings for estimation of adiposity and muscle mass in infants, children and adolescents. Anthropometric equations based on weight, girth, and skinfolds can also be used to estimate body composition; however, they are used as a surrogate and do not evaluate body composition accurately. Given the advantages and limitations of each body composition technique, a detailed assessment of these techniques is fundamental for selecting the most feasible and accurate one. Researchers and health care professionals may consider whether they are assessing fat and muscle mass at the individual or population level, which body compartment containing fat and muscle mass would answer their questions, and time and resources available. Furthermore, they may choose only those techniques and protocols that have been validated for the studied population and use the same equipment when following patients over time.

2.8.1 Air Displacement Plethysmography and Bioelectrical Impedance Analysis

Air displacement plethysmography and BIA are safe, non-invasive, and simple techniques to evaluate whole-body FM and FFM in the pediatric population (346, 347). An infant version of ADP is also available, which facilitates the measurement of body composition in infants from birth until 6 months of age (body weight ≤10 kg) (348). Both ADP and BIA use age- and sex-specific equations to estimate body composition based on body density (349) and impedance (and/or its components - resistance and reactance) to an electrical current that passes through the body (347), respectively. Most of these predictive equations, however, do not account for sexual maturation status and could, consequently, under or overestimate FM and FFM; therefore, using raw data on body density from ADP or conductivity from BIA in selected equations is an

alternative approach (347). Another limitation of these techniques is its sensitivity to hydration status, which is known to vary in children (350, 351). As children with chronic diseases can exhibit an altered fluid state, the accuracy of impedance measurements may be compromised (195, 351). Indeed, a recent study described limits of agreement greater than ±20% in FFM evaluated by BIA and DXA in children with spinal muscular atrophy, intestinal failure, and post hematopoietic stem cell transplantation, suggesting inaccurate measures of FFM using BIA (195). Furthermore, although the foot-to-foot BIA technique provides a fast and practical assessment of body composition as subjects are required to just stand on pad electrodes, its use is not recommended for the assessment of whole-body FFM because lower limbs may have a greater contribution for the estimation of FFM compared to measures obtained by hand-to-foot BIA techniques (311).

2.8.2 Dual-energy X-ray Absorptiometry

Dual-energy X-ray absorptiometry is a widely used method to estimate both whole-body and regional adiposity, FFM, and LST. Regional measurements obtained by DXA allow for calculation of appendicular skeletal muscle index as the sum of the LST masses for the arms and legs divided by height squared (292). This index has been used to assess sarcopenia in adults and elderly population (183, 352), and may improve the sensitivity in detecting changes in LST throughout linear growth. In the pediatric population, however, it remains unclear how skeletal muscle accurately scales with height as body weight is proportional to height cubed (and not height squared) during puberty (353, 354). Newer DXA instruments allow quick whole-body scans (2-3 minutes), supporting its use in pediatric population. Although the radiation exposure is considered minimal and safe by most of the radiation safety agencies, some authors argue that standardized protocols developed for adults pose an unnecessary overexposure in children and parameters need to be adjusted according to the child's body size (355).

2.8.3 Imaging Techniques

Computerized tomography and MRI are considered the reference imaging methods for body composition assessment at the tissue level; both provide accurate measures of skeletal mCSA and volume using single or multislice images, VAT, SAT and intramuscular AT (356, 357). The advantage of MRI over the CT technique is that there is no ionizing radiation, making it a preferred method for body composition assessment in pediatrics, especially in healthy children. In children with chronic illness such as cancer, CT scans available from clinical practice

are useful to evaluate muscle mass (216). Another feature of CT and MRI techniques is the characterization of "muscle quality" due to their ability to detect intramuscular AT, which is the AT within the skeletal muscle. As a predictor of health, low muscle "quality" (or increased infiltration of AT in muscles) has been associated with metabolic dysregulation, reduced muscle strength, and impaired skeletal development in children and adolescents (286, 358, 359). Furthermore, integrated positron emission tomography/CT and positron emission tomography /MRI can provide information on skeletal muscle glucose metabolism in research settings (360, 361). By using a specific positron emission tomography tracer, commonly the fluorine 18 (^{18}F) fluorodeoxyglucose, and the hyperinsulinemic euglycemic clamp, researchers can characterize the dynamics of glucose uptake by skeletal muscles to develop and evaluate the efficacy of new treatments for metabolic abnormalities (360, 361).

Ultrasound is another imaging modality that allows assessment of skeletal muscle and SAT in the pediatric population (362). It provides real-time measurement of muscle thickness and mCSA with low cost and in a relatively fast manner without any radiation exposure (363). Measurements of SAT, rectus femoris and vastus intermedius muscles taken at the mid point of the anterior superior iliac spine to the superior aspect of the patella (midthigh) have been used in pediatrics, especially to track changes of muscle thickness over time (364). In addition to muscle thickness and cross-sectional area, US is a valuable technique for quantification of muscle echo intensity (mEI), which is currently used for evaluation of muscle diseases in children and adolescents (362, 363). In diseases such as inflammatory myopathies, fasciculation, and neuromuscular diseases, a greater mEI has been observed (362, 363, 365). Given these features and advantages over other imaging techniques, the value of US as a technique to measure muscle mass is emerging in pediatric research with potential for translating the research findings to clinical settings. However, tissue edema and SAT thickness may present as issues when evaluating muscle thickness in pediatric patients with chronic conditions (365) and severely obesity, respectively. Future research is required to support the use of US when characterizing sarcopenia in the young population.

2.8.4 Potassium Counter

The whole-body counter is a non-invasive *in vivo* body composition chemical assay that can be used to assess the γ-ray decay of ^{40}K, an isotope naturally occurring in human tissues (357). By measuring the energy decay of ^{40}K, total body potassium (TBK) and body cell mass

can be estimated, as approximately 98% of the body's natural potassium content is located within this compartment. It is noteworthy that body cell mass is the metabolizing, oxygen-consuming portion of muscle mass and its value maintains constant, unless there is an alteration of the nutrition status with disease (366). The measurement procedure requires no radiation exposure, and it is independent of extracellular fluid changes, hydration status and tissue thickness (292, 367); therefore, the method can be safely applied in pediatric and pregnancy studies.

2.9 Summary

In conclusion, substantial evidence supports that biological, environmental, and lifestyle factors determine adiposity and skeletal muscle mass during childhood and adolescence. Once high levels of AT are set, the negative effects of adiposity, or its "load" on several health domains, become noticeable. Excess adiposity poses a risk for cardiometabolic diseases, sleep disordered breathing and altered physical, neuromuscular, cognitive and psychological function. Despite a growing body of evidence supporting low muscle mass as a risk factor for metabolic health in children and adolescents given its metabolic "capacity", conflicting associations were reported by the reviewed studies. Differences in body composition techniques, muscle mass indices, and clinical methods used to assess metabolic biomarkers may have contributed to a lack of a consistent conclusion. Furthermore, evidence on the metabolic risk associated with concurrent high adiposity and low muscle mass is limited in the pediatric population. To advance in the field, several body composition techniques with unique advantages and disadvantages are currently available. However, there has been no review summarizing the accuracy of body composition assessment in children and adolescents with obesity.

Table 2.1 Summary of studies assessing muscle mass and metabolic risk factors in children and adolescents.

1st author, year (Ref.); Study design	Population characteristics	BC	Outcomes
Daniels, 1996 (306); Cross-sectional	N = 201; M/F (n) = 105/96 Age = 11.7±2.7 years Race/Ethnicity (n): Black = 98; White = 103	DXA	• ↑ LST was correlated with ↑ SBP (r=0.60; p<0.001) and DBP (r=0.50; p<0.001) • LST was the main determinant of SBP (R^2=0.36, p<0.001)
Mueller, 2003 (309); Cross-sectional	N = 384; M/F = 179/205 Age: ♂ = 13.52±1.60 years; ♀ = 13.49±1.69 years Race/Ethnicity (n): Black = 141; Hispanic = 117; White = 116; Other: 10	BIA	• ↑ FFM was correlated with ↑ SBP in boys (r=0.40; p<0.01) and girls (r=0.29; p<0.01) • ↑ FFM was correlated with ↑ WC in boys (r=0.77; p<0.01) and girls (r=0.80; p<0.01)
Murphy, 2006 (278); Cohort	N = 234; M/F = 133/101 Age = 5.9±0.3 years BMI Z-score: ♂ = 0.14 (-0.04-0.33)[a]; ♀ = 0.50 (0.32-0.67)[a] Race/Ethnicity = European, White of mixed SES Sexual maturation = Prepubertal	BIA	• ↑ FFM was correlated with ↓ TG (r=-0.41; p<0.01) and total/HDL-C (r=-0.26; p<0.01) in boys only
Syme, 2009 (308); Cross-sectional	N = 425; M/F = 200/225 Age: ♂ = 14.6±1.9 years; ♀ = 14.7±1.9 years BMI: ♂ = 21.5±3.9 kg/m^2; ♀ = 21.4±3.7 kg/m^2 Race/Ethnicity = White Tanner stage: ♂ = 3.5±0.9; ♀ = 4.1±0.7	BIA	• ↑ FFM was related to ↑ SBP (r=0.41; 95% CI 0.24-0.58) and DBP (r=0.32; 95% CI 0.20-0.44)
Lee, 2012 (286); Cross-sectional	N = 40; M/F = 40/0 Age: 15±1.6 years BMI = 35.0±4.6 kg/m^2 Race/Ethnicity (n): Black = 20; White = 20 Tanner stage III/IV/V (n): 8/7/25	MRI	• SM (expressed as kg or % body weight) was not associated with insulin sensitivity, OGTT-insulin AUC, nor hepatic IR index (all p>0.1)

1st author, year (Ref.); Study design	Population characteristics	BC	Outcomes
Hou, 2015 (285); Cohort	N = 501; M/F = 278/223 Age = 15 years; Race/Ethnicity = Hong Kong Chinese	DXA[c]	• ↑ Appendicular LST[c] was associated with ↓ glucose, insulin and HOMA-IR
Weber, 2014 (287); Cross-sectional	N = 3004; M/F = 1738/1266 Age: 16.1±2.5 years BMI Z-score: ♂ = 0.51±1.2; ♀ = 0.39±1.0 Race/Ethnicity: Non-Hispanic White = 71.9%; Non-Hispanic Black = 16%; Mexican-American = 12.1%	DXA[d]	• The 74th percentiles of LST height adjusted-Z[d] was the best discriminators of MetS[e] • LST height adjusted[d] was no longer associated with MetS[e] after FMI-Z was included in the model
Kim & Valdez, 2015 (185); Cross-sectional	N = 7321; M/F = 4316/3005 Age = 8-20[f] years Race/Ethnicity (n): Black = 1685; White = 1931; Mexican-American = 2009	DXA[g]	• For each quartileg increase in relative LST, there was a ↓ in the odds of having an adverse metabolic risk factor (SBP, TC, HDL-C, LDL-C, TG, insulin)
Burrows et al., 2016 (317); Cross-sectional	N = 667; M/F = 348/319 Age = 16.8±0.3 years BMI Z-score: ♂ = 0.58±1.2; ♀ = 0.73±1.2 Race/Ethnicity = Chilean of low to middle SES Tanner stage: All post puberty (Tanner V)	DXA[h]	• Having low relative FFMh was associated with risk of having MetSe in boys (OR=21.2; 95% CI 4.18-107.5) and girls (OR=3.61; 95% CI 1.10-11.9)
Devonshire et al., 2016 (307); RCT (baseline data)	N = 730; M/F = 0/730 Age = 12.1±0.7 years BMI Z-score = 1.00±1.04 Race/Ethnicity: African American/Black = 91% Tanner stage: 3.2±1.0	BIA	• ↑ FFM was correlated with ↑ DBP (r=0.30), SBP (r=0.30) and WC (r=0.80), all p<0.001. • DBP and SBP ↑ by 0.35 and 0.32 mmHg for each kg ↑ in FFM, respectively. • Girls with BP≥90th percentile (n=40) had greater FFM than girls with BP<90th percentile (p=0.006)

1st author, year (Ref.); Study design	Population characteristics	BC	Outcomes
Garcia-Marco et al., 2016 (284); Cross-sectional	N = 1089; M/F = 509/508 Age: 14.8±1.2 years BMI: ♂ = 21.4±4.0 kg/m^2; ♀ = 21.3±3.4 kg/m^2 Race/Ethnicity (n) = European	BIA	• FFM explained 18.2% of variation in composite CVD risk score[i] in boys, and 16.7% in girls in unadjusted analyses. • After controlling for FM, FFM explaining 57% of the variation in the composite score in girls only. • A cut-off of ≥63.5kg of FFM was associated with an unhealthier clustered CVD risk[i] in boys, and ≥46.1kg in girls
Kim & Park, 2016 (277); Cross-sectional	N = 1420; M/F = 749/671 Age = 12-19[f] years BMI: Low muscle mass[j] = 24.7±0.4 kg/m^2; Normal muscle mass = 20.4±0.1 kg/m^2 Race/Ethnicity = Korean	DXA[j]	• Prevalence and OR of MetS were ↑ in children with low appendicular LST[j] than children without low appendicular LST (OR=7.26; 95%CI 4.10-12.82), adjusted for age and sex • The associations remained significant after further adjusting for energy and protein intake, resistance exercise, equivalent income, and alcohol consumption (OR=5.28; 95% CI 2.76-10.13)
Schvey et al., 2016 (288); Clinical trial (baseline data)	N = 215; M/F = 97/118 Age: 15.4±1.4 years BMI Z-score: 0.64±0.99 Race/Ethnicity (n): Black = 65; White = 127; Asian = 11; Multiracial = 6; Other = 6 Prepubertal/ early-mid pubertal/ late pubertal (n): ♂ = 5/60/30; ♀ = 3/53/61	ADP	• The odds of being classified as hyperinsulinemic ↑ by a factor of 0.92 (OR, 95%CI 0.86-0.99; p=0.03) when relative FFM[k] was included in the analysis

1st author, year (Ref.); Study design	Population characteristics	BC	Outcomes
Brion et al., 2007 (305); Cross-sectional	N = 6863; M/F = 3401/3462 Age = 9.9 (9.7-10.1)[b] years BMI: ♂ = 17.3 (15.6-18.7)[b] kg/m^2; ♀ = 17.7 (15.7-19.4)[b] kg/m^2 Race/Ethnicity (n) = European	DXA	• ↑ LST was associated with ↑ SBP (R^2=0.17; 95% CI 2.95-3.81; p<0.001) after adjusting for all evaluated confounders, which include sociodemographic, birth characteristics, and maternal health • Associations of SBP with total fat and LST were of similar magnitude
Cheng & Wiklund, 2018 (315); Longitudinal	N = 236; M/F = 0/236 Age = 11-18[f] years BMI: Pre-menarche = 18.3±2.9 kg/m^2; Post-menarche = 20.7±3.4 kg/m^2; Early adulthood = 21.9±3.2 kg/m^2 Race/Ethnicity (n) = European Tanner stage: All prepuberty at baseline	DXA and pQCT[m]	• ↑ mCSA (r^2=0.103; p<0.001) and LST of the legs (r^2=0.039; p<0.001) were associated with ↑ MetS score[m] • ↑ mDen and relative LST[n] were associated with ↓ MetS score[m] • After adjusting for FM, all associations disappeared

Symbols: ♂, male; ♀, female; ↑, increase; ↓ decrease. *Abbreviations:* ADP, air-displacement plethysmography; AUC, area under the curve; BIA, bioelectrical impedance analysis; CI, confidence interval; CVD, cardiovascular disease; DBP, diastolic blood pressure; DXA, dual-energy X-ray absorptiometry; FFM, fat-free mass; FM, fat mass; FMI-Z, standardized fat mass index; HDL-C, high-density lipoprotein cholesterol; HOMA-IR: Homeostatic model assessment of insulin resistance; IR, insulin resistance; LDL-C, low-density lipoprotein cholesterol; LST, lean soft tissue; LSTI-Z: standardized lean soft tissue index; mCSA, muscle cross-sectional area; mDen, muscle density; MetS, metabolic syndrome; MRI, magnetic resonance imaging; NR, not reported; OGTT, oral glucose tolerance test; OR, odds ratio; pQCT, peripheral quantitative computerized tomography; SBP, systolic blood pressure; SES, socioeconomic status; SM, skeletal muscle; SMI, skeletal muscle index; TG, triglycerides; Total-C; total cholesterol; WC, waist circumference**.**

[a] Values are expressed as mean and interquartile range (IQR, 25th-75th).

[b] Values are expressed as geometric mean and interquartile range (IQR, 25th-75th).

[c] Appendicular LST was calculated as {1.13 x appendicular LST (kg) – [0.02 x age (years) + (0.61 x sex)] + 0.97}/ total weight [kg] x 100).

[d] LST height adjusted was calculated as LST/height^2. Z-scores of this index were calculated using reference data from NHANHES 1999-2004.

[e] Metabolic syndrome (MetS) was defined as the presence of three or more of the following: abdominal obesity (WC), high glucose, high TG, low HDL-C, and high BP.

[f] Values are expressed as range.

[g] Relative LST was calculated as (LST/LST + FM) X 100. Participants were ranked into relative LST quartiles, from lowest to highest (≤64.2%, 64.3-70.9%, 71.0–77.4%, and ≥77.5%).

[h] Relative sarcopenia was defined as weight adjusted FFM below the 25th percentile in boys and girls.

[i] A composite CVD risk score was defined as sum of age- and sex-specific z scores of the individual risk factors (SBP, VO_{2max}, HOMA-IR, CRP, TC/HDL-C, and TG)

[j] Appendicular LST was calculated as appendicular LST/body weight. Participants were defined as having low muscle mass if the value for the Appendicular LST/body weight was below the lower quintile for each sex and age. Appendicular LST (in kg) was defined as the sum of the lean soft tissue masses of the arms and legs, assuming that all non-fat and nonbone tissues were skeletal muscle.

[k] Relative FFM was calculated as (FFM/body weight) x 100.

[l] pQCT scans were performed on the lower leg to assess mCSA and mDen.

[m] The MetS score was calculated as sum of standardized mean BP, HOMA-IR, HDL-C, and TG.

[n] Relative LST was calculated as (LST/body weight) x 100.

Table 2.2 Summary of commonly used techniques for assessment of body composition.

Technique, (Ref.)	Level; compartment measured	Advantages	Limitations
Dual energy x-ray absorptiometry, (355, 368-370)	Molecular; FM, LST, and FFM	• Non-invasive, minimal radiation exposure, and rapid whole-body scan (newer equipment 2-3 minutes) • Regional measurements allow calculation of appendicular skeletal muscle index • High precision and accuracy	• Sensitive to tissue hydration • Compared to 4-C model, DXA underestimate % of FFM in children with obesity • Some argue that standardized protocols developed for adults pose an unnecessary radiation overexposure in children and parameters need to be adjusted according to the child's body size
Bioelectrical impedance analysis, (311, 347)	Molecular; FM and FFM	• Safe, non-invasive, short duration test, portable, and low cost • Phase angle provides estimation of body cell mass	• Sensitive to hydration status • Current equations to estimate FFM do not account for sexual maturation status • Not all equipment provide raw data on conductivity that can be used in selected equations • Limited applicability in children with severe obesity; foot-to-foot BIA provide inaccurate measures of fat-free mass in children with overweight and obesity
Air-displacement plethysmography, (348, 371)	Molecular (density); FM and FFM	• Safe, rapid, and easy to perform a test (minimal training required) • Pediatric version is available, facilitating measurement of FFM in infants	• Measurement of thoracic gas volume is challenging in pediatrics; use of child-specific thoracic gas volume prediction equations • Sit still in a chamber; claustrophobia • High price of equipment

Technique, (Ref.)	Level; compartment measured	Advantages	Limitations
Computerized tomography scans, (372)	Tissue; total AT, SAT, VAT, IMAT, and SM tissue	• Reference method as it provides quantitative and qualitative measures of BC • Single slices can be used to estimate whole-body BC • High image resolution • Valuable in clinical settings where images are acquired for medical purposes	• Given the radiation exposure, CT scans are not usually taken for the purpose of body composition assessment • Costly, time-consuming technique, and required specialized skills to analyze the scans
Magnetic resonance imaging, (373)	Tissue; total AT, SAT, VAT, IMAT, and SM tissue	• Reference method as it provides quantitative and qualitative measures of SM tissue without radiation exposure (safe)	• Costly and time-consuming technique • Participant compliance; requires children to stay still and hold their breath for some procedures
Ultrasound, (374, 375)	Tissue; SAT and SM tissue (thickness and CSA)	• Real-time measurement of SAT and SM thickness, and SM cross-sectional area • Low-cost, safe, and fast measurement • Convenient method for tracking changes in skeletal muscle in clinical pediatric settings • Echo intensity provides qualitative measures of skeletal muscle tissue • Useful for diagnosis of neuromuscular disorders	• Pressure applied to the transducer and skin varies between raters; compression of the imaged tissue should be avoided • Sensitive to tissue hydration and subcutaneous thickness (especially when using portable equipment)

Abbreviations: AT, adipose tissue; BC, body composition; BIA, bioelectrical impedance imaging; CSA, cross-sectional area; CT, computerized tomography; FFM, fat-free mass; FM, fat mass; IMAT, intramuscular adipose tissue; LST, lean soft tissue; SAT, subcutaneous adipose tissue; SM, skeletal muscle; VAT, visceral adipose tissue.

2.10 References

1. Heinonen S, Jokinen R, Rissanen A, Pietiläinen KH. White adipose tissue mitochondrial metabolism in health and in obesity. Obes Rev. 2019;21(2):1–23.
2. Eckel J. Adipose tissue: A major secretory organ. In: The Cellular Secretome and Organ Crosstalk. Academic Press; 2018. p. 9–63.
3. Min SY, Desai A, Yang Z, Sharma A, DeSouza T, Genga RMJ, et al. Diverse repertoire of human adipocyte subtypes develops from transcriptionally distinct mesenchymal progenitor cells. Proc Natl Acad Sci U S A. 2019;116(36):17970–9.
4. Jung SM, Sanchez-Gurmaches J, Guertin DA. Brown adipose tissue development and metabolism. In: Brown Adipose Tissue. Springer, Cham; 2018. p. 3–36.
5. Shen W, St-Onge M, Wang Z, Heymsfield S. Study of body composition: An overview. In: Heymsfield S, Lohman T, Wang Z, Going S, editors. Human Body Composition. 2nd ed. Champaign, IL: Human Kinetics; 2005. p. 3–14.
6. Laharrague P, Casteilla L. The emergence of adipocytes. In: Levy-Marchal C, Pénicaud L, editors. Adipose tissue sevelopment: From animal models to clinical conditions. Karger Medical and Scientific Publishers; 2010. p. 21–30.
7. Lecoutre S, Petrus P, Rydén M, Breton C. Transgenerational epigenetic mechanisms in adipose tissue development. Trends Endocrinol Metab. 2018;29(10):675–85.
8. Sun K, Kusminski CM, Scherer PE. Adipose tissue remodeling and obesity. J Clin Invest. 2011;121(6):2094–101.
9. Haylett WL, Ferris WF. Adipocyte–progenitor cell communication that influences adipogenesis. Cell Mol Life Sci. 2020;77(1):115–28.
10. Sethi JK, Vidal-Puig AJ. Thematic review series: Adipocyte biology. Adipose tissue function and plasticity orchestrate nutritional adaptation. J Lipid Res. 2007;48(6):1253–62.
11. Poissonnet CM, Burdi AR, Bookstein FL. Growth and development of human adipose tissue during early gestation. Early Hum Dev. 1983;8(1):1–11.
12. Billon N, Monteiro MC, Dani C. Developmental origin of adipocytes: new insights into a pending question. Biol Cell. 2008;100(10):583–575.
13. Ziegler EE, O'Donnell AM, Nelson SE, Fomon SJ. Body composition of the reference fetus. Growth. 1976;40(4):329–41.

14. Toro-Ramos T, Paley C, Pi-Sunyer FX, Gallagher D. Body composition during fetal development and infancy through the age of 5 years. Eur J Clin Nutr. 2015;69(12):1279–89.
15. Berger-Kulemann V, Brugger PC, Reisegger M, Klein K, Hachemian N, Koelblinger C, et al. Quantification of the subcutaneous fat layer with MRI in fetuses of healthy mothers with no underlying metabolic disease vs. fetuses of diabetic and obese mothers. J Perinat Med. 2012;40(2):179–84.
16. Lapillonne A, Braillon P, Claris O, Chatelain PG, Delmas PD, Salle BL. Body composition in appropriate and in small for gestational age infants. Acta Paediatr. 1997;86(2):196–200.
17. Moulton CR. Age and chemical development in mammals. J Biol Chem. 1923;57:79–97.
18. Griffin IJ, Cooke RJ. Development of whole body adiposity in preterm infants. Early Hum Dev. 2012;88:S19–24.
19. Roggero P, Giannì ML, Amato O, Orsi A, Piemontese P, Morlacchi L, et al. Is term newborn body composition being achieved postnatally in preterm infants? Early Hum Dev. 2009;85(6):349–52.
20. Ramel SE, Gray HL, Ode KL, Younge N, Georgieff MK, Demerath EW. Body composition changes in preterm infants following hospital discharge: Comparison with term infants. J Pediatr Gastroenterol Nutr. 2011;53(3):333–8.
21. Koontz MB, Gunzler DD, Presley L, Catalano PM. Longitudinal changes in infant body composition: association with childhood obesity. Pediatr Obes. 2014;9(6):e141–4.
22. Ong KK, Emmett P, Northstone K, Golding J, Rogers I, Ness AR, et al. Infancy weight gain predicts childhood body fat and age at menarche in girls. J Clin Endocrinol Metab. 2009;94(5):1527–32.
23. Chomtho S, Wells JCK, Williams JE, Davies PSW, Lucas A, Fewtrell MS. Infant growth and later body composition: Evidence from the 4-component model. Am J Clin Nutr. 2008;87(6):1776–84.
24. Admassu B, Ritz C, Wells JCK, Girma T, Andersen GS, Belachew T, et al. Accretion of fat-free mass rather than fat mass in infancy is positively associated with linear growth in childhood. J Nutr. 2018;148(4):607–15.

25. Barbour-Tuck E, Erlandson M, Muhajarine N, Foulds H, Baxter-Jones A. Influence of childhood and adolescent fat development on fat mass accrual during emerging adulthood: a 20-year longitudinal study. Obesity. 2018;26(3):613–20.
26. Knittle JL, Timmers K, Ginsberg-Fellner F, Brown RE, Katz DP. The growth of adipose tissue in children and adolescents: cross-sectional and longitudinal studies of adipose cell number and size. J Clin Invest. 1979;63(2):239–46.
27. Landgraf K, Rockstroh D, Wagner I V, Weise S, Tauscher R, Schwartze JT, et al. Evidence of early alterations in adipose tissue biology and function and its association with obesity-related inflammation and insulin resistance in children. Diabetes. 2015;64(April):1249–61.
28. Spalding KL, Arner E, Westermark PO, Bernard S, Buchholz BA, Bergmann O, et al. Dynamics of fat cell turnover in humans. Nature. 2008;453(7196):783–7.
29. Jeffery E, Church CD, Holtrup B, Colman L, Rodeheffer MS. Rapid depot-specific activation of adipocyte precursor cells at the onset of obesity. Nat Cell Biol. 2015;17(4):376–85.
30. McConnell-Nzunga J, Patti-Jean N, Macdonald HM, Rhodes RE, Hofer SM, McKay HA. Body fat accrual trajectories for a sample of Asian-Canadian and Caucasian-Canadian children and youth: A longitudinal DXA-based study. Pediatr Obes. 2020;15:e12570.
31. McCarthy HD, Cole TJ, Fry T, Jebb SA, Prentice AM. Body fat reference curves for children. Int J Obes. 2006;30(4):598–602.
32. Ripka WL, Orsso CE, Haqq AM, Luz TG, Prado CM, Ulbricht L. Lean mass reference curves in adolescents using dual-energy x-ray absorptiometry (DXA). PLoS One. 2020;15(2):e0228646.
33. Arfai K, Pitukcheewanont PD, Goran MI, Tavare CJ, Heller L, Gilsanz V. Bone, muscle, and fat: sex-related differences in prepubertal children. Radiology. 2002;224(2):338–44.
34. Aguilera CM, Gomez-Llorente C, Tofe I, Gil-campos M, Canete R, Gil A. Genome-wide expression in visceral adipose tissue from obese prepubertal children. Int J Mol Sci. 2015;16:7723–37.
35. Taylor RW, Grant AM, Williams SM, Goulding A. Sex differences in regional body fat distribution from pre- to postpuberty. Obesity. 2010;18(7):1410–6.

36. Shen W, Punyanitya M, Silva AM, Chen J, Gallagher D, Sardinha LB, et al. Sexual dimorphism of adipose tissue distribution across the lifespan: A cross-sectional whole-body magnetic resonance imaging study. Nutr Metab (Lond). 2009;6(17):1–9.
37. Kjellberg E, Roswall J, Andersson J, Bergman S, Karlsson AK, Svensson PA, et al. Metabolic risk factors associated with visceral and subcutaneous adipose tissue in a sex-specific manner in seven-year-olds. Obesity. 2019;27(6):982–8.
38. Kaplan HS, Lancaster JB. An evolutionary and ecological analysis of human fertility, mating patterns, and parental investment. In: Wachter K., Bulatao R., editors. Offspring: Human fertility behavior in biodemographic perspective panel. National Academy of Sciences; 2003. p. 170–223.
39. Palmer BF, Clegg DJ. The sexual dimorphism of obesity. Mol Cell Endocrinol. 2015;15:113–9.
40. Brown L, Clegg D. Central effects of estradiol in the regulation of adiposity. J Steroid Biochem Mol Biol. 2010;122(1–3):65–73.
41. Currie C, Ahluwalia N, Godeau E, Nic Gabhainn S, Due P, Currie DB. Is obesity at individual and national level associated with lower age at menarche? Evidence from 34 countries in the health behaviour in school-aged children study. J Adolesc Heal. 2012;50(6):621–6.
42. Nieuwenhuis D, Pujol-Gualdo N, Arnoldussen IA, Kiliaan AJ. Adipokines : a gear shift in puberty. Obes Rev. 2020;(January):1–10.
43. Anderson SE, Whitaker RC. Prevalence of obesity among US preschool children in different racial and ethnic groups. Arch Pediatr Adolesc Med. 2009;163(4):344–8.
44. Rodd C, Sharma AK. Prevalence of overweight and obesity in Canadian children, 2004 to 2013: Impact of socioeconomic determinants. Paediatr Child Health. 2017;22(3):153–8.
45. Paley C, Hull H, Ji Y, Toro-Ramos T, Thornton J, Bauer J, et al. Body fat differences by self-reported race/ethnicity in healthy term newborns. Pediatr Obes. 2016;11(5):361–8.
46. Freedman DS, Wang J, Thornton JC, Mei Z, Pierson Jr RN, Dietz WH, et al. Racial/ethnic differences in body fatness among children and adolescents. Obesity. 2008;16(5):1105–11.
47. Peña M-M, Dixon B, Taveras EM. Are you talking to ME? The importance of ethnicity and culture in childhood obesity prevention and management. Child Obes. 2012;8(1):23–7.

48. Sauder KA, Kaar JL, Starling AP, Ringham BM, Glueck DH, Dabelea D. Predictors of infant body composition at 5 months of age: the Healthy Start Study. J Pediatr. 2017;183:94–9.
49. Wong WW, Nicolson M, Stuff JE, Butte NF, Ellis KJ, Hergenroeder AC, et al. Serum leptin concentrations in Caucasian and African-American girls. J Clin Endocrinol Metab. 1998;83(10):3574–7.
50. Nagy TR, Gower BA, Trowbridge CA, Dezenberg C, Shewchuk RM, Goran MI. Effects of gender, ethnicity, body composition, and fat distribution on serum leptin concentrations in children. J Clin Endocrinol Metab. 1997;82(7):2148–52.
51. Isong IA, Rao SR, Bind M-A, Avendaño M, Kawachi I, Richmond TK. Racial and ethnic disparities in early childhood obesity. Pediatrics. 2018;141(1):1–11.
52. Wardle J, Carnell S, Haworth CM, Plomin R. Evidence for a strong genetic influence on childhood adiposity despite the force of the obesogenic environment. Am J Clin Nutr. 2008;87:398–404.
53. Bouchard C, Tremblay A, Despres J-P, Nadeau A, Lupien PJ, Theriault G, et al. The response to long-term overfeeding in identical twins. N Engl J Med. 1990;332(21):1477–82.
54. Pigeyre M, Yazdi FT, Kaur Y, Meyre D. Recent progress in genetics, epigenetics and metagenomics unveils the pathophysiology of human obesity. Clin Sci. 2016;130:943–86.
55. Pigeyere M, Meyre D. Monogenic obesity. In: Freemark MS, editor. Pediatric Obesity: Etiology, pathogenesis and treatment. Second edition. New York: Springer International Publishing; 2018. p. 135–52.
56. Irizarry KA, Haqq AM. Syndromic obesity. In: Freemark MS, editor. Pediatric Obesity: Etiology, Pathogenesis and Treatment. Second edition. New York: Springer International Publishing; 2018. p. 153–82.
57. Hinney A, Giuranna J. Polygenic obesity. In: Freemark MS, editor. Pediatric Obesity: Etiology, Pathogenesis and Treatment. Second edition. New York: Springer International Publishing; 2018. p. 183–204.
58. Helgeland Ø, Vaudel M, Juliusson PB, Holmen OL, Juodakis J, Bacelis J, et al. Genome-wide association study reveals dynamic role of genetic variation in infant and early childhood growth. Nat Commun. 2019;10(4448).

59. Alves AC, Silva NMG De, Karhunen V, Sovio U, Das S, Taal HR, et al. GWAS on longitudinal growth traits reveals different genetic factors influencing infant, child, and adult BMI. Sci Adv. 2019;5:1–18.
60. Kwon EJ, Kim YJ. What is fetal programming?: A lifetime health is under the control of in utero health. Obs Gynecol Sci. 2017;60(6):506–19.
61. Harding J, Johnston B. Nutrition and fetal growth. Reprod Fertil Dev. 1995;7(3):539–47.
62. Dalrymple K V., Thompson JMD, Begum S, Godfrey KM, Poston L, Seed PT, et al. Relationships of maternal body mass index and plasma biomarkers with childhood body mass index and adiposity at 6 years: The Children of SCOPE study. Pediatr Obes. 2019;14(10):1–12.
63. Lowe Jr WL, Lowe LP, Kuang A, Catalano PM, Nodzenski M, Talbot O, et al. Maternal glucose levels during pregnancy and childhood adiposity in the Hyperglycemia and Adverse Pregnancy Outcome Follow-up Study. Diabetologia. 2019;62(4):598–610.
64. Hockett CW, Harrall KK, Moore BF, Starling AP, Bellatorre A, Sauder KA, et al. Persistent effects of in utero overnutrition on offspring adiposity: The Exploring Perinatal Outcomes among Children (EPOCH) study. Diabetologia. 2019;62(11):2017–24.
65. Wang J, Pan L, Liu E, Liu H, Liu J, Wang S, et al. Gestational diabetes and offspring's growth from birth to 6 years old. Int J Obes. 2019;43(4):663–72.
66. Symonds ME, Mostyn A, Pearce S, Budge H, Stephenson T. Endocrine and nutritional regulation of fetal adipose tissue development. J Endocrinol. 2003;179(3):293–9.
67. Bispham J, Gopalakrishnan GS, Dandrea J, Wilson V, Budge H, Keisler DH, et al. Maternal endocrine adaptation throughout pregnancy to nutritional manipulation: Consequences for maternal plasma leptin and cortisol and the programming of fetal adipose tissue development. Endocrinology. 2003;144(8):3575–85.
68. Khanal P, Pandey D, Binti Ahmad S, Safayi S, Kadarmideen HN, Olaf Nielsen M. Differential impacts of late gestational over-and undernutrition on adipose tissue traits and associated visceral obesity risk upon exposure to a postnatal high-fat diet in adolescent sheep. Physiol Rep. 2020;8(3):e14359.
69. Tahir MJ, Haapala JL, Foster LP, Duncan KM, Teague AM, Kharbanda EO, et al. Higher maternal diet quality during pregnancy and lactation is associated with lower infant weight-for-length, body fat percent, and fat mass in early postnatal life. Nutrients. 2019;11(3):1–15.

70. Sebastiani G, García-Beltran C, Pie S, Guerra A, López-Bermejo A, de Toledo JS, et al. The sequence of prenatal growth restraint and postnatal catch-up growth: Normal heart but thicker intima-media and more pre-peritoneal fat in late infancy. Pediatr Obes. 2019;14(3):e12476.
71. Villela LD, Méio MDBB, Gomes Jr. SCS, de Abranches AD, Soares FVM, Moreira MEL. Body composition in preterm infants with intrauterine growth restriction: A cohort study. J Perinat Med. 2018;46(7):804–10.
72. Hoepner LA. Bisphenol A: A narrative review of prenatal exposure effects on adipogenesis and childhood obesity via peroxisome proliferator-activated receptor gamma. Environ Res. 2019;173(March):54–68.
73. Shafei AES, Nabih ES, Shehata KA, Abd Elfatah ESM, Sanad ABA, Marey MY, et al. Prenatal exposure to endocrine disruptors and reprogramming of adipogenesis: An early-life risk factor for childhood obesity. Child Obes. 2018;14(1):18–25.
74. Victora CG, Bahl R, Barros AJD, França GVA, Horton S, Krasevec J, et al. Breastfeeding in the 21st century: Epidemiology, mechanisms, and lifelong effect. Lancet. 2016;387(10017):475–90.
75. Rollins NC, Bhandari N, Hajeebhoy N, Horton S, Lutter CK, Martines JC, et al. Why invest, and what it will take to improve breastfeeding practices? Lancet. 2016;387(10017):491–504.
76. Breij LM, Abrahamse-Berkeveld M, Acton D, De Lucia Rolfe E, Ong KK, Hokken-Koelega ACS. Impact of early infant growth, duration of breastfeeding and maternal factors on total body fat mass and visceral fat at 3 and 6 months of age. Ann Nutr Metab. 2017;71(3–4):203–10.
77. Rodríguez-Cano AM, Mier-Cabrera J, Allegre-Dávalos AL, Muñoz-Manrique C, Perichart-Perera O. Higher fat mass and fat mass accretion during the first six months of life in exclusively breastfed infants. Pediatr Res. 2019;(April):1–7.
78. Bell KA, Wagner CL, Feldman HA, Shypailo RJ, Belfort MB. Associations of infant feeding with trajectories of body composition and growth. Am J Clin Nutr. 2017;106(2):491–8.
79. Gridneva Z, Rea A, Tie WJ, Lai CT, Kugananthan S, Ward LC, et al. Carbohydrates in human milk and body composition of term infants during the first 12 months of lactation. Nutrients. 2019;11(1472):1–24.

80. Gingras V, Aris IM, Rifas-Shiman SL, Switkowski KM, Oken E, Hivert MF. Timing of complementary feeding introduction and adiposity throughout childhood. Pediatrics. 2019;144(6):e20191320.
81. Wosje KS, Khoury PR, Claytor RP, Copeland KA, Hornung RW, Daniels SR, et al. Dietary patterns associated with fat and bone mass in young children. Am J Clin Nutr. 2010;92(2):294–303.
82. Suissa K, Benedetti A, Henderson M, Gray-Donald K, Paradis G. Effects of dietary glycemic index and load on children's cardiovascular risk factors. Ann Epidemiol. 2019;40:1–7.
83. Okubo H, Crozier SR, Harvey NC, Godfrey KM, Inskip HM, Cooper C, et al. Diet quality across early childhood and adiposity at 6 years: The Southampton Women's Survey. Int J Obes. 2015;39(10):1456–62.
84. Setayeshgar S, Maximova K, Ekwaru JP, Gray-Donald K, Henderson M, Paradis G, et al. Diet quality as measured by the Diet Quality Index-International is associated with prospective changes in body fat among Canadian children. Public Health Nutr. 2017;20(3):456–63.
85. Boswell N, Byrne R, Davies PSW. Aetiology of eating behaviours: a possible mechanism to understand obesity development in early childhood. Neurosci Biobehav Rev. 2018;95(November):438–48.
86. Appelhans BM. Neurobehavioral inhibition of reward-driven feeding: Implications for dieting and obesity. Obesity. 2009;17(4):640–7.
87. Campbell KJ, Crawford DA, Salmon J, Carver A, Garnett SP, Baur LA. Associations between the home food environment and obesity-promoting eating behaviors in adolescence. Obesity. 2007;15(3):719–30.
88. Hill DC, Moss RH, Sykes-Muskett B, Conner M, O'Connor DB. Stress and eating behaviors in children and adolescents: Systematic review and meta-analysis. Appetite. 2018;123:14–22.
89. Fuemmeler BF, Sheng Y, Schechter JC, Do E, Zucker N, Majors A, et al. Associations between attention deficit hyperactivity disorder symptoms and eating behaviors in early childhood. Pediatr Obes. 2020;e12631:1–10.
90. He J, Cai Z, Fan X. Prevalence of binge and loss of control eating among children and adolescents with overweight and obesity: An exploratory meta-analysis. Int J Eat Disord. 2017;50(2):91–103.

91. Bäckhed F, Roswall J, Peng Y, Feng Q, Jia H, Kovatcheva-Datchary P, et al. Dynamics and stabilization of the human gut microbiome during the first year of life. Cell Host Microbe. 2015;17(5):690–703.
92. Mueller NT, Whyatt R, Hoepner L, Oberfield S, Dominguez-Bello MG, Widen EM, et al. Prenatal exposure to antibiotics, cesarean section and risk of childhood obesity. Int J Obes. 2015;39(4):665–70.
93. Tun HM, Bridgman SL, Chari R, Field CJ, Guttman DS, Becker AB, et al. Roles of birth mode and infant gut microbiota in intergenerational transmission of overweight and obesity from mother to offspring. JAMA Pediatr. 2018;172(4):368–77.
94. Miller SA, Wu RKS, Oremus M. The association between antibiotic use in infancy and childhood overweight or obesity: A systematic review and meta-analysis. Obes Rev. 2018;19(11):1463–75.
95. Forbes JD, Azad MB, Vehling L, Tun HM, Konya TB, Guttman DS, et al. Association of exposure to formula in the hospital and subsequent infant feeding practices with gut microbiota and risk of overweight in the first year of life. JAMA Pediatr. 2018;172(7):e181161.
96. Caesar R, Tremaroli V, Kovatcheva-Datchary P, Cani PD, Bäckhed F. Crosstalk between gut microbiota and dietary lipids aggravates WAT inflammation through TLR signaling. Cell Metab. 2015;22(4):658–68.
97. Kincaid HJ, Nagpal R, Yadav H. Microbiome-immune-metabolic axis in the epidemic of childhood obesity: Evidence and opportunities. Obes Rev. 2019;(July):1–13.
98. Nicolucci AC, Hume MP, Martínez I, Mayengbam S, Walter J, Reimer RA. Prebiotics reduce body fat and alter intestinal microbiota in children who are overweight or with obesity. Gastroenterology. 2017;153(3):711–22.
99. Chambers ES, Viardot A, Psichas A, Morrison DJ, Murphy KG, Zac-Varghese SEK, et al. Effects of targeted delivery of propionate to the human colon on appetite regulation, body weight maintenance and adiposity in overweight adults. Gut. 2015;64(11):1744–54.
100. Larraufie P, Martin-Gallausiaux C, Lapaque N, Dore J, Gribble FM, Reimann F, et al. SCFAs strongly stimulate PYY production in human enteroendocrine cells. Sci Rep. 2018;8(1):74.

101. Willemsen LE, Koetsier MA, van Deventer SJ, van Tol EA. Short chain fatty acids stimulate epithelial mucin 2 expression through differential effects on prostaglandin E(1) and E(2) production by intestinal myofibroblasts. Gut. 2003;52(10):1442–7.
102. Cani PD, Amar J, Iglesias MA, Poggi M, Knauf C, Bastelica D, et al. Metabolic endotoxemia initiates obesity and insulin resistance. Diabetes. 2007;56(5):1232–42.
103. Borgo F, Verduci E, Riva A, Lassandro C, Riva E, Morace G, et al. Relative abundance in bacterial and fungal gut microbes in obese children: a case control study. Child Obes. 2017;13(1):78–84.
104. López-Contreras BE, Morán-Ramos S, Villarruel-Vázquez R, Macías-Kauffer L, Villamil-Ramírez H, León-Mimila P, et al. Composition of gut microbiota in obese and normal-weight Mexican school-age children and its association with metabolic traits. Pediatr Obes. 2018;13(6):381–8.
105. Indiani CMDSP, Rizzardi KF, Castelo PM, Ferraz LFC, Darrieux M, Parisotto TM. Childhood obesity and Firmicutes/Bacteroidetes ratio in the gut microbiota: A systematic review. Child Obes. 2018;14(8):501–9.
106. Statistics Canada. Physical activity and screen time among Canadian children and youth, 2016 and 2017. 82-625-X. 2019.
107. Adamo KB, Colley RC, Hadjiyannakis S, Goldfield GS. Physical activity and sedentary behavior in obese youth. J Pediatr. 2015;166(5):1270–5.
108. Herman KM, Sabiston CM, Mathieu ME, Tremblay A, Paradis G. Sedentary behavior in a cohort of 8- to 10-year-old children at elevated risk of obesity. Prev Med (Baltim). 2014;60:115–20.
109. Thompson AA, Duckham RL, Desai MM, Choy CC, Sherar LB, Naseri T, et al. Sex differences in the associations of physical activity and macronutrient intake with child body composition: a cross-sectional study of 3- to 7-year-olds in Samoa. Pediatr Obes. 2020;e12603.
110. Saelens BE, Seeley RJ, van Schaick K, Donnelly LF, O'Brien KJ. Visceral abdominal fat is correlated with whole-body fat and physical activity among 8-y-old children at risk of obestiy. Am J Clin Nutr. 2007;85(1):46–53.
111. Dias KA, Ingul CB, Tjønna AE, Keating SE, Gomersall SR, Follestad T, et al. Effect of high-intensity interval training on fitness, fat mass and cardiometabolic biomarkers in children with obesity: a randomised controlled trial. Sport Med. 2018;48(3):733–46.

112. Sirico F, Bianco A, D'Alicandro G, Castaldo C, Montagnani S, Spera R, et al. Effects of physical exercise on adiponectin, leptin, and inflammatory markers in childhood obesity: systematic review and meta-analysis. Child Obes. 2018;14(4):207–17.
113. Pontzer H. Constrained total energy expenditure and the evolutionary biology of energy balance. Exerc Sport Sci Rev. 2015;43(3):110–6.
114. Martin CK, Johnson WD, Myers CA, Apolzan JW, Earnest CP, Thomas DM, et al. Effect of different doses of supervised exercise on food intake, metabolism, and non-exercise physical activity: The E-MECHANIC randomized controlled trial. Am J Clin Nutr. 2019;110(3):583–92.
115. Riou MÈ, Jomphe-Tremblay S, Lamothe G, Finlayson GS, Blundell JE, Décarie-Spain L, et al. Energy compensation following a supervised exercise intervention in women living with overweight/obesity is accompanied by an early and sustained decrease in non-structured physical activity. Front Physiol. 2019;10(August):1–12.
116. Wu Y, Yu X, Li Y, Li G, Cheng H, Xiao X, et al. Adipose tissue mediates associations of birth weight with glucose metabolism disorders in children. Obesity. 2019;27(5):746–55.
117. Van Hulst A, Paradis G, Benedetti A, Barnett TA, Henderson M. Pathways linking birth weight and insulin sensitivity in early adolescence: A double mediation analysis. J Clin Endocrinol Metab. 2018;103(12):4524–32.
118. Kindler JM, Lobene AJ, Vogel KA, Martin BR, McCabe LD, Peacock M, et al. Adiposity, insulin resistance, and bone mass in children and adolescents. J Clin Endocrinol Metab. 2018;104(3):892–9.
119. Hübers M, Geisler C, Plachta-Danielzik S, Müller MJ. Association between individual fat depots and cardio-metabolic traits in normal- and overweight children, adolescents and adults. Nutr Diabetes. 2017;7(5):1–8.
120. Kim JY, Tfayli H, Bacha F, Lee SJ, Michaliszyn SF, Yousuf S, et al. β-cell function, incretin response, and insulin sensitivity of glucose and fat metabolism in obese youth: relationship to OGTT-time-to-glucose-peak. Pediatr Diabetes. 2020;21(1):18–27.
121. Chung ST, Ha J, Onuzuruike AU, Kasturi K, Galvan-De La Cruz, M. Bingham BA, Sumner AE. Time to glucose peak during an oral glucose tolerance test identifies prediabetes risk. Clin Endocrinol (Oxf). 2017;87(5):484–91.

122. Sinha R, Dufour S, Petersen KF, LeBon V, Enoksson S, Ma Y, et al. Assessment of skeletal muscle triglyceride content by ^{1}H nuclear magnetic resonance spectroscopy in lean and obese adolescents. Diabetes. 2002;51:1022–7.
123. Kim JY, Bacha F, Tfayli H, Michaliszyn SF, Yousuf S, Arslanian S. Adipose tissue insulin resistance in youth on the spectrum from normal weight to obese and from normal glucose tolerance to impaired glucose tolerance to type 2 diabetes. Diabetes Care. 2019;42(2):265–72.
124. Cote AT, Harris KC, Panagiotopoulos C, Sandor GGS, Devlin AM. Childhood obesity and cardiovascular dysfunction. J Am Coll Cardiol. 2013;62(15):1309–19.
125. Kavey REW. Combined dyslipidemia in childhood. J Clin Lipidol. 2015;9(5):S41–56.
126. Wibaek R, Vistisen D, Girma T, Admassu B, Abera M, Abdissa A, et al. Associations of fat mass and fat-free mass accretion in infancy with body composition and cardiometabolic risk markers at 5 years: The Ethiopian iABC birth cohort study. PLoS Med. 2019;16(8):1–22.
127. Li H, Huang T, Liu J, Yan Y, Zhao X, Xiao P, et al. Body fat indicators perform better than body mass index in identifying abnormal lipid profiles in boys but not in girls. Pediatr Res. 2019;85(5):617–24.
128. Yan Y, Liu J, Zhao X, Cheng H, Huang G, Mi J. Abdominal visceral and subcutaneous adipose tissues in association with cardiometabolic risk in children and adolescents: The China Child and Adolescent Cardiovascular Health (CCACH) study. BMJ Open Diabetes Res Care. 2019;7(e000824):1–9.
129. van Hoek E, Koopman LP, Feskens EJM, Janse AJ. Assessment of epicardial adipose tissue in young obese children. Child Adolesc Obes. 2019;2(1):96–107.
130. Chen X, Wang Y. Tracking of blood pressure from childhood to adulthood: A systematic review and meta-regression analysis. Circulation. 2008;117(25):3171–80.
131. Theodore RF, Broadbent J, Nagin D, Ambler A, Hogan S, Ramrakha S, et al. Childhood to early mid-life systolic blood pressure trajectories: Early life predictors, effect modifiers, and adult cardiovascular outcomes. Hypertension. 2015;66(6):1108–15.
132. Pausova Z, Mahboubi A, Abrahamowicz M, Leonard GT, Perron M, Richer L, et al. Sex differences in the contributions of visceral and total body fat to blood pressure in adolescence. Hypertension. 2012;59(3):572–9.

133. Darabian S, Hormuz M, Latif MA, Pahlevan S, Budoff MJ. The role of carotid intimal thickness testing and risk prediction in the development of coronary atherosclerosis. Curr Atheroscler Rep. 2013;15(3):1–6.
134. Näslund U, Lundgren A, Vanoli D, Norberg M. Is intima-media thickness a predictor for cardiovascular risk? – Authors' reply. Lancet. 2019;394(10196):381.
135. Loureiro C, Campino C, Martinez-Aguayo A, Godoy I, Aglony M, Bancalari R, et al. Positive association between aldosterone-renin ratio and carotid intima-media thickness in hypertensive children. Clin Endocrinol (Oxf). 2013;78(3):352–7.
136. Bassols J, Martínez-Calcerrada JM, Prats-Puig A, Carreras-Badosa G, Xargay-Torrent S, Lizarraga-Mollinedo E, et al. Perirenal fat is related to carotid intima-media thickness in children. Int J Obes. 2018;42(4):641–7.
137. Akyol B, Boyraz M, Aysoy C. Relationship of epicardial adipose tissue thickness with early indicators of atherosclerosis and cardiac functional changes in obese adolescents with metabolic syndrome. J Clin Res Pediatr Endocrinol. 2013;5(3):156–63.
138. Gepstein V, Weiss R. Obesity as the main risk factor for metabolic syndrome in children. Front Endocrinol (Lausanne). 2019;10(August):1–7.
139. Gishti O, Gaillard R, Durmus B, Abrahamse M, Van Der Beek EM, Hofman A, et al. BMI, total and abdominal fat distribution, and cardiovascular risk factors in school-age children. Pediatr Res. 2015;77(5):710–8.
140. Taksali SE, Caprio S, Dziura J, Dufour S, Calı AMG, Goodman TR, et al. High visceral and low abdominal subcutaneous fat stores in the obese adolescent: a determinant of an adverse metabolic phenotype. Diabetes. 2008;57(February):367–71.
141. Umano GR, Shabanova V, Pierpont B, Mata M, Nouws J, Tricò D, et al. A low visceral fat proportion, independent of total body fat mass, protects obese adolescent girls against fatty liver and glucose dysregulation: A longitudinal study. Int J Obes. 2019;43(4):673–82.
142. Nouws J, Fitch M, Mata M, Santoro N, Galuppo B, Kursawe R, et al. Altered in vivo lipid fluxes and cell dynamics in subcutaneous adipose tissues are associated with the unfavorable pattern of fat distribution in obese adolescent girls. Diabetes. 2019;68(6):1168–77.
143. Marginean CO, Melit LE, Ghica D V., Mărginean MO. Early inflammatory status related to pediatric obesity. Front Pediatr. 2019;7:1–7.

144. Araújo AJS, Santos ACO, Prado WL. Body composition of obese adolescents: association between adiposity indicators and cardiometabolic risk factors. J Hum Nutr Diet. 2017;30(2):193–202.
145. MacLean JE, DeHaan K, Chowdhury T, Nehme J, Bendiak GN, Hoey L, et al. The scope of sleep problems in Canadian children and adolescents with obesity. Sleep Med. 2018;47:44–50.
146. Bhatia R, Lesser DJ, Oliveira FGSA, Tran WH, Keens TG, Khoo MCK, et al. Body fat composition: A predictive factor for sleep related breathing disorder in obese children. J Clin Sleep Med. 2015;11(9):1039–45.
147. Canapari CA, Hoppin AG, Kinane TB, Thomas BJ, Torriani M, Katz ES. Relationship between sleep apnea, fat distribution, and insulin resistance in obese children. J Clin Sleep Med. 2011;7(3):268–73.
148. Joosten SA, Landry SA, Terrill PI. Statistical uncertainty of the apnea-hypopnea index is another reason to question the utility of this metric. Sleep Med. 2020;65:159–60.
149. Gulotta G, Iannella G, Vicini C, Polimeni A, Greco A, de Vincentiis M, et al. Risk factors for obstructive sleep apnea syndrome in children: State of the art. Int J Environ Res Public Health. 2019;16(3235):1–20.
150. Schwab RJ, Kim C, Bagchi S, Keenan BT, Comyn FL, Wang S, et al. Understanding the anatomic basis for obstructive sleep apnea syndrome in adolescents. Am J Respir Crit Care Med. 2015;191(11):1295–309.
151. Li AM, Chan D, Wong E, Yin J, Nelson EAS, Fok TF. The effects of obesity on pulmonary function. Arch Dis Child. 2003;88(1):361–3.
152. Gaines J, Vgontzas AN, Fernandez-Mendoza J, Calhoun SL, He F, Liao D, et al. Inflammation mediates the association between visceral adiposity and obstructive sleep apnea in adolescents. Am J Physiol - Endocrinol Metab. 2016;311:E851–8.
153. Kheirandish-Gozal L, Bhattacharjee R, Bandla HPR, Gozal D. Antiinflammatory therapy outcomes for mild OSA in children. Chest. 2014;146(1):88–95.
154. Hui W, Slorach C, Guerra V, Parekh RS, Hamilton J, Messiha S, et al. Effect of obstructive sleep apnea on cardiovascular function in obese youth. Am J Cardiol. 2019;123(2):341–7.

155. Rizzoli R, Bonjour J. Determinants of peak bone mass acquisition. In: Osteoporosis Contemporary Endocrinology. Humana, Cham; 2020. p. 115–37.
156. Sioen I, Lust E, De Henauw S, Moreno LA, Jiménez-Pavón D. Associations between body composition and bone health in children and adolescents: A systematic reriew. Calcif Tissue Int. 2016;99(6):557–77.
157. Glass NA, Torner JC, Letuchy EM, Burns TL, Janz KF, Eichenberger Gilmore JM, et al. Does visceral or subcutaneous fat influence peripheral cortical bone strength during adolescence? A longitudinal study. J Bone Miner Res. 2018;33(4):580–8.
158. Hetherington-Rauth M, Bea JW, Blew RM, Funk JL, Hingle MD, Lee VR, et al. Relative contributions of lean and fat mass to bone strength in young Hispanic and non-Hispanic girls. Bone. 2018;113:144–50.
159. Duran I, Martakis K, Hamacher S, Stark C, Semler O, Schoenau E. Are there effects of age, gender, height, and body fat on the functional muscle-bone unit in children and adults? Osteoporos Int. 2018;29(5):1069–79.
160. Meng T, Thayer S, Venn A, Wu F, Cicuttini F, March L, et al. Association of childhood adiposity measures with adulthood knee cartilage defects and bone marrow lesions: A 25-year cohort study. Osteoarthr Cartil. 2018;26(8):1055–62.
161. Mahaffey R, Morrison SC, Bassett P, Drechsler WI, Cramp MC. Biomechanical characteristics of lower limb gait waveforms: Associations with body fat in children. Gait Posture. 2018;61(January):220–5.
162. Ortega FB, Ruiz JR, Castillo MJ, Sjöström M. Physical fitness in childhood and adolescence: A powerful marker of health. Int J Obes. 2008;32(1):1–11.
163. Lee SJ, Arslanian SA. Cardiorespiratory fitness and abdominal adiposity in youth. Eur J Clin Nutr. 2007;61(4):561–5.
164. Moliner-Urdiales D, Ruiz JR, Vicente-Rodriguez G, Ortega FB, Rey-Lopez JP, España-Romero V, et al. Associations of muscular and cardiorespiratory fitness with total and central body fat in adolescents: The HELENA study. Br J Sports Med. 2011;45(2):101–8.
165. Haapala EA, Väistö J, Lintu N, Tompuri T, Brage S, Westgate K, et al. Adiposity, physical activity, and neuromuscular performance in children. J Sports Sci. 2016;34(18):1699–706.

166. Füssenich LM, Boddy LM, Green DJ, Graves LEF, Foweather L, Dagger RM, et al. Physical activity guidelines and cardiovascular risk in children: A cross sectional analysis to determine whether 60 minutes is enough. BMC Public Health. 2016;16(1):1–7.
167. Scheurer JM, Zhang L, Plummer EA, Hultgren SA, Demerath EW, Ramel SE. Body composition changes from infancy to 4 Years and associations with early childhood cognition in preterm and full-term children. Neonatology. 2018;114(2):169–76.
168. Abera M, Tesfaye M, Girma T, Hanlon C, Andersen GS, Wells JC, et al. Relation between body composition at birth and child development at 2 years of age: A prospective cohort study among Ethiopian children. Eur J Clin Nutr. 2017;71(12):1411–7.
169. Abera M, Tesfaye M, Hanlon C, Admassu B, Girma T, Wells JC, et al. Body composition during early infancy and mental health outcomes at 5 years of age: A prospective cohort study of Ethiopian children. J Pediatr. 2018;200:225–31.
170. Kamijo K, Khan NA, Pontifex MB, Scudder MR, Eric S, Raine LB, et al. The relation of adiposity to cognitive control and scholastic achievement in preadolescent children. Obes (Silver Spring). 2012;20(12):2406–11.
171. Yau PL, Javier DC, Ryan CM, Tsui WH, Ardekani BA, Ten S, et al. Preliminary evidence for brain complications in obese adolescents with type 2 diabetes mellitus. Diabetologia. 2010;53(11):2298–306.
172. Raine LB, Khan NA, Drollette ES, Pontifex MB, Kramer AF, Hillman CH. Obesity, visceral adipose tissue, and cognitive function in childhood. J Pediatr. 2017;187(617):134-140.e3.
173. Schaeffer DJ, Krafft CE, Schwarz NF, Chi L, Rodrigue AL, Pierce JE, et al. An 8-month exercise intervention alters frontotemporal white matter integrity in overweight children. Psychophysiology. 2014;51(8):728–33.
174. Nguyen-Rodriguez ST, Gallo LC, Isasi CR, Buxton OM, Thomas KS, Sotres-Alvarez D, et al. Adiposity, depression symptoms and inflammation in Hispanic/Latino youth: Results from HCHS/SOL youth. Ann Behav Med. 2020;1–6.
175. Szwimer E, Mougharbel F, Goldfield GS, Alberga AS. The association between weight-based teasing from peers and family in childhood and depressive symptoms in childhood and adulthood: A systematic review. Curr Obes Rep. 2020;

176. Schvey NA, Marwitz SE, Mi SJ, Galescu OA, Broadney MM, Young-Hyman D, et al. Weight-based teasing is associated with gain in BMI and fat mass among children and adolescents at-risk for obesity: A longitudinal study. Pediatr Obes. 2019;14(10):1–14.
177. Pearl RL, Puhl RM. Weight bias internalization and health: A systematic review. Obes Rev. 2018;8(1):1141–63.
178. Wolfe RR. The underappreciated role of muscle in health and disease. Am J Clin Nutr. 2006;84(3):475–82.
179. Wolfe RR, Rutherfurd SM, Kim IY, Moughan PJ. Protein quality as determined by the Digestible Indispensable Amino Acid Score: Evaluation of factors underlying the calculation. Nutr Rev. 2016;74(9):584–99.
180. Meyer C, Dostou JM, Welle SL, Gerich JE. Role of human liver, kidney, and skeletal muscle in postprandial glucose homeostasis. Am J Physiol - Endocrinol Metab. 2002;282(2):E419–27.
181. Frontera WR, Ochala J. Skeletal muscle: A brief review of structure and function. Calcif Tissue Int. 2015;96(3):183–95.
182. Illner K, Brinkmann G, Heller M, Bosy-Westphal A, Muller MJ. Metabolically active components of fat free mass and resting energy expenditure in nonobese adults. Am J Physiol Endocrinol Metab. 2000;278(2):E308-15.
183. Prado CMM, Wells JCK, Smith SR, Stephan BCM, Siervo M. Sarcopenic obesity: A critical appraisal of the current evidence. Clin Nutr. 2012;31(5):583–601.
184. Cleasby ME, Jamieson PM, Atherton PJ. Insulin resistance and sarcopenia: Mechanistic links between common co-morbidities. J Endocrinol. 2016;229(2):R67–81.
185. Kim S, Valdez R. Metabolic risk factors in U.S. youth with low relative muscle mass. Obes Res Clin Pract. 2015;9(2):125–32.
186. Peterson MD, Zhang P, Saltarelli WA, Visich PS, Gordon PM. Low muscle strength thresholds for the detection of cardiometabolic risk in adolescents. Am J Prev Med. 2016;50(5):593–9.
187. Fukada SI. The roles of muscle stem cells in muscle injury, atrophy and hypertrophy. J Biochem. 2018;163(5):353–8.
188. Sass FA, Fuchs M, Pumberger M, Geissler S, Duda GN, Perka C, et al. Immunology guides skeletal muscle regeneration. Int J Mol Sci. 2018;19(3):1–19.

189. Romero NB, Mezmezian M, Fidziańska A. Main steps of skeletal muscle development in the human. Morphological analysis and ultrastructural characteristics of developing human muscle. Handb Clin Neurol. 2013;113:1299–310.
190. Verdijk LB, Snijders T, Drost M, Delhaas T, Kadi F, Van Loon LJC. Satellite cells in human skeletal muscle: From birth to old age. Age (Omaha). 2014;36(2):545–57.
191. Sayer AA, Cooper C. Fetal programming of body composition and musculoskeletal development. Early Hum Dev. 2005;81(9):735–44.
192. Brand-Saberi B. Genetic and epigenetic control of skeletal muscle development. Ann Anat. 2005;187(3):199–207.
193. Costa-Orvay JA, Figueras-Aloy J, Romera G, Closa-Monasterolo R, Carbonell-Estrany X. The effects of varying protein and energy intakes on the growth and body composition of very low birth weight infants. Nutr J. 2011;10(1):1–9.
194. Wackerhage H, Rennie MJ. How nutrition and exercise maintain the human musculoskeletal mass. J Anat. 2006;208(4):451–8.
195. Martinez EE, Smallwood CD, Quinn NL, Ariagno K, Bechard LJ, Duggan CP, et al. Body composition in children with chronic illness: Accuracy of bedside assessment techniques. J Pediatr. 2017;190:56–62.
196. Wu H, Ballantyne CM. Skeletal muscle inflammation and insulin resistance in obesity. J Clin Invest. 2017;127(1):43–54.
197. Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyère O, Cederholm T, et al. Sarcopenia: Revised European consensus on definition and diagnosis. Age Ageing. 2018;0(1):1–16.
198. Cabeço LC, Budri PE, Baroni M, Castan EP, Carani FR, De Souza PAT, et al. Maternal protein restriction induce skeletal muscle changes without altering the MRFs MyoD and myogenin expression in offspring. J Mol Histol. 2012;43(5):461–71.
199. Wang H, Wilson GJ, Zhou D, Lezmi S, Chen X, Layman DK, et al. Induction of autophagy through the activating transcription factor 4 (ATF4)-dependent amino acid response pathway in maternal skeletal muscle may function as the molecular memory in response to gestational protein restriction to alert offspring to materna. Br J Nutr. 2015;4(2015):1–14.
200. Tong JF, Yan X, Zhu MJ, Ford SP, Nathanielsz PW, Du M. Maternal obesity downregulates myogenesis and β-catenin signaling in fetal skeletal muscle. AJP Endocrinol Metab. 2009;296(4):E917–24.

201. Chomtho S, Wells JCK, Williams JE, Lucas A, Fewtrell MS. Associations between birth weight and later body composition: Evidence from the 4-component model. Am J Clin Nutr. 2008;88(4):1040–8.
202. Baker J, Workman M, Bedrick E, Frey MA, Hurtado M, Pearson O. Brains versus brawn: An empirical test of barkers brain sparing model. Am J Hum Biol. 2010;22(2):206–15.
203. Bielemann RM, Gigante DP, Horta BL. Birth weight, intrauterine growth restriction and nutritional status in childhood in relation to grip strength in adults: From the 1982 Pelotas (Brazil) birth cohort. Nutrition. 2016;32(2):228–35.
204. Sayer AA, Dennison EM, Syddall HE, Jameson K, Martin HJ, Cooper C. The developmental origins of sarcopenia: using peripheral quantitative computed tomography to assess muscle size in older people. J Gerontol A Biol Sci Med Sci. 2008;63(8):835-40 OD-2008/09/06.
205. Dodds R, Denison HJ, Ntani G, Cooper R, Cooper C, Sayer a a, et al. Birth weight and muscle strength: A systematic review and meta-analysis. J Nutr Health Aging. 2012;16(7):609–15.
206. Boyle KE, Patinkin ZW, Shapiro ALB, Baker PR, Dabelea D, Friedman JE. Mesenchymal stem cells from infants born to obese mothers exhibit greater potential for adipogenesis: The healthy start babybump project. Diabetes. 2016;65(3):647–59.
207. Malfatti E, Romero NB. Diseases of the skeletal muscle. 1st ed. Vol. 145, Handbook of Clinical Neurology. Elsevier B.V.; 2017. 429–451 p.
208. Gawlik KI. At the crossroads of clinical and preclinical research for muscular dystrophy-are we closer to effective treatment for patients? Int J Mol Sci. 2018;19(5).
209. Wagner KR. Genetic diseases of muscle. Neurol Clin. 2002;20(3):645–78.
210. Romitti PA, Zhu Y, Puzhankara S, James KA, Nabukera SK, Zamba GKD, et al. Prevalence of Duchenne and Becker muscular dystrophies in the United States. Pediatrics. 2015;135(3):513–21.
211. Cassidy SB, Schwartz S, Miller JL, Driscoll DJ. Prader-Willi syndrome. Genet Med. 2012;14(1):10–26.
212. Reus L, Pillen S, Pelzer J, Hokken-koelega ACS, Otten BJ, Maria WG, et al. Growth hormone therapy , muscle thickness , and motor development in Prader-Willi syndrome : An RCT. 2014;134(6).

213. Mackenzie ML, Triador L, Gill JK, Pakseresht M, Mager D, Field CJ, et al. Dietary intake in youth with prader-willi syndrome. Am J Med Genet Part A. 2018;(In press).
214. Rayar M, Webber CE, Nayiager T, Sala A, Barr RD. Sarcopenia in children with acute lymphoblastic leukemia. J Pediatr Hematol Oncol. 2013;35(2):98–102.
215. Suzuki D, Kobayashi R, Sano H, Hori D, Kobayashi K. Sarcopenia after induction therapy in childhood acute lymphoblastic leukemia: Its clinical significance. Int J Hematol. 2018;107(4):486–9.
216. Lee DY, Wetzsteon RJ, Zemek BS, Shults J, Organ JM, Foster BJ, et al. Muscle torque relative to cross-sectional area and the functional muscle-bone unit in children and adolescents with chronic disease. J Bone Min Res. 2015;30(3):575–83.
217. Salehian B, Kejriwal K. Glucocorticoid-induced muscle atrophy: Mechanisms and therapeutic strategies. Endocr Pract. 1999;5(5):277–81.
218. Marriott CJC, Beaumont LF, Farncombe TH, Cranston AN, Athale UH, Yakemchuk VN, et al. Body composition in long-term survivors of acute lymphoblastic leukemia diagnosed in childhood and adolescence: A focus on sarcopenic obesity. Cancer. 2018;124(6):1225–31.
219. Hurtado-López EF, Vásquez-Garibay EM, Trujillo X, Larrosa-Haro A. Body composition predicts growth in infants and toddlers with chronic liver disease. J Pediatr Gastroenterol Nutr. 2017;65(6):e117–9.
220. Maratova K, Soucek O, Matyskova J, Hlavka Z, Lenka P, Obermannova B, et al. Muscle functions and bone strength are impaired in adolescents with type 1 diabetes. Bone. 2018;106:22–7.
221. Thangarajah D, Hyde MJ, Konteti VKS, Santhakumaran S, Frost G, Fell JME. Systematic review: Body composition in children with inflammatory bowel disease. Aliment Pharmacol Ther. 2015;42(2):142–57.
222. Mager DR, Carroll MW, Wine E, Siminoski K, MacDonald K, Kluthe CL, et al. Vitamin D status and risk for sarcopenia in youth with inflammatory bowel diseases. Eur J Clin Nutr. 2018;72(4):623–6.
223. Zhou J, Liu B, Liang C, Li Y, Song YH. Cytokine signaling in skeletal muscle wasting. Trends Endocrinol Metab. 2016;27(5):335–47.

224. Barnes MJ, Lynch MK, Lisenby MD, Jester T, Maclin J, Knight T, et al. Conceptual model of lean body mass in pediatric inflammatory bowel disease. J Pediatr Gastroenterol Nutr. 2019;68(3):301–5.
225. Veldhuis JD, Roemmich JN, Richmond EJ, Rogol AD, Lovejoy JC, Sheffield-Moore M, et al. Endocrine control of body composition in infancy, childhood, and puberty. Endocr Rev. 2005;26(1):114–46.
226. Webber CE, Barr RD. Age and gender-dependent values of skeletal muscle mass in healthy children and adolescents. J Cachexia Sarcopenia Muscle. 2012;3(1):25–9.
227. McCarthy HD, Samani-Radia D, Jebb SA, Prentice AM. Skeletal muscle mass reference curves for children and adolescents. Pediatr Obes. 2014;9(4):249–59.
228. Cole TJ, Ahmed ML, Preece MA, Hindmarsh P, Dunger DB. The relationship between insulin-like growth factor 1, sex steroids and timing of the pubertal growth spurt. Clin Endocrinol (Oxf). 2015;82(6):862–9.
229. Neu CM, Rauch F, Rittweger J, Manz F, Schoenau E. Influence of puberty on muscle development at the forearm. Am J Physiol - Endocrinol Metab. 2002;283(1):E103–7.
230. Salvatore D, Simonides WS, Dentice M, Zavacki AM, Larsen PR. Thyroid hormones and skeletal muscle — new insights and potential implications. Nat Rev Endocrinol. 2014;10(4):206–14.
231. Tauber M, Jouret B, Cartault A, Lounis N, Gayrard M, Marcouyeux C, et al. Adolescents with partial growth hormone (GH) deficiency develop alterations of body composition after GH discontinuation and require follow-up. J Clin Endocrinol Metab. 2003;88(11):5101–6.
232. Viswanathan V, Eugster EA. Etiology and treatment of hypogonadism in adolescents. Pediatr Clin North Am. 2011;58(5):1181–x.
233. Deillon E, Hauschild M, Faouzi M, Stoppa-Vaucher S, Elowe-Gruau E, Dwyer A, et al. Natural history of growth hormone deficiency in a pediatric cohort. Horm Res Paediatr. 2015;83(4):252–61.
234. Hulthén L, Bengtsson BÅ, Sunnerhagen KS, Hallberg L, Grimby G, Johannsson G. GH is needed for the maturation of muscle mass and strength in adolescents. J Clin Endocrinol Metab. 2001;86(10):4765–70.

235. Kuppens RJ, Bakker NE, Siemensma EPC, Tummers-De Lind Van Wijngaarden RFA, Donze SH, Festen DAM, et al. Beneficial effects of GH in young adults with Prader-Willi syndrome: A 2-year crossover trial. J Clin Endocrinol Metab. 2016;101(11):4110–6.
236. Gregory JW, Greene SA, Thompson J, Scrlmgeour CM, Rennle MJ. Effects of oral testosterone undecanoate on growth, body composition, strength and energy expenditure of adolescent boys. Clin Endocrinol (Oxf). 1992;37(3):207–13.
237. Arslanian S, Suprasongsin C. Testosterone treatment in adolescents with delayed puberty: Changes in body composition, protein, fat, and glucose metabolism. J Clin Endocrinol Metab. 1997;82(10):3213–20.
238. Mitchell WK, Wilkinson DJ, Phillips BE, Lund JN, Smith K, Atherton PJ. Human skeletal muscle protein metabolism responses to amino acid nutrition. Adv Nutr. 2016;7(Suppl):828S-838S.
239. Jen V, Karagounis LG, Jaddoe VWV, Franco OH, Voortman T. Dietary protein intake in school-age children and detailed measures of body composition: The Generation R Study. Int J Obes. 2018;
240. Harris C, Buyken A, Von Berg A, Berdel D, Lehmann I, Hoffmann B, et al. Prospective associations of meat consumption during childhood with measures of body composition during adolescence: Results from the GINIplus and LISAplus birth cohorts. Nutr J. 2016;15(1).
241. Assmann KE, Joslowski G, Buyken AE, Cheng G, Remer T, Kroke A, et al. Prospective association of protein intake during puberty with body composition in young adulthood. Obesity. 2013;21(12):782–9.
242. Cameron JD, Sigal RJ, Kenny GP, Alberga AS, Prud'homme D, Phillips P, et al. Body composition and energy intake — skeletal muscle mass is the strongest predictor of food intake in obese adolescents: The HEARTY trial. Appl Physiol Nutr Metab. 2016;41(6):611–7.
243. Garlick PJ. Protein requirements of infants and children. Nestle Nutr Work Ser Pediatr Progr. 2006;58:39–50.
244. Joint WHO/FAO/UNU Expert Consultation. Protein and amino acid requirements in human nutrition. Vol. 935, World Health Organization Technical Report Series. 2007.
245. Kalhan SC. Optimal protein intake in healthy infants. Am J Clin Nutr. 2009;89:1719–20.

246. Voortman T, Braun KVE, Kiefte-de Jong JC, Jaddoe VW V, Franco OH, van den Hooven EH. Protein intake in early childhood and body composition at the age of 6 years: The Generation R Study. Int J Obes. 2016;40(6):1018–25.
247. Rolland-Cachera M, Deheeger M, Akrout M, Bellisle F. Influence of macronutrients on adiposity development: A follow up study of nutrition and growth from 10 months to 8 years of age. Int J Obes Relat Metab Disord. 1995;19(8):573–8.
248. Pesta DH, Samuel VT. A high-protein diet for reducing body fat: Mechanisms and possible caveats. Nutr Metab. 2014;11(1):1–8.
249. Koletzko B, Broekaert I, Demmelmair H, Franke J, Hannibal I, Oberle D, et al. Early nutrition and its later consequences: New opportunities. In: Advances in Experimental Medicine and Biology. Dordrecht: Springer; 2005. p. 69–79.
250. Ong K, Kratzsch J, Kiess W, Dunger D. Circulating IGF-I levels in childhood are related to both current body composition and early postnatal growth rate. J Clin Endocrinol Metab. 2002;87(3):1041–4.
251. Socha P, Grote V, Gruszfeld D, Janas R, Demmelmair H, Closa-Monasterolo R, et al. Milk protein intake, the metabolic-endocrine response, and growth in infancy: Data from a randomized clinical trial. Am J Clin Nutr. 2011;94(SUPPL):1776S-1784S.
252. Weber M, Grote V, Closa-monasterolo R, Escribano J, Langhendries J, Dain E, et al. Lower protein content in infant formula reduces BMI and obesity risk at school age: Follow-up of a randomized trial. Am J Clin Nutr. 2014;1041–51.
253. Dulloo AG, Jacquet J, Seydoux J, Montani JP. The thrifty 'catch-up fat' phenotype: Its impact on insulin sensitivity during growth trajectories to obesity and metabolic syndrome. Int J Obes. 2006;30:S23–35.
254. van Vliet S, Burd NA, van Loon LJ. The Skeletal Muscle Anabolic Response to Plant- versus Animal-Based Protein Consumption. J Nutr. 2015;145(9):1981–91.
255. Gunther AL, Remer T, Kroke A, Buyken AE. Early protein intake and later obesity risk: Which protein sources at which time points throughout infancy and childhood are important for body mass index and body fat percentage at 7 y of age ? Am J Clin Nutr. 2007;(86):1765–72.
256. Pearson N, Timperio A, Salmon J, Crawford D, Biddle SJH. Family influences on children's physical activity and fruit and vegetable consumption. Int J Behav Nutr Phys Act. 2009;6:1–7.

257. Nettle H, Sprogis E. Pediatric Exercise : Truth and/or consequences. Sport Med Arthrosc Rev. 2011;19(1):75–80.
258. Colley RC, Carson V, Garriguet D, Janssen I, Roberts KC, Tremblay MS. Physical activity of Canadian children and youth, 2007 to 2015. Heal Reports. 2017;28(10):8–16.
259. Dotan R, Mitchell C, Cohen R, Klentrou P, Gabriel D, Bareket F. Child-adult differences in muscle activation - A review. Pediatr Exerc Sci. 2012;24(1):2–21.
260. Boisseau N, Delamarche P. Metabolic and hormonal responses to exercise in children and adolescents. Sport Med. 2000;30(6):405–22.
261. Schoenfeld BJ. The mechanisms of muscle hypertrophy and their application to resistance training. J of Strength Cond Res. 2010;24(10):2857–72.
262. Behm DG, Faigenbaum AD, Falk B, Klentrou P. Canadian Society for Exercise Physiology position paper: Resistance training in children and adolescents. Appl Physiol Nutr Metab. 2008;33(3):547–61.
263. Watson K, Baar K. MTOR and the health benefits of exercise. Semin Cell Dev Biol. 2014;36:130–9.
264. Granacher U, Goesele A, Roggo K, Wischer T, Fischer S, Zuerny C, et al. Effects and mechanisms of strength training in children. Int J Sport Med. 2011;32:357–64.
265. Alberga AS, Prud'homme D, Sigal RJ, Goldfield GS, Hadjiyannakis S, Phillips P, et al. Effects of aerobic training, resistance training, or both on cardiorespiratory and musculoskeletal fitness in adolescents with obesity: the HEARTY trial. Appl Physiol Nutr Metab. 2016;41(3):255–65.
266. Ng M, Fleming T, Robinson M, Thomson B, Graetz N. Global, regional and national prevalence of overweight and obesity in children and adults 1980-2013: A systematic analysis. Lancet. 2014;384(9945):766–81.
267. Cauley JA. An Overview of Sarcopenic Obesity. J Clin Densitom. 2015;18(4):499–505.
268. Tomlinson DJ, Erskine RM, Morse CI, Winwood K, Onambélé-Pearson G. The impact of obesity on skeletal muscle strength and structure through adolescence to old age. Biogerontology. 2016;17(3):467–83.
269. Thivel D, Ring-Dimitriou S, Weghuber D, Frelut M-L, O'Malley G. Muscle strength and fitness in pediatric obesity: A systematic review from the European Childhood Obesity Group. Obes Facts. 2016;9(1):52–63.

270. Blimkie CJR, Sale DG, Bar-Or O. Voluntary strength, evoked twitch contractile properties and motor unit activation of knee extensors in obese and non-obese adolescent males. Eur J Appl Physiol Occup Physiol. 1990;61(3–4):313–8.
271. Smith JJ, Eather N, Morgan PJ, Plotnikoff RC, Faigenbaum AD, Lubans DR. The health benefits of muscular fitness for children and adolescents: A systematic review and meta-analysis. Sport Med. 2014;44(9):1209–23.
272. Garcia-Vicencio S, Martin V, Kluka V, Cardenoux C, Jegu AG, Fourot AV, et al. Obesity-related differences in neuromuscular fatigue in adolescent girls. Eur J Appl Physiol. 2015;115(11):2421–32.
273. Miller JD, Sterczala AJ, Trevino MA, Herda TJ. Examination of muscle composition and motor unit behavior of the first dorsal interosseous of normal and overweight children. J Neurophysiol. 2018;119(5):1902–11.
274. Phillips CM. Metabolically healthy obesity across the life course: Epidemiology, determinants, and implications. Ann N Y Acad Sci. 2017;1391(1):85–100.
275. Akhmedov D, Berdeaux R. The effects of obesity on skeletal muscle regeneration. Front Physiol. 2013;4 DEC(December):1–12.
276. Reilly SM, Saltiel AR. Adapting to obesity with adipose tissue inflammation. Nat Rev Endocrinol. 2017;13(11):633–43.
277. Kim JH, Park YS. Low muscle mass is associated with metabolic syndrome in Korean adolescents: The Korea National Health and Nutrition Examination Survey 2009-2011. Nutr Res. 2016;36(12):1423–8.
278. Murphy MJ, Metcalf BS, Jeffery AN, Voss LD, Wilkin TJ. Does lean rather than fat mass provide the link between birth weight, BMI, and metabolic risk? EarlyBird 23. Pediatr Diabetes. 2006;7(4):211–4.
279. Blakeley CE, Van Rompay MI, Schultz NS, Sacheck JM. Relationship between muscle strength and dyslipidemia, serum 25(OH)D, and weight status among diverse schoolchildren: A cross-sectional analysis. BMC Pediatr. 2018;18(1):23.
280. Dorsey KB, Thornton JC, Heymsfield SB, Gallagher D. Greater lean tissue and skeletal muscle mass are associated with higher bone mineral content in children. Nutr Metab (Lond). 2010;7(1):41.

281. Kim HY, Jung HW, Hong H, Kim JH, Shin CH, Yang SW, et al. The role of overweight and obesity on bone health in Korean adolescents with a focus on lean and fat mass. J Korean Med Sci. 2017;32(10):1633–41.
282. DeFronzo RA, Jacot E, Jequier E, Maeder E, Wahren J, Felber JP. The effect of insulin on the disposal of intravenous glucose: Results from indirect calorimetry and hepatic and femoral venous catheterization. Diabetes. 1981;30(12):1000–7.
283. Rudvik A, Månsson M. Evaluation of surrogate measures of insulin sensitivity - Correlation with gold standard is not enough. BMC Med Res Methodol. 2018;18(1):1–8.
284. Gracia-Marco L, Moreno LA, Ruiz JR, Ortega FB, de Moraes ACF, Gottrand F, et al. Body composition indices and single and clustered cardiovascular disease risk factors in adolescents: Providing clinical-based cut-points. Prog Cardiovasc Dis. 2016;58(5):555–64.
285. Hou WW, Tse MA, Lam TH, Leung GM, Schooling CM. Adolescent testosterone, muscle mass and glucose metabolism: Evidence from the "Children of 1997" birth cohort in Hong Kong. Diabet Med. 2015;32(4):505–12.
286. Lee S, Kim Y, White DA, Kuk JL, Arslanian S. Relationships between insulin sensitivity, skeletal muscle mass and muscle quality in obese adolescent boys. Eur J Clin Nutr. 2012;66(12):1366–8.
287. Weber DR, Leonard MB, Shults J, Zemel BS. A comparison of fat and lean body mass index to BMI for the identification of metabolic syndrome in children and adolescents. J Clin Endocrinol Metab. 2014;99(9):3208–16.
288. Schvey NA, Shomaker LB, Kelly NR, Pickworth CK, Cassidy O, Galescu O, et al. Pressure to be thin and insulin sensitivity among adolescents. J Adolesc Heal. 2016;58(1):104–10.
289. Kim J, Bang H. Three common misuses of P values. Dent Hypotheses. 2016;7(3):73–80.
290. Wells JCK. Toward body composition reference data for infants, children, and adolescents. Adv Nutr An Int Rev J. 2014;5(3):320S-329S.
291. O'Brien C, Young AJ, Sawka MN. Bioelectrical impedance to estimate changes in hydration status. Int J Sports Med. 2002;23(5):361–6.
292. Prado CMM, Heymsfield SB. Lean tissue imaging: A new era for nutritional assessment and intervention. J Parenter Enter Nutr. 2014;38(8):940–53.

293. Goodpaster BH, Wolf D. Skeletal muscle lipid accumulation in obesity, insulin resistance, and type 2 diabetes. Pediatr Diabetes. 2004;5(4):219–26.
294. Levy-Marchal C, Arslanian S, Cutfield W, Sinaiko A, Druet C, Marcovecchio ML, et al. Insulin resistance in children: Consensus, perspective, and future directions. J Clin Endocrinol Metab. 2010;95(12):5189–98.
295. Muniyappa R, Lee S, Chen H, Quon MJ. Current approaches for assessing insulin sensitivity and resistance in vivo: advantages, limitations, and appropriate usage. AJP Endocrinol Metab. 2007;294(1):E15–26.
296. Andersen LB, Harro M, Sardinha LB, Froberg K, Ekelund U, Brage S, et al. Physical activity and clustered cardiovascular risk in children: a cross-sectional study (The European Youth Heart Study). Lancet. 2006;368(9532):299–304.
297. Blackett PR, Wilson DP, McNeal CJ. Secondary hypertriglyceridemia in children and adolescents. J Clin Lipidol. 2015;9(5):S29–40.
298. Ramires VV, Dumith SC, Wehrmeister FC, Hallal PC, Menezes AMB, Gonçalves H. Physical activity throughout adolescence and body composition at 18 years: 1993 Pelotas (Brazil) birth cohort study. Int J Behav Nutr Phys Act. 2016;13(1).
299. Loprinzi PD, Cardinal BJ. Measuring children's physical activity and sedentary behaviors. J Exerc Sci Fit. 2011;9(1):15–23.
300. Adamo KB, Prince SA, Tricco AC, Connor-Gorber S, Tremblay M. A comparison of indirect versus direct measures for assessing physical activity in the pediatric population: A systematic review. Int J Pediatr Obes. 2009;4(1):2–27.
301. Subar AF, Freedman LS, Tooze JA, Kirkpatrick SI, Boushey C, Neuhouser ML, et al. Addressing current criticism regarding the value of self-report dietary data. J Nutr. 2015;145(12):2639–45.
302. Dhuper S, Sakowitz S, Daniels J, Buddhe S, Cohen HW. Association of lipid abnormalities with measures and severity of adiposity and insulin resistance among overweight children and adolescents. J Clin Hypertens. 2009;11(10):594–600.
303. Ruiz JR, Ortega FB, Tresaco B, Wärnberg J, Mesa JL, González-Gross M, et al. Serum lipids, body mass index and waist circumference during pubertal development in Spanish adolescents: The AVENA study. Horm Metab Res. 2006;38(12):832–7.

304. Donin AS, Nightingale CM, Owen C, Rudnicka AR, McNamara M, Prynne CJ, et al. Ethnic differences in blood lipids and dietary intake between UK children of black African, black Caribbean, South Asian, and white European origin: The Child Heart and Health Study in England (CHASE). Am J Clin Nutr. 2010;92(4):776–83.
305. Brion MA, Ness AR, Davey Smith G, Leary SD. Association between body composition and blood pressure in a contemporary cohort of 9-year-old children. J Hum Hypertens. 2007;21(4):283–90.
306. Daniels SR, Kimball TR, Khoury P, Witt S, Morrison JA. Correlates of the hemodynamic determinants of blood pressure. Hypertension. 1996;28(1):37–41.
307. Devonshire AL, Hager ER, Black MM, Diener-West M, Tilton N, Snitker S. Elevated blood pressure in adolescent girls: Correlation to body size and composition. BMC Public Health. 2016;16(1):1–7.
308. Syme C, Abrahamowicz M, Leonard GT, Perron M, Richer L, Veillette S, et al. Sex differences in blood pressure and its relationship to body composition and metabolism in adolescence. Arch Pediatr Adolesc Med. 2009;163(9):818–25.
309. Mueller WH, Chan W, Meininger JC. Utility of different body composition indicators: Demographic influences and associations with blood pressures and heart rates in adolescents (Heartfelt Study). Ann Hum Biol. 2003;30(6):714–27.
310. Naggara O, Raymond J, Guilbert F, Roy D, Weill A, Altman DG. Analysis by categorizing or dichotomizing continuous variables is inadvisable: An example from the natural history of unruptured aneurysms. Am J Neuroradiol. 2011;32(3):437–40.
311. Radley D, Cooke C, Fuller N, Oldroyd B, Truscott J, Coward W, et al. Validity of foot-to-foot bio-electrical impedance analysis body composition estimates in overweight and obese children. Int J Body Compos Res. 2009;7(1):15–20.
312. Flynn JT, Kaelber DC, Baker-Smith CM, Blowey D, Carroll AE, Daniels SR, et al. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. Pediatrics. 2017;140(3):e20171904.
313. He Q, Horlick M, Fedun B, Wang J, Pierson RN, Heshka S, et al. Trunk fat and blood pressure in children through puberty. Circulation. 2002;105(9):1093–8.
314. Korthuis RJ. Skeletal muscle circulation. In Colloquium Series on Integrated Systems Physiology: From Molecule to Function. Morgan & Claypool Life Sciences. 2011;3(4):1-144

315. Cheng S, Wiklund P. The effects of muscle mass and muscle quality on cardio-metabolic risk in peripubertal girls: A longitudinal study from childhood to early adulthood. Int J Obes. 2018 Oct 30;42:648.
316. Wittcopp C, Conroy R. Metabolic syndrome in children and adolescents. Pediatr Rev. 2016;37(5):193–202.
317. Burrows R, Correa-Burrows P, Reyes M, Blanco E, Albala C, Gahagan S. High cardiometabolic risk in healthy Chilean adolescents: Associations with anthropometric, biological and lifestyle factors. Public Health Nutr. 2015;19(3):486–93.
318. Rauch F, Schoenau E. The developing bone: Slave or master of its cells and molecules? Pediatr Res. 2001;50(3):309–14.
319. Rauch F, Bailey DA, Baxter-Jones A, Mirwald R, Faulkner R. The "muscle-bone unit" during the pubertal growth spurt. Bone. 2004;34(5):771–5.
320. Rizzoli R, Bianchi ML, Garabédian M, McKay HA, Moreno LA. Maximizing bone mineral mass gain during growth for the prevention of fractures in the adolescents and the elderly. Bone. 2010;46(2):294–305.
321. Fricke O, Schoenau E. The "Functional Muscle-Bone Unit": Probing the relevance of mechanical signals for bone development in children and adolescents. Growth Horm IGF Res. 2007;17(1):1–9.
322. Schoenau E. From mechanostat theory to development of the "Functional Muscle-Bone-Unit." J Musculoskelet Neuronal Interact. 2005;5(3):1–7.
323. Valdimarsson Ö, Kristinsson JÖ, Stefansson SÖ, Valdimarsson S, Sigurdsson G. Lean mass and physical activity as predictors of bone mineral density in 16-20-year old women. J Intern Med. 1999;245(5):489–96.
324. Wey HE, Binkley TL, Beare TM, Wey CL, Specker BL. Cross-sectional versus longitudinal associations of lean and fat mass with pQCT bone outcomes in children. J Clin Endocrinol Metab. 2011;96(1):106–14.
325. Kâ K, Rousseau M, Lambert M, O'Loughlin J, Henderson M, Tremblay A, et al. Association between lean and fat mass and indicators of bone health in prepubertal caucasian children. Horm Res Paediatr. 2013;80(3):154–62.

326. Chan DCC, Lee WTK, Lo DHS, Leung JCS, Kwok AWL, Leung PC. Relationship between grip strength and bone mineral density in healthy Hong Kong adolescents. Osteoporos Int. 2008;19(10):1485–95.
327. Tsuji S, Tsunoda N, Yata H, Katsukawa F, Onishi S, Yamazaki H. Relation between grip strength and radial bone mineral density in young athletes. Arch Phys Med Rehabil. 1995;76(3):234–8.
328. Kristinsson J, Valdimarsson O, Steingrimsdottir L, Sigurdsson G. Relation between calcium intake, grip strength and bone mineral density in the forearms of girls aged 13 and 15. J Intern Med. 1994;236(4):385–90.
329. Pate R, Oria M, Pillsbury L, editors. Fitness measures and health outcomes in youth. Washington: The National Academic Press; 2012.
330. Saint-Maurice PF, Laurson K, Welk GJ, Eisenmann J, Gracia-Marco L, Artero EG, et al. Grip strength cutpoints for youth based on a clinically relevant bone health outcome. Arch Osteoporos. 2018;13(1).
331. Black PMM, Walker PSP, Fernald LCH, Andersen CT, Digirolamo AM, Lu C, et al. Advancing early childhood development: From science to scale 1: Early childhood development coming of age: science through the life course. Lancet. 2017;389(10064):77–90.
332. Walker SP, Wachs TD, Grantham-Mcgregor S, Black MM, Nelson CA, Huffman SL, et al. Inequality in early childhood: Risk and protective factors for early child development. Lancet. 2011;378(9799):1325–38.
333. Wade M, Browne DT, Madigan S, Plamondon A, Jenkins JM. Normal birth weight variation and children's neuropsychological functioning: Links between language, executive functioning, and theory of mind. J Int Neuropsychol Soc. 2014;20(9):909–19.
334. Boulet SL, Schieve LA, Boyle CA. Birth weight and health and developmental outcomes in US children, 1997-2005. Matern Child Health J. 2011;15(7):836–44.
335. Andersen GS, Girma T, Wells JCK, Kastel P, Michaelsen KF, Friis H. Fat and fat-free mass at birth: Air displacement plethysmography measurements on 350 Ethiopian newborns. Pediatr Res. 2011;70(5):501–6.
336. Lee S, Bountziouka V, Lum S, Stocks J, Bonner R, Naik M, et al. Ethnic variability in body size, proportions and composition in children aged 5 to 11 years: Is ethnic-specific calibration of bioelectrical impedance required? PLoS One. 2014;9(12):1–17.

337. Ramel SE, Gray HL, Christiansen E, Boys C, Georgieff MK, Demerath EW. Greater early gains in fat-free mass, but not fat mass, are associated with improved neurodevelopment at 1 year corrected age for prematurity in very low birth weight preterm infants. J Pediatr. 2016;173:108–15.
338. Pfister KM, Gray HL, Miller NC, Demerath EW, Georgieff MK, Ramel SE. Exploratory study of the relationship of fat-free mass to speed of brain processing in preterm infants. Pediatr Res. 2013;74(5):576–83.
339. Abera M, Tesfaye M, Admassu B, Hanlon C, Ritz C, Wibaek R, et al. Body composition during early infancy and developmental progression from 1 to 5 years of age: The Infant Anthropometry and Body Composition (iABC) cohort study among Ethiopian children. Br J Nutr. 2018;119(11):1263–73.
340. Delezie J, Handschin C. Endocrine crosstalk between skeletal muscle and the brain. Front Neurol. 2018;9:698.
341. Kang S-Y, Lim GE, Kim YK, Kim HW, Lee K, Park T-J, et al. Association between sarcopenic obesity and metabolic syndrome in postmenopausal women: A cross-sectional study based on the Korean National Health and Nutritional Examination Surveys from 2008 to 2011. J Bone Metab. 2017;24(1):9–14.
342. Van Aller C, Lara J, Stephan BCM, Donini LM, Heymsfield S, Katzmarzyk PT, et al. Sarcopenic obesity and overall mortality: Results from the application of novel models of body composition phenotypes to the National Health and Nutrition Examination Survey 1999–2004. Clin Nutr. 2018; 38(1):264-70.
343. Siervo M, Prado CM, Mire E, Broyles S, Wells JC, Heymsfield S, et al. Body composition indices of a load-capacity model: Gender-and BMI-specific reference curves. Public Health Nutr. 2014;18(7):1245–54.
344. Burrows R, Correa-Burrows P, Reyes M, Blanco E, Albala C, Gahagan S. Low muscle mass is associated with cardiometabolic risk regardless of nutritional status in adolescents: A cross-sectional study in a Chilean birth cohort. Pediatr Diabetes. 2017;18:895–902.
345. Damanhoury S, Newton AS, Rashid M, Hartling L, Byrne JLS, Ball GDC. Defining metabolically healthy obesity in children: A scoping review. Obes Rev. 2018;(November):1476–91.

346. Fields DA, Goran MI, McCrory MA. Body-composition assessment via air-displacement plethysmography in adults and children: A review. Am J Clin Nutr. 2002;75(3):453–67.
347. Horan M, Gibney E, Molloy E, McAuliffe F. Methodologies to assess paediatric adiposity. Irish Journal of Medical Science. 2015.
348. Mazahery H, von Hurst PR, McKinlay CJD, Cormack BE, Conlon CA. Air displacement plethysmography (Pea Pod) in full-term and pre-term infants: A comprehensive review of accuracy, reproducibility, and practical challenges. Matern Heal Neonatol Perinatol. 2018;4(1):12.
349. Lohman TG. Applicability of body composition techniques and constants for children and youths. In: Pandolf KB, editor. Exercise and Sport Sciences Reviews. New York: Macmillan; 1986. p. 325–57.
350. Carvennec M Le, Fagour C, Adenis-lamarre E, Perlemoine C, Gin H, Rigalleau V. Body composition of obese subjects by air displacement plethysmography: The influence of hydration. Obesity. 2007;15(1):78–84.
351. Kyle UG, Earthman CP, Pichard C, Coss-Bu JA. Body composition during growth in children: Limitations and perspectives of bioelectrical impedance analysis. Eur J Clin Nutr. 2015;
352. 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(8):755–63.
353. Peterson CM, Su H, Thomas DM, Heo M, Golnabi AH, Pietrobelli A, et al. Tri-ponderal mass index vs body mass index in estimating body fat during adolescence. JAMA Pediatr. 2017;171(7):629–36.
354. Cole TJ. Weight/height$_p$ compared to weight/height^2 for assessing adiposity in childhood: Influence of age and bone age on p during puberty. Ann Hum Biol. 1986;13(5):433–51.
355. Lawrence AE, Adler BH, Minneci PC. Response to: Evaluation of sarcopenia in children. J Surg Res. 2018;2–3.
356. Shen W, Chen J, Kwak S, Punyanitya M, Heymsfield SB. Between-slice intervals in quantification of adipose tissue and muscle in children. Int J Pediatr Obes. 2011;6(2):149–56.
357. Heymsfield SB, Wang Z, Baumgartner RN, Ross R. Human body composition: Advances in models and methods. Annu Rev Nutr. 1997;17:527–58.

358. Lee SJ, Guerra N, Arslanian S. Skeletal muscle lipid content and insulin sensitivity in black versus white obese adolescents: Is there a race differential? J Clin Endocrinol Metab. 2010;95(5):2426–32.
359. Laddu DR, Farr JN, Lee VR, Blew RM, Stump C, Houtkooper L, et al. Muscle density predicts changes in bone density and strength: A prospective study in girls. J Musculoskelet Neuronal Interact. 2014;14(2):195–204.
360. Ng JM, Bertoldo A, Minhas DS, Helbling NL, Coen PM, Price JC, et al. Dynamic PET imaging reveals heterogeneity of skeletal muscle insulin resistance. J Clin Endocrinol Metab. 2014;99(1):102–6.
361. Johansson E, Lubberink M, Heurling K, Eriksson JW, Skrtic S, Ahlström H, et al. Whole-body imaging of tissue-specific insulin sensitivity and body composition by using an integrated PET/MR system: A feasibility study. Radiology. 2018;286(1):271–8.
362. Pillen S, Van Alfen N, Zwarts MJ. Muscle ultrasound: A grown-up technique for children with neuromuscular disorders. Muscle and Nerve. 2008;38(3):1213–4.
363. Pillen S. Skeletal muscle ultrasound. Eur J Transl Myol 2010; 2010;1(4):145–55.
364. Jacobs J, Jansen M, Janssen H, Raijmann W, Van Alfen N, Pillen S. Quantitative muscle ultrasound and muscle force in healthy children: A 4-year follow-up study. Muscle and Nerve. 2013;47(6):856–63.
365. Ong C, Lee JH, Leow MKS, Puthucheary ZA. Skeletal muscle ultrasonography in nutrition and functional outcome assessment of critically ill children: Experience and insights from pediatric disease and adult critical care studies. J Parenter Enter Nutr. 2017;41(7):1091–9.
366. Murphy AJ, Ellis KJ, Kurpad A V., Preston T, Slater C. Total body potassium revisited. Eur J Clin Nutr. 2014;68(2):153–4.
367. Moore FD, Boyden CM. Body Cell mass and limits of hydration of the fat-free body: Their relation to estimated skeletal weight. Ann N Y Acad Sci. 1963;110(1):62–71.
368. Pietrobelli A, Forminca C, Wang Z, Heymsfield SB. Dual-energy X-ray absorptiometry body composition model: Review of physical concepts. Am J Physiol Metab. 1996;271(6):941–51.
369. Goran MI. Measurement issues related to studies of childhood obesity: Assessment of body composition, body fat distribution, physical activity, and food intake. Pediatrics. 1998;101(Supplement 2):505–18.

370. Gately PJ, Radley D, Cooke CB, Carroll S, Oldroyd B, Truscott JG, et al. Comparison of body composition methods in overweight and obese children. J Appl Physiol. 2003;95(5):2039–46.
371. Fields DA, Allison DB. Air-displacement plethysmography pediatric option in 2–6 years old using the 4-compartment model as a criterion method. Obes (Silver Spring). 2012;20(8):1732–7.
372. Zemel BS. Quantitative computed tomography and computed tomography in children. Curr Osteoporos Rep. 2011;9:284–90.
373. Cejas CP, Serra MM, Galvez DFG, Cavassa EA, Taratuto AL, Vazquez GA, et al. Muscle MRI in pediatrics: Clinical, pathological and genetic correlation. Pediatr Radiol. 2017;47:724–35.
374. Pillen S, Verrips A, van Alfen N, Arts I, Sie L, Zwarts M. Quantitative skeletal muscle ultrasound: Diagnostic value in childhood neuromuscular disease. Neuromuscul Disord. 2007;17:509–16.
375. Scholten RR, Pillen S, Verrips A, Zwarts MJ. Quantitative ultrasonography of skeletal muscle in children: Normal values. Muscle Nerve. 2003;27(June):693–8.

Chapter 3 Assessment of Body Composition in Pediatric Overweight and Obesity: A Systematic Review of The Reliability and Validity of Common Techniques

3.1 Preface

This chapter evaluates the existing literature on reliability and validity of body composition techniques used in pediatric overweight and obesity studies. A version of Chapter 3 has been published in Obesity Reviews (Orsso CE, Silva MIB, Gonzalez MC, Rubin DA, Heymsfield SB, Prado CM, Haqq AM. 2020; *In press*). I was responsible for concept formation, literature search, critical analysis, and draft of the initial version. MIB Silva acted as a second reviewer and equally contributed to the literature search and critical analysis. All authors have contributed to interpretation and approved the final manuscript.

3.2 Introduction

The prevalence of overweight and obesity during childhood and adolescence continues to rise in many countries (1). Excess body adiposity impairs not only functional mobility and mental health, but also metabolic function, increasing the risk of cardiovascular diseases (2). Given these detrimental effects, there is an international call to develop preventive and management strategies for pediatric overweight and obesity (3). Accurate diagnosis and monitoring of excess adiposity are, however, the first step to address these conditions.

Research on the topic often describes adiposity and evaluates intervention effectiveness by measuring body weight and its changes using absolute values or adjusted for height, age, and sex (i.e. body mass index z-score [BMI-z]) (4). Due to their availability and feasibility, these approaches have been widely used as surrogate measures of adiposity. However, as BMI-z has inherent low specificity (5), measuring body composition is preferred. Accurate assessments of fat mass (FM), fat-free mass (FFM), and percent body fat (%BF) may increase the ability to detect the effects of excess adiposity as well as the effectiveness of interventions to reduce obesity outcomes.

Several field and laboratory methods are currently available for body composition assessment. Simple and accessible anthropometric measures (i.e. weight, height, circumferences, and skinfolds) can be used as a surrogate to assess body composition through predictive equations. Another popular field method to assess body composition is bioelectrical impedance analysis (BIA), which estimates FM and FFM using device- and population-specific equations (6). Ultrasound (US) is also considered a field technique that has gained attention in recent years. More sophisticated approaches are used in research settings, including air-displacement plethysmography (ADP), dual-energy X-ray absorptiometry (DXA), magnetic resonance imaging (MRI), and multicompartment (i.e. three-compartment [3-C] and four-compartment [4-C]) models. Both field and laboratory methods are considered indirect, requiring that one or more of their underlying assumptions be met to reduce errors in the prediction of body composition (7). Therefore, assessing body composition in children and adolescents with overweight and obesity is challenging, as conditions such as hydration and body shape may camouflage the methods' underlying assumptions (8).

When choosing a method to measure body composition, reliability and validity must also be examined. A method is considered reliable if it has high repeatability and reproducibility, or

the variability between measures obtained by the same observers or between observers, respectively, is minimal (7). Validity refers to the extent that an index test agrees with a reference standard, which is defined as more established method. In body composition validation studies, the 4-C model is considered a reference standard technique as it does not assume a constant hydration status, reducing its effects on FM and FFM estimation (9). To our knowledge, there are no reviews discussing the reliability and validity of techniques used to assess body composition in children with overweight and obesity. Therefore, our aim was to summarize the reliability and validity of common techniques used for body composition assessment in this population, guiding technique selection for research and clinical practice implementation.

3.3 Methods

We conducted this systematic review following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline.

3.3.1 Eligibility Criteria

Eligible studies evaluated the reliability or validity of techniques used to assess body composition in children and adolescents (aged <18 years) with overweight or obesity. Studies employing anthropometric measures as index tests were included only if raw data were imputed into equations to estimate body composition. Validity studies were only included if they compared an index test with multicompartment (i.e. 3-C or 4-C) models, DXA, isotope dilution, underwater weighing, or MRI for agreement and/or diagnostic tests analysis. All studies reporting reliability and/or validity findings were eligible regardless of the statistical method used. We excluded studies if they met the following criteria: (1) data from adults and children were combined; (2) included solely infants or children of normal-weight; (3) combined data from children of normal-weight and children with overweight or obesity; (4) included children with acute clinical conditions or immunosuppressive therapy; (5) only evaluated the ability of body composition to predict clinical outcomes; (6) used BIA, ADP, or skinfolds as reference standard techniques.

3.3.2 Search Strategy

A comprehensive search of electronic databases including CINAHL, Embase, MEDLINE (Ovid), and SPORTDiscuss was conducted from inception to December 2019. Key words related to the following concepts were combined to design the search strategy: body composition, pediatric population, overweight and obesity, validity and reliability (**Table A1**). The search was

limited to the pediatric population (<18 years old) and articles published in English language. Retrieved articles were screened for eligibility using Covidence online software (Vertitas Health Innovation Ltd). Two reviewers (CEO, MIBS) independently assessed titles and abstracts, and then full text, for inclusion; discrepancies were resolved through discussion. Additionally, reference lists were scanned to identify missing studies.

3.3.3 Data Extraction

One reviewer (CEO) extracted data from included studies using a standardized form, and a second reviewer (MIBS) checked data for accuracy. Extracted data included demographic and sample characteristics, study design and settings, methodological characteristics of index tests and reference standards, reliability measures (i.e. intra- and inter-rater reliability), and validity measures (i.e. systematic effect, agreement, sensitivity, and specificity). The Plot Digitizer, an open source software (v.2.6.8; http://plotdigitizer.sourceforge.net), was used for conversion of plots into numerical values for data that was not available from full text (10).

3.3.4 Quality Assessment

Risk of bias was independently assessed by two reviewers (CEO, MIBS) using the revised Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool (11). The QUADAS-2 consists of signaling questions organized into four domains: (1) patient selection; (2) index tests; (3) reference standard; and (4) flow and timing. The risk of bias and study applicability were rated as “low risk”, “high risk”, or “unclear risk”. If two or more index tests were made available, the risk of bias was completed for each test. The QUADAS-2 assessment was summarized using a graphic format. Disagreements were resolved by consensus.

3.4 Results

3.4.1 Study Selection and Characteristics

The search identified 3,066 studies of which 66, published between 1992 and 2019, were included (**Figure A1; Appendix A**). Study sample sizes ranged from 10 to 3507 participants, with a mean age range of 7.0 to 16.5 years (**Table A2**). The racial/ethnic makeup of participants varied across studies, with 51.5% focused on Caucasians or children and adolescents from European countries. Most studies (62.1%) did not report sexual maturity of included participants; when available, sexual maturity also varied across studies and only 24.2% of studies evaluated agreement within each pubertal stage. Almost 58% of studies included children and adolescents

with obesity exclusively; 27.3% studies combined children and adolescents with overweight and obesity; only 9.1% reported results according to weight status (i.e. overweight and obesity).

Of the included studies, 19.7% reported reliability, 80.3% evaluated the validity of body composition techniques cross-sectionally, 13.6% of studies assessed the agreement between body composition techniques to estimate changes over time, and 10.6% evaluated the diagnostic test accuracy (**Table 3.1**). Several statistical methods available for reliability and validity analyses were employed by the selected studies. Common approaches to test reliability included: intraclass correlation coefficient (ICC), coefficient of variation (CV), coefficient of repeatability, and test-retest correlation coefficient. Regarding agreement analysis, most studies used results from Bland-Altman plots and/or linear correlation coefficients (i.e. Pearson and Spearman) and a few reported regression, standard error of estimate (SEE), concordance correlation coefficient, and paired t-test. Bias of included studies are summarized in the main text and readers are referred to tables in the Supporting Information for detailed information on the limits of agreement (LoA). For diagnostic test accuracy, the specificity and sensitivity of an index test to identify abnormalities in body composition compared to a reference standard was a common approach, but the Cohen's Kappa was also used.

Findings are hereby organized by reliability and validity (i.e. agreement and diagnostic test accuracy) stratified by type of index test (i.e. field and laboratory) for cross-sectional evaluations. Additionally, we compared the agreement between multiple index tests validated in the pediatric overweight and obesity population using either multicompartment (i.e. 3-C or 4-C) models or DXA as reference standards. Lastly, we reported the validity of techniques when monitoring body composition changes over time.

3.4.2 Study Quality

Risk of bias and study applicability are summarized in **Figure 3.1** and provided in detail in **Table A3**. Most studies had low risk of bias for patient selection, index test, and reference standard domains. Of those studies reporting BIA findings, risk of bias in the index test domain was unclear for 59.4% of studies as they did not provide an adequate test description, challenging the assessment of flaws in pre-test procedures or test administration (e.g. controlling participants' hydration status, timing of measurement, and body position) (7). Furthermore, the flow and timing domain presented with unclear risk of bias for most studies, except for US and

3-C model (66.7% and 100% high risk of bias, respectively) because these studies failed to employ a reference standard (or the same reference standard) in all participants.

Concerns about applicability were rated as "low" for all included studies with regards to the patient selection domain. On the other hand, most studies had applicability concerns rated as "high" for the index test (i.e. studies evaluating anthropometric, skinfolds, BIA, ADP, and 3-C model studies as the index test) and reference standard (i.e. studies using DXA, isotope dilution, and 3-C models as the reference standard) domains. These studies used predictive equations, either as an index test or reference standard, that were not developed or previously validated in children and adolescents with overweight and obesity. Moreover, risk of bias or applicability concerns were considered not applicable if studies reported only findings on reliability or employed a reference standard that did not require predictive equations to assess body composition, respectively.

3.4.3 Reliability and Validity of Field Body Composition Methods

3.4.3.1 Anthropometrics

Reliability

The reliability of anthropometric equations to predict body composition in pediatric populations with overweight and obesity were not evaluated in the included studies.

Validity - Agreement

Small, non-significant bias with wide LoA was reported for sex-specific equations based on age and BMI to predict %BF and FM index (FM/height squared, kg/m^2) compared to DXA (bias = -0.04% and 0.06%, respectively; $p > 0.5$) (12) (**Table A4**). However, poor agreement was reported in one study using hip or waist circumference (WC) indices to predict %BF (bias = -3.48% and -7.17%, respectively) (13). Two studies also evaluated the ability of anthropometric equations using WC to estimate abdominal adiposity (13, 14). Agreement between estimated and measured visceral adipose tissue (VAT; by MRI) was greater among girls as they presented with smaller bias (4.8 cm^2) than boys (-50.7 cm^2), and high correlation coefficients were found for both sexes (r range = -0.799 to -0.827) (14). Interestingly, sex-specific equations proposed by Thivel et al. for visceral adiposity accounted for metabolic markers in addition to anthropometric measures and a high ICC between estimated and measured visceral adiposity by DXA was reported (13). Furthermore, estimated upper arm adipose tissue (AT) area was underestimated by

anthropometric equations (based on arm circumference) compared to MRI measurements (bias= -2.1 to -10.3 cm^2) (15).

Validity - Diagnostic Test Accuracy

Bray et al. reported a high specificity (96%), but low sensitivity (47%), of sex- and ethnicity-specific equations based on height and weight measures for detecting high %BF (based on a 4-C model) (16). The ability of an age-specific index using height and WC (termed pediatric relative FM index) to identify children with %BF ≥85^{th} percentile measured by DXA (17) was tested by Woolcott & Bergman. The authors found a false negative rate of 26.7% and 21.8%, and a false positive rate of 5.0% and 3.7% for girls and boys, respectively.

3.4.3.2 Skinfolds

Reliability

The reliability of measuring the thickness of the bicipital, tricipital, subscapular, and iliac-crest skinfolds was investigated by trained observers in 8 adolescents with obesity (18). The mean intra- and inter-rater ICC for skinfold measures were 0.975 and 0.962, respectively. Another study reported a mean CV of 0.7% for skinfold measures taken in triplicate at six different sites (i.e. triceps, subscapular, iliac crest, abdominal, anterior thigh, and medial calf) in 38 children (19). Although a detailed description of intra- and inter-rater CV was provided for each measurement site, reliability of findings by weight status was not provided (including normal weight in the analysis) (20).

Validity – Agreement

Skinfold equations used by included studies are described in **Table A5**. Two studies compared skinfolds estimates of body adiposity with a 3-C model (21, 22) (**Table A6**). Despite wide LoA, the smallest bias for %BF in females was found using the Huang equation (bias = -0.04%) followed by Ramirez and Slaughter equations (bias = -4.67% and -12.69%, respectively) (21). However, the Huang equation presented the weakest correlation with a 3-C model (r^2 = 0.34; r^2 range = 0.34 to 0.68) and the greatest SEE (SEE = 0.09; SEE range = 0.06 to 0.09). In boys, the smallest bias was found for the Ramirez equation (bias= -2.51%) followed by the Huang and Slaughter equations (bias = -2.89% and -8.97%, respectively). Strong correlations were reported for all equations in boys (r^2 = 0.65 to 0.70) and SEE values ranged from 0.05 to 0.07 (21). In another study, Bamman et al. evaluated the agreement between a predictive equation developed by their group and reported a bias of -0.10 kg for FM (22).

Eight studies investigated the agreement between skinfolds and DXA (18, 19, 23-28), with most using the Slaughter equation to estimate adiposity (n = 6) (18, 19, 23-25, 27). Percent body fat was overestimated by the Slaughter equation in two studies (23, 27) (bias range = 0.49% to 8.09%), but underestimated in other two (18, 25) (bias range = -4.1% to -11.1%). Watts et al. reported moderate, positive correlations between %BF by the Slaughter equation and by DXA as well as using the 3- or 4-sites equations ($r = 0.51$ to 0.61; $P < 0.01$) (19). Furthermore, Chan et al. compared the agreement for %BF estimates using distinct equations in Chinese children and adolescents (23). The smallest bias was obtained using an equation developed by the authors, followed by Durin & Rahaman and Lohman equations (23). Using the National Health and Nutrition Examination Survey (NHANES) database, Stevens et al. cross-validated a new equation that includes the triceps skinfolds to estimate %BF; this equation slightly underestimated %BF in children, independently of obesity status and sex (28).

Two studies assessed the agreement of skinfold equations to imaging techniques (29, 30). Asayama et al. computed body density using a specific equation for Japanese children and the Brozek equation to determine %BF (29). The authors then examined the correlation between %BF by skinfolds and abdominal fat measures (i.e. total AT, VAT, and subcutaneous AT [SAT]) obtained through a single CT scan at the umbilicus level; moderate to strong correlations were reported (r range = 0.524 to 0.708). Furthermore, Ball et al. evaluated the agreement between a new predictive equation for VAT and SAT using skinfold measures and MRI (1.5 T Signa LX) (30). T1- weighted single-slice images were taken at the umbilicus level and a manual segmentation approach was used for identification of VAT and SAT. Bias for VAT was greater than for SAT (bias = -3.0 cm^2 and -1.0 cm^2; respectively; $p \geq 0.2$) and systematic error ranged from 0.05% to 0.12%.

Validity - Diagnostic Test Accuracy

Compared to a 4-C model, the Slaughter and Pennington equations had high specificity (98% and 94%, respectively) but low sensitivity (71% and 82%, respectively) to accurately classify African American and White adolescents into a group above or below the median %BF (16). Likewise, the Slaughter equation also had a high specificity (93.3%) and low sensitivity (78.5%) when classifying boys with %BF greater than 25% and girls greater than 30% (20).

3.4.3.3 Bioelectrical Impedance Analysis

Reliability

Kasvis et al. explored the intra-rater reliability of a single-frequency, foot-to-foot (or lower body) BIA (Tanita TBF-310; Tanita Corp., Tokyo, Japan) in three children with overweight or obesity (31). Coefficients of variation for triplicate measures were 0.47% for FFM (kg), 0.93% for FM (kg), and 0.64% for %BF. Using a multifrequency, hand-to-foot (or whole body) BIA (Human IM Plus II; DS Medica, Milan, Italy), the CV for repeated same-day measures in ten adolescents with obesity was 2.2% (32). Another study evaluated the intra-rater reliability of raw values from a multifrequency, hand-to-foot BIA (ImpediMed SFB7; Impedimed Inc., Sydney, Australia) (33). Triplicate measurements were taken from all participants with obesity (derivation cohort: n = 27; validation cohort: n = 65); the ICC for electrical resistance was 0.99 and for electrical reactance was 0.98. The between day variability of another multifrequency, hand-to-foot BIA device (Tanita MC-780; Tanita Corp., Tokyo, Japan) was evaluated for three consecutive days in 32 adolescents with obesity and the ICC was high for %BF, FM, and FFM (all ICC = 0.99) (34).

Validity – Agreement

Five studies assessed the agreement between a multifrequency, hand-to-foot Tanita BC-418 BIA device (Tanita Corp., Tokyo, Japan) and a reference standard using Bland-Altman analysis. Results are summarized in **Table A7**. The use of manufacturer's equations underestimated %BF compared to DXA (bias = -5.3%) (35), 3-C model (bias range = -7.09% to -4.7%) (21), and 4-C model (bias range = -6.5% to -0.6%) (36). Furthermore, FM was underestimated by -2.4 kg compared to DXA (35) and -3.5 kg (37) compared to a 3-C model. Interestingly, the use of the Ramirez equation overestimated %BF in boys by 3.58% and in girls by 0.86% compared to a 3-C model (21). Only one study investigated the bias for FFM against a 3-C model, and found that the manufacturers' equation overestimated FFM by 2.3 kg (37). Using authors standard scores, Atherton et al. found an improved performance of BIA against a 4-C model compared to other equations; it underestimated %BF only by 0.25% (38). Regression analysis showed a strong association between manufacturer's equation to estimate %BF and 3-C model in boys (r = 0.80) and girls (r = 0.78) (21), and compared to a 4-C model in girls only (r = 0.63 to 0.78) (36); boys presented with a weak association (r = 0.34 to 0.43) (36). The Ramirez equation did not improve the association between %BF by BIA and 3-C model (r = 0.72 to 0.73) (21). As device-specificity is important when interpreting body composition results, please refer to **Table A7** for a detailed description of validity findings on other Tanita devices.

The agreement between multifrequency, hand-to foot RJL devices and a reference standard was evaluated in four studies (39-42). Most of them compared the BIA device (using the manufacturer's equations or several other validated equations to estimate body composition) with DXA (39-41). The best performing equations were the Bray, Kushner, and Lewy equations (bias range = -0.4 to 0.5), although LoA were wide (lower LoA = -8.0 to -6.9 kg; upper LoA = 6.6 to 8.0 kg). One study evaluated the RJL 101A (RJL Systems Inc., Detroit, USA) device against the underwater weighing techniques, and found a bias of 0.93 kg for FFM assessment using the Houtkooper equation (42).

Two studies used a single-frequency, hand-to-foot BodyStat1500 device (BodyStat Ltd., Douglas, Isle of Man, British Isles) to assess body composition (43, 44). For %BF evaluation, the Schaffer had the smallest bias and LoA and the difference between BIA and DXA was not significant ($p = 0.121$ using paired t-test) (44). For FM and FFM assessments, the Houtkooper equation presented the strongest correlation with DXA, but paired analysis showed statistically difference for all the equations. Compared to the deuterium dilution method, the Bodystat 1500 overestimated total body water (TBW) by 5.6 L using the Kushner equation, affecting the evaluation of FM and FFM; FM was underestimated by 5.8 kg using the manufacturer's equation and FFM overestimated by 5.9 kg using the Houtkooper equation (43).

Several other less commonly used BIA devices were tested against DXA, ADP or isotope dilution to evaluate the agreement between techniques for body composition assessment in pediatric overweight and obesity (**Table A7**) (27, 32, 33, 39, 45-48). Interestingly, one study evaluated the agreement between a single frequency, hand-to-foot Muscle-α BIA device (Art Haven 9 Co, Kyoto, Japan) device and DXA for measurement of segmental FFM in Japanese children with overweight using predictive equation developed by the authors; there were small bias for FFM of arms, trunk and leg (bias range = -0.3 to 0.26) and narrow LoA (lower LoA = -3.52 to -0.26 kg; upper LoA = 0.78 to 3.21 kg) (48). Furthermore, there was a strong correlation range between index test and reference standard ($r^2 = 0.89$ to 0.94) and small SEE (0.25 to 1.71 kg).

Validity – Diagnostic Test Accuracy

The ability of a multifrequency, hand-to-foot BIA (Tanita BC-418) to classify children with overweight as having abnormal FM or FFM based on ± 2SD of a 4-C model reference data was evaluated by Atherton et al (38). In their study, FFM was calculated as squared height

divided by impedance at 50 kHz (also known as impedance index). A moderate agreement was observed for FM (Kappa = 0.470 [0.342-0.590]; percentage agreement = 76.2%), and a good agreement for FFM (Kappa = 0.762 [0.667-0.857]; 88.2% agreement). Using a similar device (Tanita BC-418), Luque et al. compared the accuracy between a regression equation developed by authors and manufacturer's predictive equations to correctly classify children above the 90.8th percentile of FM index as measured by DXA (49). The regression equation had a greater sensitivity (100%), but similar specificity (95.9%) than BIA output (84.6% and 95.9%, respectively). Furthermore, the ability of these equations to classify children with excess trunk FM were improved compared to the assessment of whole-body FM by a Tanita BC-418 device (regression equation: sensitivity = 88.2%, specificity = 98.7%; manufacturer's equation: sensitivity = 76.5%, specificit y= 97.4%) (50). The diagnostic test accuracy of a single-frequency, foot-to-foot BIA device that is specific for body composition assessment in children (Tanita BF-689; Tanita Corp., Tokyo, Japan) was evaluated by Butcher et al (51). In this study, the sex- and age-specific cut-offs proposed by McCarthy et al were used to classify %BF status (i.e."underfat", "overfat", and obesity) (52). Compared to %BF estimates from DXA, the BIA device had greater sensitivity to identify children and adolescents with obesity (50%) than those with "overfat" (28%); the specificity was also higher for children and adolescents with obesity compared to "overfat" (100% vs. 92%, respectively). This device was further explored by Kabiri et al, who also found a greater sensitivity and specificity for assessment of obesity (43% and 100%) than "overfat" (22% and 78%, respectively) (53).

Another study compared the specificity and sensitivity of several predictive equations using a multifrequency, hand-to-foot BIA (Xitron Technologies, San Diego, USA) to identify excess FM obtained by a 4-C model (16). Although specificity was high for the Goran and Suprasongsin equations (100%), sensitivity was low (45% and 11%, respectively). The best overall performing equations were the Schaefer (specificity = 89%, sensitivity = 84%) followed by the Pennington equation (specificity = 87%, sensitivity = 84%). Additionally, the Deurenberg equation had the highest sensitivity (93%) but a specificity of 65% (16).

3.4.3.4 Ultrasound

Reliability

Experienced radiologists used a B-mode US device (Philips ATL HDI 5000) with a 3.5 MHz transducer to assess the reliability of repeated VAT thickness measures taken above the

umbilicus with a one-week interval in 19 children with obesity (54). The intra-rater CV and ICC for VAT thickness were 1.9% and 0.73, respectively. The inter-rater values for CV and ICC were 2.8% and 0.80, respectively. Pineau et al. evaluated SAT using an A-mode US (TEA Company) coupled with a 2.25 MHz transducer at the umbilical and midthigh levels in 94 children and adolescents with obesity (18). In a subsample of the study (n = 8), the authors calculated the intra- and inter-rater ICC values as 0.966 and 0.979, respectively.

The reliability of assessing skeletal muscle thickness and cross-sectional area was also evaluated in seven girls with obesity (55). In this study, a B-mode US device (Echo Blaster 128 CEXT-1Z) with a 5-10 MHz linear transducer was employed and images were taken at two distinct locations: 66% of the tight length for knee flexors (i.e. rectus femoris, vastus lateralis, vastus medialis) and 33% of the leg length for plantar flexors (i.e. gastrocnemius lateralis and gastrocnemius medialis). The best intra-rater reliability was found for the rectus femoris (thickness ICC and CV = 0.974 and 2.70%; cross-sectional area ICC and CV = 0.988 and 3.94%; respectively) and gastrocnemius lateralis (thickness ICC and CV = 0.973 and 2.84%; cross-sectional area ICC and CV = 0.981 and 2.68%; respectively).

Validity – Agreement

Compared to DXA, US measures imputed into multiple regression analysis overestimated %BF in females by 0.11% and underestimated %BF by 0.42% in males (18) (**Table A8**). Correlations were moderate to strong in males ($r^2 = 0.94$; SEE = 2.3) and females ($r^2 = 0.61$; SEE = 2.7). Authors also evaluated the agreement between US measurements of VAT thickness and volume of VAT using MRI images captured at the level of the third lumbar vertebrae. Only Spearman correlation coefficients were reported, but no significant correlations were found for males nor females.

Validity – Diagnostic Test Accuracy

We did not identify any studies evaluating the accuracy of US to distinguish between body composition phenotypes.

3.4.4 Reliability and Validity of Laboratory Body Composition Methods

3.4.4.1 Air-displacement Plethysmography

Reliability

Precision of body volume and %BF obtained from duplicated measurements of children and adolescents with overweight or obesity on the same day was 0.241% (56) and 4.0% (57), respectively.

Validity – Agreement

Three studies evaluated the agreement between body adiposity assessed by ADP and a 4-C model (36, 56, 57) (**Table A9**); the reported bias ranged from -0.4% to 3.17% for %BF and -1.33 kg to 0.45 kg for FM. One study compared the accuracy of two different ADP equations to predict %BF and found that, as expected, the Siri equation overestimated %BF to a greater extent than the age and sex-specific Lohman equation with a greater total error (TE; TE_{Siri} range = 2.33 to 2.74; TE_{Lohman} range = 1.56 to 2.11) and no significant differences for the Lohman equation (57). Furthermore, %BF by ADP and 4-C model were strongly and positively correlated (r range = 0.82 to 0.97) (36, 57). Only one study reported the SEE with values ranging from 0.03 to 0.23, according to pubertal stages and sex (36).

Although three other studies evaluated the validity of ADP against DXA (GE Lunar Prodigy and GE Lunar DPX-IQ) (32, 58, 59), only one used the Bland-Altman analysis to assess agreement between techniques (32). The authors reported a greater negative bias using the Lohman equation to predict %BF (bias = -3.80; LoA= -10.27% to 2.67%) compared to the Siri equation (bias = -2.11; LoA = -8.82% to 4.61%). Furthermore, there was a greater association between ADP and DXA when using the Siri equation (Pitman's test: $r = 0.401$, $p = 0.002$) compared to the Lohman equation (Pitman's test; $r = 0.315$, $p = 0.001$) (32). Another study using the Siri equation reported a moderate and positive correlation for both %BF and FM ($r = 0.75$, $p \leq 0.05$; $r = 0.92$, $p \leq 0.05$; respectively) (59). Additionally, the ICC for %BF by ADP against DXA was 0.37 and ADP against underwater weighing was 0.19 (58).

Body composition by ADP is estimated from body density, which can be calculated using either predicted or measured thoracic gas volume (TGV). To evaluate whether predicted and measured TGV yield similar values, Radley et al. used two different TGV predictive equations (i.e. Crapo and Fields) and found smaller bias for the Fields' equation (bias range = 0.11 L to 0.53 L) compared to the Crapo equation (bias range = 0.32 L to 0.75 L) (60). Consequently, %BF calculated using the Fields' equation was overestimated to a smaller extent (bias range = 0.4% to 1.1%) compared to %BF by Crapo (bias range = 1.1% to 1.8%) (60).

Validity – Diagnostic Test Accuracy

There were no studies investigating the ability of ADP to accurately classify children and adolescents into abnormal categories of body composition.

3.4.4.2 Dual-energy X-ray Absorptiometry

Reliability

The reliability of three repeated scans using a Hologic Discovery A DXA system was evaluated by Kasvis et al. in three children with overweight or obesity; authors reported a CV of 0.96%, 1.06%, and 0.41% for %BF, FM, and FFM, respectively (31). Similar findings were obtained in a larger study, where the reliability of same-day repeated scans by a Hologic QDR 4500A system was assessed in 32 children with obesity (61). The CV for FM, lean mass (defined as FFM minus bone), and bone mass were 1.29%, 0.94%, and 1.05% respectively.

The intra- and inter-rater reliability of assessing FM at six different abdominal regions were explored using a Lunar Prodigy DXA system in sixteen adolescents with overweight and obesity (62). The regions with the least intra-rater variation were the android (CV assessor 1 = 1.77%; CV assessor 2 = 1.32), trunk (CV assessor 1 = 1.69%; CV assessor 2 = 1.71%), and the top of iliac crest (CV assessor 1 = 1.51%; CV assessor 2 = 1.46). Inter-rater analysis revealed that the android region had the smallest coefficient of repeatability, followed by the region between the top of lumbar vertebrae 2 and bottom of lumbar vertebrae 4, and region between the top of lumbar vertebrae 1 to bottom of lumbar vertebrae 4 (62).

Validity – Agreement

Compared to a 4-C model, DXA slightly overestimated FM in two studies with bias ranging from 0.46 kg to 0.96 kg (8, 63) (**Table A10**). Percent body fat by DXA was greater than %BF by a 4-C model in three studies (bias range: 1.0% to 2.2%) (8, 36, 57). One study also evaluated the accuracy of FM adjusted for age and sex and found an insignificant bias and small LoA (-0.4 kg to 0.4 kg) (38). Total error was calculated in one study and varied from 2.52% in males to 3.05% in females (57). Although associations between the index test and reference standard were explored, different correlation coefficients were used challenging these studies to be conflated. For example, two studies performed a Pearson correlation test and reported a strong correlation for %BF ($r \geq 0.89$), independent of sex or pubertal stage (36, 57). Three studies used the Bland-Altman correlation test to evaluate the association between bias and mean values of FM (8, 38, 63). Bias FM was positively and weakly correlated with mean values in females ($r = 0.30$; $p = 0.003$) but not in males ($r = -0.19$; $p = 0.16$) (63). In contrast, two other studies reported

negative correlations: bias %BF was moderately correlated with mean values only in females (r^2 = -0.52; p <0.01) (8); bias FM adjusted for age and sex was weakly correlated with mean values when both sexes were combined (r = -0.15; p <0.001) (38). Two studies also evaluated the SEE for %BF and found a small SEE in both males (SEE range = 0.06 to 1.97) and females (SEE range = 0.07 to 2.14) (36, 57).

Fat-free mass was underestimated in two studies compared to a 4-C model, with bias ranging from -1.20 kg to -0.67 kg (8, 63). After adjusting for age and sex, FFM was slightly overestimated (bias = 0.07) and bias FFM was positively correlated to mean values (r = 0.18; p <0.001) (38). Furthermore, bias FFM was negatively correlated with mean FFM only in females (r = -0.43; p <0.0001) (63).

Validity – Diagnostic Test Accuracy

The sensitivity and specificity of DXA (Hologic QDR-2000, software v. 5.64) to accurately identify children as having high %BF compared to a 4-C model were 82% and 98%, respectively (16). DXA showed a high agreement with 4-C model to identify excess FM (95.1%; Cohen's kappa = 0.900) or FFM (91.4%; Cohen's kappa = 0.831), defined as +2SD in children and adolescents with overweight (38). Furthermore, another study compared the ability of two different DXA software versions (Discovery QDR-4000A, v.11.2. versus v.12.1) to classify children and adolescents with obesity as those having %BF >36% (64). In males, the updated version (v.12.1) classified 19.1% of the study sample as having obesity and the older version classified only 14.3%. In girls, 14.6% and 8.5% of the study sample were identified to have obesity by the updated and older versions, respectively (64).

3.4.4.3 Isotope Dilution

Reliability

None of the included studies evaluated the reliability of isotope dilution in assessing body composition specifically in children and adolescents with overweight or obesity.

Validity - Agreement

Vasquez et al. reported that isotope dilution underestimated %BF in boys (bias = -0.941% to -0.155%) but overestimated %BF in girls (bias = 0.861% to 2.684%) (36), compared to a 4-C model. Percent body fat evaluated by isotope dilution was moderately to strongly correlated to 4-C model (r = 0.689 to 0.959), independent of sex (**Table A11**). The authors also evaluated SEE,

which ranged from 0.02 to 0.22. Furthermore, girls at Tanner Stages 1 and 2 had greater bias, lower correlation coefficient, and greater SEE compared to other groups (36).

Gately et al. evaluated the agreement between isotope dilution and 4-C model using two different equations (57). One of the equations considered water as being stable at 73% of body weight, with %BF bias values of -2.7% and -1.6% in females and males, respectively. Another equation proposed by Lohman included age- and sex-specific water contents, resulting in a smaller bias (bias = -0.6% to -0.1%). Interestingly, correlations were statistically significant only for the equation considering TBW as 73% of body weight, but not for the Lohman equation. On the other hand, the Lohman equation produced the lowest TE compared to the first equation (TE range = 1.84% to 2.00%; TE = 2.55% to 3.27%; respectively) (57).

Validity – Diagnostic Test Accuracy

One study investigated the ability of the isotope dilution technique (Pennington equation) to identify children and adolescents as having %BF greater than the median of the study group (16). The specificity and sensitivity were 94% and 93%, respectively.

3.4.4.4 Three-compartment Model

Reliability

The reliability of 3-C models to assess body composition was not investigated by any of the included studies.

Validity – Agreement

Haroun et al. evaluated the agreement between 3-C and 4-C models for the assessment of %BF, FM, FFM, hydration of FFM (%) and density of FFM (kg/m^2) in children with obesity (65). All body compartments presented with small bias (bias range = -0.5 to 1.0) and narrow LoA (lower LoA = -1.284 to -0.284; upper LoA = 0.007 to 1.484) (65).

Validity – Diagnostic Test Accuracy

The diagnostic test accuracy of a 3-C model was assessed by Bray et al. (16); authors found a high specificity (100%) and sensitivity (84%) of the model to identify children having high %BF, defined as greater than the median of the study group measured by a 4-C model (16).

3.4.4.5 Magnetic Resonance Imaging

Reliability

Using a semi-automatic segmentation technique, single slices of 10 mm at the umbilicus level were reanalyzed twice in a subsample of 18 children with overweight or obesity (30).

Correlations between trials were strong for both VAT ($r = 0.98$, $p < 0.001$) and SAT ($r = 0.99$, $p < 0.001$) and no differences were noted using paired t-test (VAT: $p = 0.5$; SAT: $p = 0.2$). Furthermore, the reliability of assessing VAT by a different semi-automatic approach in 5-slices at the third lumbar vertebrae level using MRI was evaluated in another study using a subsample of 30 children and adolescents with obesity (54). Both intra- and inter-rater CV were <0.01%, with an inter-rater ICC of 0.94 and 0.97 for single and multiple measurements, respectively (54).

Validity – Agreement

Hui et al. employed a 3.0 T MRI scanner to acquire images at three distinct abdominal sections, ranging from the dome of diaphragm (section 1) to the pubic symphysis (section 3) in adolescents with obesity (66) (**Table A12**). The segmentation method proposed by the authors consisted of several steps, including image correction, tissue masking, and tissue subtraction. The segmentation approach considered the reference standard used the seven-peak spectral model of fat and monoexponential T2 for fitting. Bland-Altman analysis of abdominal AT demonstrated the smallest bias for total AT (64.19 cm^3), compared to VAT (-143.58 cm^3) and SAT (173.58 cm^3). Correlation coefficient was also computed, and most AT depots had a strong correlation between the two segmentation approaches (r range = 0.866 to 0.996; ICC range = 0.818 to 0.994), except for VAT at section 3 ($r = 0.636$; ICC= 0.509) (66). Raschpichler et al. compared the assessment of total AT, VAT, and SAT using a semi-automatic segmentation in ImageJ and SliceOmatic softwares (67). Images were obtained from the level of the ninth thoracic vertebrae to the symphysis using a 1.5 T MRI scanner in children and adolescents with obesity. Adipose tissue volume, in milliliters, differed between the two segmentation approaches ($p \leq 0.05$) (67).

The use of MRI in research settings is often limited due to its availability, high costs, scan duration, and movement artifacts as some children are unable to stay still. To improve the feasibility of MRI for body composition assessment, a single image may be used if representative of the whole-body (68). Springer et al. evaluated whether single slices or 5-slices at different body regions (femoral head, head of humerus, and umbilicus) would best correlate with whole-body SAT and total AT (69). The strongest correlations between single slice and whole-body total AT for both males and female were found at the femoral head level ($r = 0.93$ to 0.95; $p < 0.0001$). Correlations between whole-body SAT and single slice SAT at umbilicus level ($r = 0.91$ to 0.92; $p < 0.0001$) presented with similar values compared to 5-slice stacks SAT ($r =$

0.89 to 0.93; p <0.0001). The strongest correlations between 5-slice stacks of SAT and whole-body total AT were observed for the femoral head (r = 0.92 to 0.94; p <0.0001). For VAT, single slice was more strongly correlated to whole-body VAT (r = 0.71-0.94; p <0.0001) than 5-slice stacks (r = 0.58-0.68; p <0.05) (69). Thus, single slice MRI may be used instead of 5-slice to assess total AT (slice at femoral head), and SAT and VAT (slice at umbilicus level) in children and adolescents with obesity.

Validity – Diagnostic Test Accuracy

There were no studies assessing the ability of MRI to identify abnormal body composition in the pediatric population with overweight or obesity.

3.4.5 Summary of Findings on Validity Using Multicompartment and DXA as Reference Standards

Compared to a multicompartment (i.e. 3-C or 4-C) model as the reference standard, %BF was overestimated in most studies using DXA and ADP, but underestimated using isotope dilution, skinfolds, and BIA (**Figure 3.2**). In validation studies employing Bland-Altman analysis, reduced random error of the index test is indicated when the mean difference between index test and reference standard is close to zero and the LoA are narrowed (7). The latter LoA suggests that the two techniques are in agreement across all individuals. However, there are no established LoA for body composition assessment in the pediatric population, and it is the researcher's role to define if the LoA are acceptable for substituting the reference standard by the index test. Therefore, the limit of agreement of ≤5% points in %BF was considered acceptable for single measurements at one point in time. In our systematic review, we observed that DXA, ADP and isotope dilution have the smallest bias and narrowest LoA for %BF estimation in boys and girls. Most studies presented acceptable lower and upper LoA for these techniques, with the exception of one study (36) showing upper limits >5% for DXA in boys and for DXA, ADP, and isotope dilution in girls. Skinfolds and BIA had greater bias and wide LoA, with unacceptable lower LoA in both sexes but acceptable upper LoA in boys only for skinfolds.

We also compared field techniques and ADP with DXA as the reference standard method for %BF estimation (**Figure 3.3**). Bias between index test and reference standard was heterogeneous across studies, but most presented with wide and unacceptable LoA. Because only few studies investigated the validity of index tests to assess FFM, findings of those studies using multicompartment models or DXA as the reference standard are summarized in **Figure 3.4**.

Agreement between FFM measured by DXA and 4-C model was superior to results obtained by BIA versus multicompartment models.

3.4.6 Agreement Between Index Tests and Reference Standards to Monitor Changes in Body Composition

After eight weeks of exercise training, changes in abdominal FM assessed by skinfolds (3-or 4-sites equations) and DXA were moderately correlated in children ($r = 0.36$ to 0.37; $p < 0.05$) (19). However, changes in whole-body FM were not significantly or strongly correlated (19). The accuracy of evaluating longitudinal growth changes in %BF over one year was examined in another study using the Dezenberg equation (26), showing changes in %BF being underestimated in African Americans but overestimated in White boys and girls.

Meredith-Jones et al. investigated the mean difference between a standing hand-to-foot BIA device (Tanita BC-418) and DXA to track longitudinal changes in body composition in children with overweight and obesity undergoing a lifestyle intervention (70). Mean differences ranged from -0.38% to 0.18% for %BF, -0.07 to -0.04 kg for FM, and -0.14 to 0.08 kg for FFM after the 12-month follow-up assessment. Using another BIA device (RJL 101Q), changes in %BF were significantly underestimated compared to DXA only in African American girls (bias = -2.3%) by the Lewy equation ($p < 0.05$); differences were insignificant for African American boys using the Lewy equation and White boys and girls using the Suprasongsin equation (bias range= -0.6 to 0.5) (26). Although Hofsteenge et al. found the Gray equation as the best performing equation for estimating FFM in children and adolescents with obesity, longitudinal changes were underestimated by approximately 1 kg ($p = 0.037$) (45).

Longitudinal changes in body adiposity were assessed in two studies using ADP as the index test (26, 56). Compared to a 4-C model, ADP slightly overpredicted changes in FM in children and adolescents with obesity (bias range = 0.14 kg to 0.31 kg) (56). The opposite was found when DXA was employed as the reference standard test; ADP underestimated %BF in White males and females ($bias_{Siri}$ = -1.1% and -1.6%; $bias_{Lohman}$ = -1.4 % and -2.7 %, respectively) and in African American females ($bias_{Siri}$ = -0.2%; $bias_{Lohman}$ = -0.7%) (26). Moreover, %BF was slightly overestimated in African American males ($bias_{Siri}$ = 0.9%; $bias_{Lohman}$ = 0.3%) (26).

Using a longitudinal design, one study also assessed the agreement of DXA compared to a 4-C model to evaluate changes in body composition (63). There was a good agreement between

the index test and reference standard for both FM changes (bias = 0.04 kg; LoA = -2.96 kg to 3.04 kg) and FFM changes (bias = -0.02 kg; LoA = -3.18 kg to 3.14 kg) (63). Another study evaluated the agreement between DXA and MRI for measuring changes in VAT of children with obesity after completing a three-month lifestyle intervention (i.e. exercise and/or nutrition) (71). Although bias of relative changes for VAT cross-sectional area, volume, and mass raged from -4.2% to -3.7%, wide LoA (lower LoA = -38.6% to -39.6%; upper LoA = 31.2% to 31.6%) and weak and insignificant correlations after adjusting for changes in %BF (r^2 = 0.20 to 0.23; p = 0.120 to 0.144) were reported (71). Interesting, Wosje et al. determined that the smallest detectable differences for Hologic QDR 4500A repeated measures were 1.39 kg for FM, 2.60 kg for lean mass, and 2.91 kg for bone mass, suggesting that absolute changes in body composition may be a result of measurement error if they are not greater than these values (61).

3.5 Discussion

This systematic review is the first to summarize the reliability and validity of field and laboratory techniques to assess body composition in pediatric overweight and obesity. Overall, our findings revealed that skinfolds, ADP, DXA, and US are reliable methodologies as they presented with either high ICC or low CV. However, the repeatability and reproducibility of anthropometric equations and isotope dilution have not yet been evaluated in this population. Significant variability was observed regarding the validity of body composition methodologies given that different techniques were used as reference standards. To summarize the agreement levels across index tests for %BF, we compared the results from Bland-Altman analyses of those studies validating field and laboratory tests against multicompartment models (i.e. 3- or 4-C models). These revealed that DXA, ADP (Lohman equation) and isotope dilution had similar and the smallest bias, as well as narrowest and acceptable LoA. Furthermore, DXA and isotope dilution presented with high sensitivity and specificity to detect high body fat. On the other hand, skinfolds and BIA had the greatest bias and widest LoA with upper and lower values >5% as well as inferior diagnostic test accuracy. Studies using anthropometric equations to estimate body composition also presented with poor validity results, when compared to DXA as the reference standard. These findings highlight that it is not possible to accurately predict body composition using anthropometrics and skinfolds, despite their simplicity and readily available equations.

Although multicompartment models are preferred reference standards for %BF assessment, other techniques such as DXA are also satisfactory. Less preferred standard methods are often called as convergent methods (72). In our systematic review, we noticed wide and clinically unacceptable LoA between index tests and DXA. In validation studies, a large systemic error of an index test compared to a multicompartment model will likely lead to a more pronounced over or underestimation of a body compartment when a convergent method is used (73). As a hypothetical example, a child with a %BF value of 40% by DXA could present with values ranging from 21.0 to 49.9%, 14.9 to 62.8%, and 29.7 to 44.6% if %BF would be estimated using anthropometrics, skinfolds, and ADP, respectively. To clarify whether these LoA are clinically significant, we used the threshold for DXA assessed %BF recently proposed by Kelly et al. that identifies children and adolescents at increased risk for cardiometabolic diseases (74). For this hypothetical child with a 40% BF, the risk for cardiometabolic complications would be high, considering the excessive %BF (cut-offs for boys = 33% and girls = 38%) (74). However, the relatively low lower LoA reported for field techniques and ADP indicates this child could be misdiagnosed if these techniques are used (versus DXA).

The ability of several field and laboratory index tests to accurately classify children with excess %BF was comprehensively tested by Bray et al (16). Compared to a 4-C criterion model, all laboratory methods (i.e. DXA, isotope dilution, and underwater weighing) presented with high specificity (>0.90) and sensitivity (>0.80), meaning a high likelihood to classify individuals correctly and a low likelihood of misclassifications. Most anthropometric and BIA models had low specificity or sensitivity, with exception for the skinfold thickness Pennington equation (75). Furthermore, changes over time in BF%, FM and FFM assessed by DXA were nearly identical to changes assessed by a 4-C model (63). Findings from our review also demonstrated the poor performance of skinfolds to evaluate changes in body composition longitudinally; mixed results were found for BIA, varying according to device, sex, and ethnicity. The best performing techniques were ADP and DXA for whole-body FM, although Wosje et al. demonstrated that changes must be greater than the smallest detectable differences (FM = 1.39 kg; FFM = 2.60 kg) to represent actual modifications in body composition using a specific DXA device (61). Nevertheless, longitudinal changes in abdominal adiposity by DXA were not comparable to MRI measures (71). Thus, researchers and health care providers in the field of pediatric obesity currently have limited options for studies employing a longitudinal analysis.

Several factors may explain the poor validity of field techniques for body composition assessment in children and adolescents with overweight and obesity. First, predictive equations should be specific for the population being evaluated in terms of age and/or sexual maturation, weight and health status, and ethnicity (6). In our systematic review, we noticed that eight BIA equations were developed for adult populations and eleven equations in children with mixed weight status (normal weight/overweight/obesity) (**Table A13**). Several studies also used undisclosed manufacturers' equations from BIA devices, which limit the understanding to whether these equations are applicable to the population in study (6). Particularly for BIA, equations should additionally be device specific and as noted in this systematic review, there is a large variability in devices' brand, model, and frequency of analysis. As shown by Newton Jr et al. in a study employing a RJL 101 BIA, only equations developed using this device and similar population had the smallest bias. Furthermore, body geometry characterized by a greater volume in the trunk in relation to limbs and the use of foot-to-foot devices are also factors that contributed to the low agreement between test index and reference standard (76). To overcome this limitation, one study explored the utilization of the ratio of body surface area to impedance (instead of height squared) for the prediction of TBW, with an improved bias between BIA and isotope dilution (47).

The hydration of tissues and TBW content may also affect the accuracy of some techniques relying on a constant coefficient for hydration status. To minimize the effects of maturational changes in FFM hydration and mineral content on %BF measures by densitometric techniques (e.g. ADP, body weighting), Lohman proposed modifications to the Siri equation (validated in adults) by including coefficients that are age- and sex-specific (77). However, it has been shown that children with overweight and obesity have a greater tissue hydration, leading to FFM overestimation and FM underestimation (or %BF) (8, 37, 42). For instance, children with obesity had 1.6% higher TBW than children of normal weight ($p = 0.01$) (8). Thus, measuring TBW or applying a hydration coefficient that is specific for the pediatric obesity population into predictive equations would minimize measurement errors. To the best of our knowledge, hydration coefficients for children and adolescents with obesity have not been proposed in the literature.

It is noteworthy that the lower mean age of participants in the selected studies was seven years old. Currently, there is a gap in validated and practical techniques to assess body

composition in younger children (particularly under 5 years old), independent of weight categories (78). Factors challenging body composition assessment in younger children include compliance to exam due to requirement of lying still, concern with radiation exposure, and scarcity of age-specific predictive equations as well as cadaver studies evaluating body composition (78). In addition to these factors, adiposity rebound appears to occur at a younger age in children with obesity (around three years old) than in children with normal weight (around six years old), requiring special attention when validating techniques in young children with obesity (79).

Findings from this systematic review suggest that DXA, ADP and isotope dilution have the best and similar validity (i.e. agreement and diagnostic test accuracy) to assess adiposity in children and adolescents with overweight or obesity cross-sectionally. Giving this similarity, researchers and health care providers should consider other factors such as costs and availability, subject compliance, device limitations, invasiveness and duration to complete a body composition assessment when choosing among techniques. For example, some DXA systems have a weight limit of 125 kg or scanning beds that are narrow for larger individuals, resulting in scans with overlapping tissues (i.e. arms are arranged tightly to the trunk) or cut of limbs in the image processing (45, 62). Combining body composition results (e.g. pre- and post-interventions) that were obtained using different software versions, but the same DXA device, is also a limitation that can introduce important measurement errors. Furthermore, children and adolescents may have difficulties to complete an ADP test when measurements of TGV is required. The isotope dilution methods also present with limitations, including lengthened duration and costs. In short, to optimize technique selection, researchers and health care providers should initially have a clear idea over the exact body compartment that is intended to be measured, then evaluate whether published intra- and/or inter-rater reliability analyses presented with high ICC and/or low CV, and finally they should check the validity (i.e. agreement or diagnostic test accuracy) of available techniques against a reference standard that measures the same body compartment (7, 73). For agreement analysis, either smaller bias accompanied by smaller LoA, higher Lin's concordance correlation coefficient, or higher correlation accompanied by smaller measures of errors (e.g. SEE, TE, root mean square error) suggest a greater validity. Additionally, some studies also used ICC for agreement analysis. Regarding diagnostic test accuracy, higher sensitivity and specificity as well as higher Cohen's

kappa coefficient are indicative of greater validity. It is noteworthy to mention that there is no established consensus about what level of these reliability and validity coefficients are acceptable for research and clinical practice.

In addition to summarizing the evidence on reliability and validity of techniques to assess body composition in childhood overweight and obesity, we also identified research gaps that need to be addressed. For instance, there is a lack of studies evaluating the reliability of anthropometric indices and isotope dilution. The diagnostic test accuracy of ADP and US have also not been investigated in this population. Moreover, with the evolving body composition field, newer techniques remain to be tested in regard to their reliability and validity in children and adolescents with overweight and obesity. Three-dimensional optical scanners, for example, are promising techniques due to their ability to evaluate several anthropometrics and body composition in a reduced time, absence of radiation exposure, and relatively lower costs than other techniques. A recent study has assessed the reliability and validity of a Fit3D ProScanner v. 4.x.(Fit3D Inc., San Mateo, California) in 112 children and adolescents aged 5.3 to 18 years with varied weight status, and found acceptable coefficients of variation (3.30% and 1.34% for FM and FFM, respectively) and strong associations with DXA for %BF, FM, and FFM ($r^2 = 0.83$ to 0.98) (80). Although the analysis was not stratified by weight, outliers in regression scatterplots and Bland-Altman plots for body volume had higher circumferences but were not outliers in %BF, demonstrating consistency of equations (80). Nevertheless, further studies should evaluate the reliability and validity of three-dimensional optical in children and adolescents with overweight and obesity.

Our systematic review has some limitations that should be acknowledged. First, only those studies that reported reliability and validity analyses stratified by weight were included, which limited the comparability with other relevant studies that included children with overweight and obesity but reported findings combining these individuals with those with normal weight. Second, we did not compare the findings between individuals having different %BF amounts, as most studies defined overweight and obesity using BMI categories, which is known to have intrinsic limitations. Third, we did not evaluate the accuracy of body composition techniques in terms of identifying clinical outcomes, such as cardiometabolic diseases and functional mobility. Fourth, differences in sample characteristics (e.g. sexual maturation, ethnicity, number of participants), test procedures (e.g. time of assessment, fasting state, voided

bladder), and quality of included studies may have increased the heterogeneity between studies. Fifth, it is noteworthy that index and reference techniques must assess the same body compartment in validation studies. Although ADP, DXA, and 4-C model evaluate body composition at the molecular level, different principles are used by each technique and it is unclear to what extent these techniques are directly equivalent to each other (81). Hübers et al. have shown that despite FM (by 4-C) and total AT (by MRI) being highly correlated, there was a great variability in the associations between metabolic risk factors and the ratio of FM to total AT in adults (82). Sixth, although the 4-C model is considered robust for body composition assessment (9), the FM equation employed in this method, and used in most studies, was developed using a small group of healthy, normal weight adults (83) and later validated in children with normal weight (84), lacking evidence of whether the FM equation is also applicable to children with overweight and obesity.

In conclusion, laboratory techniques for body composition assessment in the pediatric overweight and obesity population cannot be replaced by field methods in cross-sectional and longitudinal analyses. Predictive equations using anthropometric, skinfolds, and bioimpedance measures should be improved to reduce errors and enhance accuracy of results. This is important when access to body composition analysis is unavailable. Although US presented as a reliable and affordable technique free of radiation exposure, findings on its validity are still limited to %BF estimation; research is required to evaluate the agreement between US and MRI for skeletal muscle and subcutaneous measures. Likewise, three-dimensional optical scanners should also have their reliability and validity further explored for the assessment of whole and segmental body composition in children and adolescents with overweight and obesity. Such changes may enhance the accuracy of diagnosing and monitoring body composition abnormalities in the pediatric population.

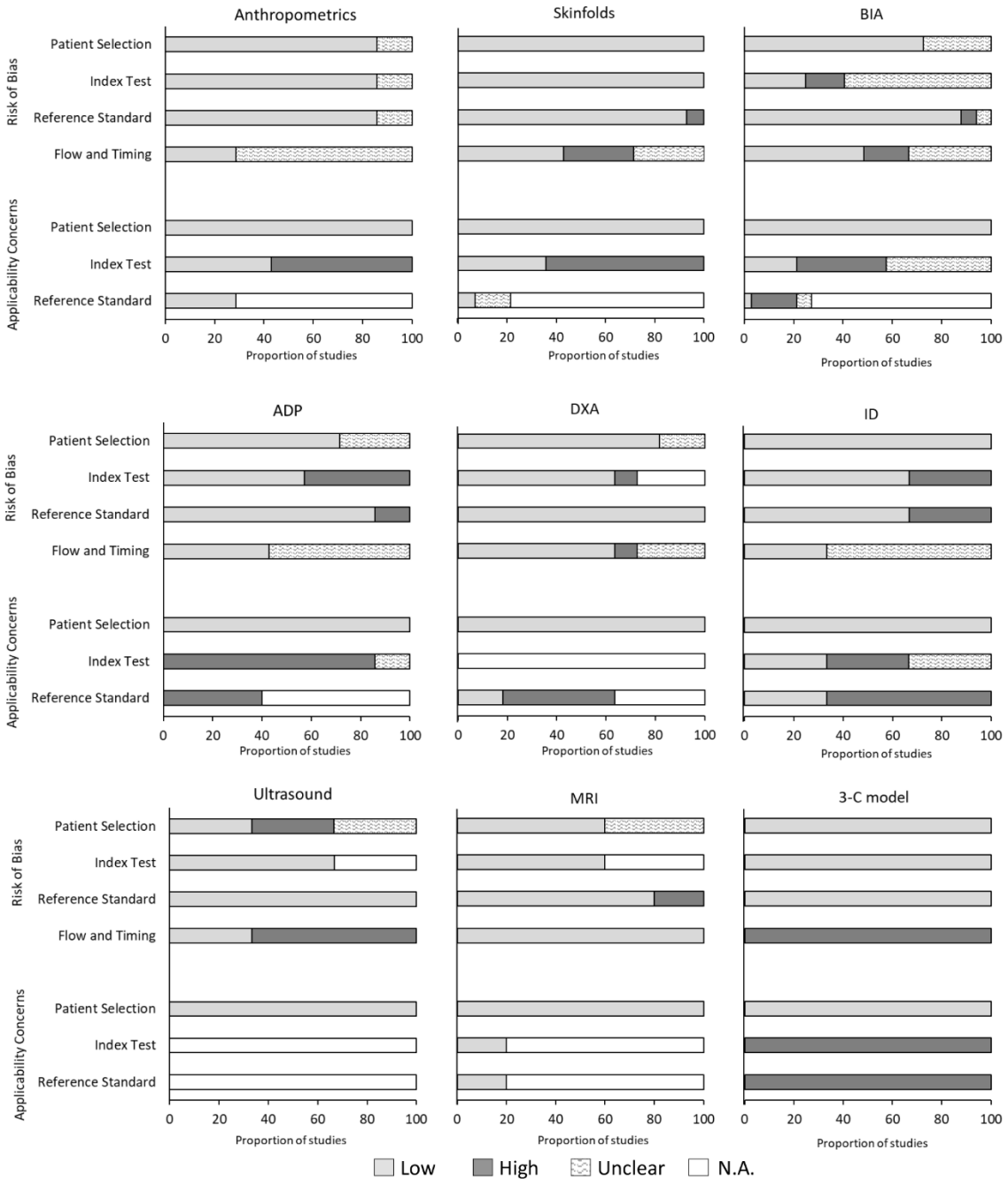


Figure 3.1 Quality assessment summary of included studies. The bar graphs above depict the proportion of studies with low, high, and unclear risk of bias or applicability concerns, as proposed by the revised Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2). Studies that reported only reliability findings or employed a reference standard not requiring predictive equations to assess body composition had risk of bias or applicability concerns defined as not applicable. *Abbreviations:* ADP, air-displacement plethysmography; BIA, bioelectrical impedance analysis; DXA, dual-energy X-ray absorptiometry; ID, isotope dilution; MRI, magnetic resonance imaging; N.A., not applicable; 3-C, three-compartment model.

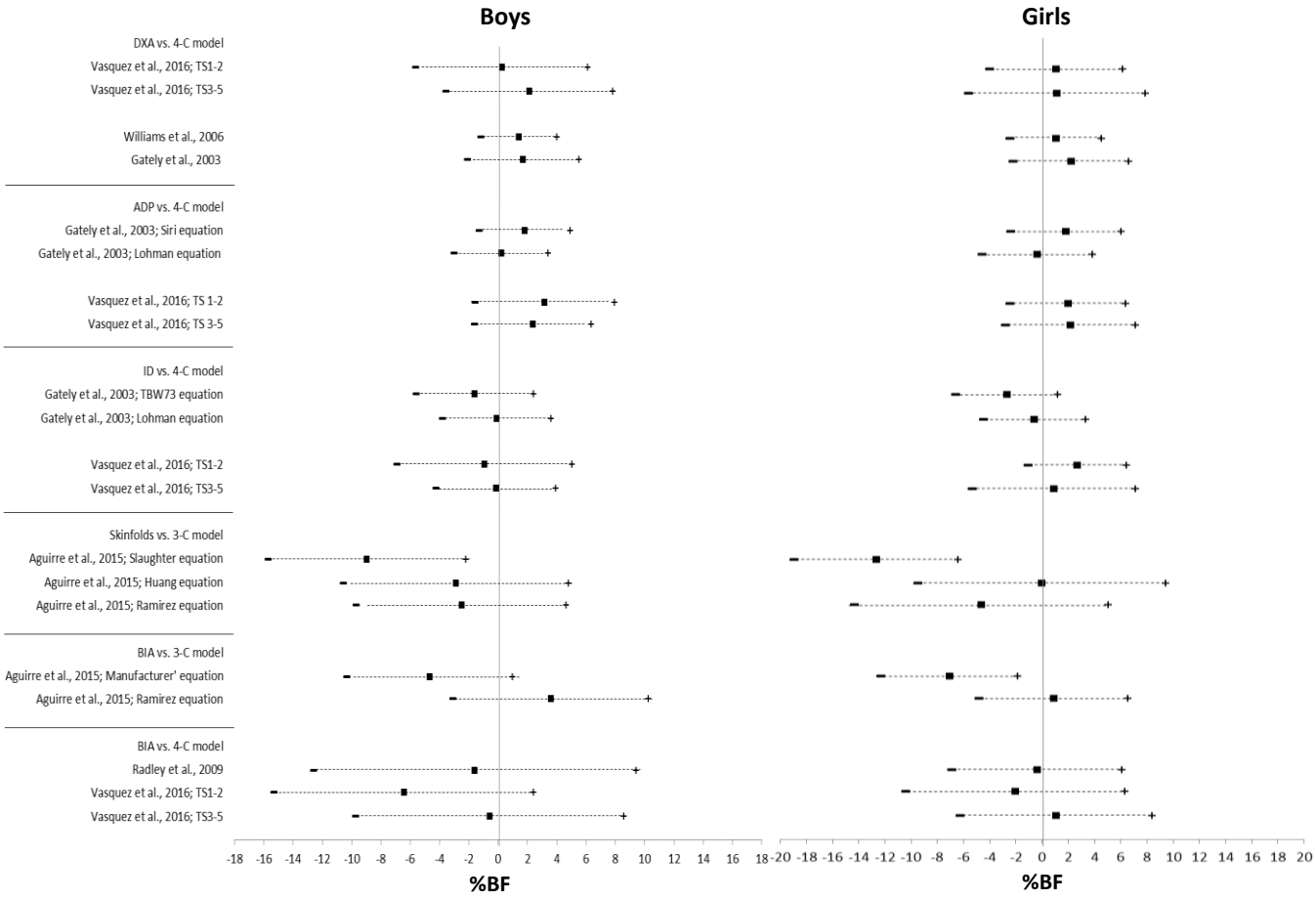


Figure 3.2 Bias (■) and upper (+) and lower (–) limits of agreement for percent body fat between index test and multicompartment models in boys (left panel) and girls (right panel). Note that some authors have evaluated the agreement stratified by tanner stages or specific equations, as showed above. *Abbreviations:* %BF, percent body fat; ADP, air-displacement plethysmography; BIA, bioelectrical impedance analysis; ID, isotope dilution; DXA, dual-energy X-ray absorptiometry; 3-C model, three-compartment model; 4-C, four-compartment model.

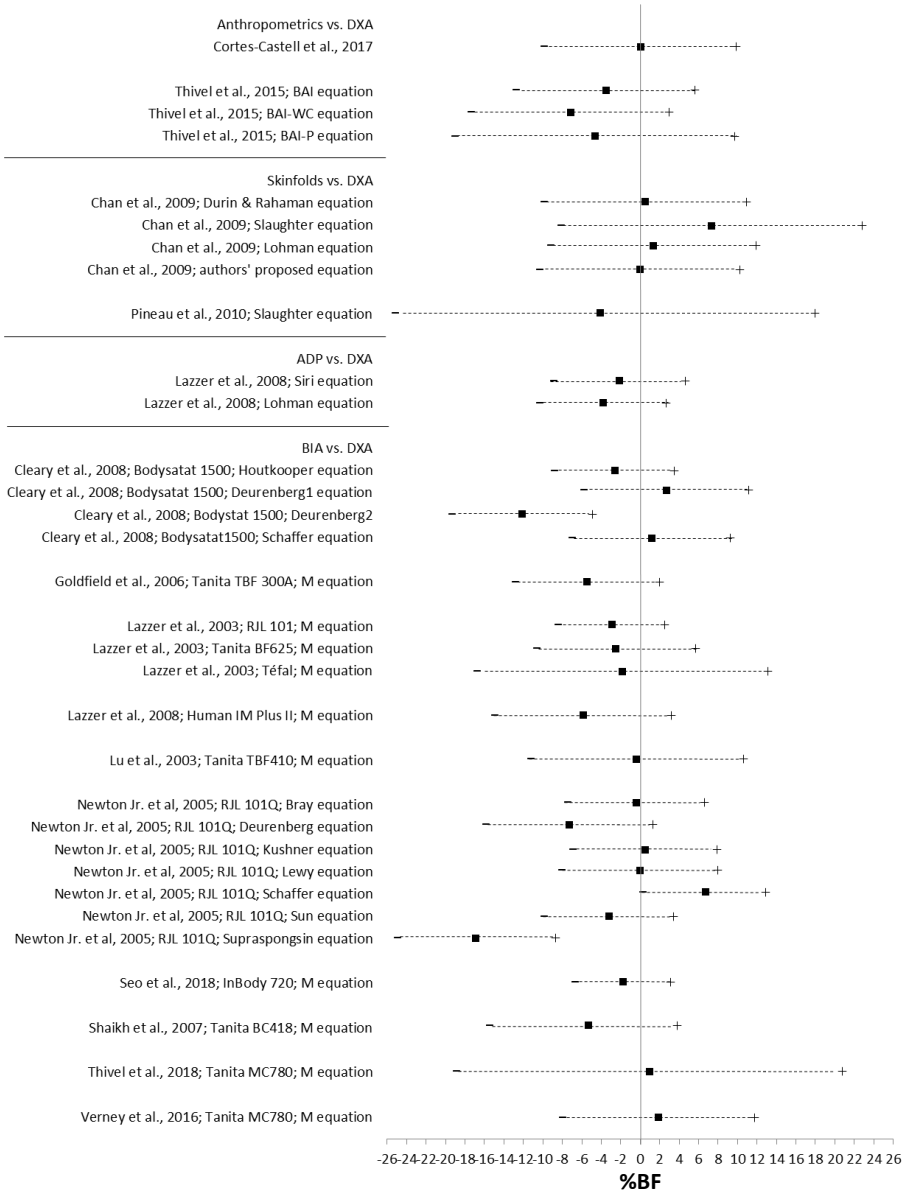


Figure 3.3 Bias (■) and upper (+) and lower (–) limits of agreement for percent body fat between index test and dual-energy X-ray as the reference standard in boys and girls combined. Note that some authors have evaluated the agreement stratified by specific equations or bioelectrical impedance device, as showed above. *Abbreviations:* %BF, percent body fat; ADP, air-displacement plethysmography; BIA, bioelectrical impedance analysis; ID, isotope dilution; DXA, dual-energy X-ray absorptiometry; 3-C model, three-compartment model; 4-C, four-compartment model; M equation, manufacturer's equation.

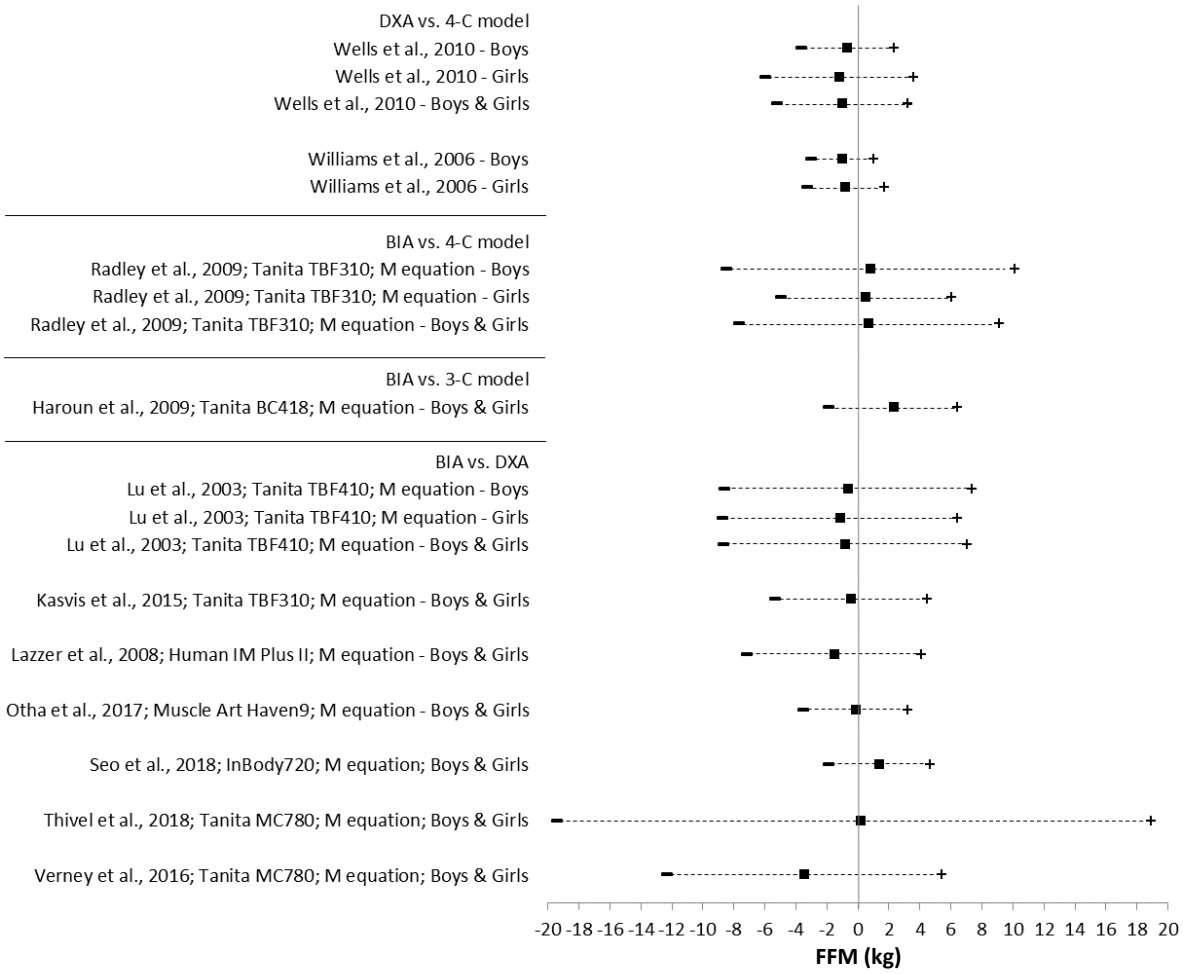


Figure 3.4 Bias (■) and upper (+) and lower (–) limits of agreement for fat-free mass between index test and reference standard in boys and girls. *Abbreviations:* BIA, bioelectrical impedance analysis; DXA, dual-energy X-ray absorptiometry; FFM, fat-free mass; 3-C model, three-compartment model; 4-C, four-compartment model; M equation, manufacturer's equation.

Table 3.1 Number of studies evaluation reliability and validity of body composition techniques in childhood overweight and obesity.

		Field BC methods			Laboratory techniques					
	Number of studies, n (%)	Anthropometrics	Skinfolds	BIA	ADP	DXA	Isotope dilution	Ultrasound	MRI	3-C model
Reliability Studies										
Intra-rater	13 (19.7)	0	2 [18,19]	4 [31-34]	2 [56, 57]	3 [31, 61, 62]	0	3 [18, 54, 55]	2 [30, 54]	0
Inter-rater	2 (3.0)	0	1 [18]	0	0	0	0	2 [18, 54]	1 [54]	0
Validity - Agreement between index test and reference standard										
Bland-Altman or systematic effect analyses	45 (68.2)	5 [12-15,85]	10 [18, 21-28, 30]	26 [21, 25, 27, 31, 32, 34-47, 76, 86-91]	6 [32, 36, 56-58, 60]	5 [8, 36, 38, 57, 63]	2 [36, 57]	1 [18]	2 [66, 67]	1 [65]
Association statistical tests	37 (56.1)	3 [13-15]	6 [18, 19, 21, 25, 29, 30]	19 [21, 25, 31, 32, 34-38, 41-44, 46, 47, 76, 86, 87, 89, 90]	5 [36, 56-59]	5 [8, 36, 38, 57, 63]	2 [36, 57]	2 [18, 54]	2 [66, 69]	0
Validity - Diagnostic test accuracy										
Sensitivity or specificity analyses	7 (10.6)	2 [16, 17]	2 [16, 20]	5 [16, 38, 50, 51, 53]	0	3 [16, 38, 64]	1 [16]	0	0	1 [16]

Abbreviations: ADP, air-displacement plethysmography; BIA, bioelectrical impedance analysis; DXA, dual-energy X-ray absorptiometry; MRI, magnetic resonance imaging; 3-C, three-compartment.

3.6 References:

1. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: A pooled analysis of 2416 population-based measurement studies in 128·9 million children, adolescents, and adults. Lancet. 2017;390(10113):2627–42.

2. Di Cesare M, Sorić M, Bovet P, Miranda JJ, Bhutta Z, Stevens GA, et al. The epidemiological burden of obesity in childhood: A worldwide epidemic requiring urgent action. BMC Med. 2019;17(1):212.

3. World Health Organization (WHO). Report of the comission on ending childhood obesity: implementation plan: Executive summary. Vol. 1, Executive summary, Geneva: World Health OrganizationCC BYNC-SA 3.0 IGO. 2017.

4. Kelly AS, Fox CK, Rudser KD, Gross AC, Ryder JR. Pediatric obesity pharmacotherapy: Current state of the field, review of the literature and clinical trial considerations. Int J Obes. 2016;40(7):1043–50.

5. Vanderwall C, Eickhoff J, Randall Clark R, Carrel AL. BMI z-score in obese children is a poor predictor of adiposity changes over time. BMC Pediatr. 2018;18(1):1–6.

6. Gonzalez MC. Using bioelectrical impedance analysis for body composition assessment: Sorting out some misunderstandings. J Parenter Enter Nutr. 2019;43(8):954–5.

7. Earthman CP. Body composition tools for assessment of adult malnutrition at the bedside: A tutorial on research considerations and clinical applications. J Parenter Enter Nutr. 2015;39(7):787–822.

8. Williams JE, Wells JCK, Wilson CM, Haroun D, Lucas A, Fewtrell MS. Evaluation of Lunar Prodigy dual-energy X-ray absorptiometry for assessing body composition in healthy persons and patients by comparison with the criterion 4-component model. Am J Clin Nutr. 2006;83(5):1047–54.

9. Fields DA, Goran MI. Body composition techniques and the four-compartment model in children. J Appl Physiol. 2000;89(2):613–20.

10. Jelicic Kadic A, Vucic K, Dosenovic S, Sapunar D, Puljak L. Extracting data from figures with software was faster, with higher interrater reliability than manual extraction. J Clin Epidemiol. 2016;74:119–23.

11. Whiting P, Rutjes A, Westwood M, Mallett S, Deeks J, Reitsma J, et al. QUADAS-2: A revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med. 2011;154(4):529–36.
12. Cortés-Castell E, Juste M, Palazón-Bru A, Monge L, Sánchez-Ferrer F, Rizo-Baeza MM. A simple equation to estimate body fat percentage in children with overweightness or obesity: A retrospective study. PeerJ. 2017;2017(4):1–14.
13. Thivel D, O'Malley G, Pereira B, Duché P, Aucouturier J. Comparison of total body and abdominal adiposity indexes to dual x-ray absorptiometry scan in obese adolescents. Am J Hum Biol. 2015;27(3):334–8.
14. Samouda H, De Beaufort C, Stranges S, Van Nieuwenhuyse JP, Dooms G, Keunen O, et al. Subtraction of subcutaneous fat to improve the prediction of visceral adiposity: Exploring a new anthropometric track in overweight and obese youth. Pediatr Diabetes. 2017;18(5):399–404.
15. Rolland-Cachera MF, Brambilla P, Manzoni P, Akrout M, Sironi S, Del Maschio A, et al. Body composition assessed on the basis of arm circumference and triceps skinfold thickness: A new index validated in children by magnetic resonance imaging. Am J Clin Nutr. 1997;65(6):1709–13.
16. Bray GA, DeLany JP, Volaufova J, Harsha DW, Champagne C. Prediction of body fat in 12-y-old African American and white children: Evaluation of methods. Am J Clin Nutr. 2002;76(5):980–90.
17. Woolcott OO, Bergman RN. Relative Fat Mass as an estimator of whole-body fat percentage among children and adolescents: A cross-sectional study using NHANES. Sci Rep. 2019;9(1):1–14.
18. Pineau JC, Lalys L, Bocquet M, Guihard-Costa AM, Polak M, Frelut ML, et al. Ultrasound measurement of total body fat in obese adolescents. Ann Nutr Metab. 2010;56(1):36–44.
19. Watts K, Naylor L, Davis E, Jones T, Beeson B, Bettenay F, et al. Do skinfolds accurately assess changes in body fat in obese children and adolescents? Med Sci Sport Exerc. 2006;38(3):439–70.
20. Wohlfahrt-Veje C, Tinggaard J, Winther K, Mouritsen A, Hagen CP, Mieritz MG, et al. Body fat throughout childhood in 2647 healthy Danish children: Agreement of BMI, waist circumference, skinfolds with dual X-ray absorptiometry. Eur J Clin Nutr. 2014;68(6):664–70.

21. Aguirre CA, Salazar GDC, Lopez De Romaña DV, Kain JA, Corvalán CL, Uauy RE. Evaluation of simple body composition methods: Assessment of validity in prepubertal Chilean children. Eur J Clin Nutr. 2015;69(2):269–73.
22. Bammann K, Huybrechts I, Vicente-Rodriguez G, Easton C, De Vriendt T, Marild S, et al. Validation of anthropometry and foot-to-foot bioelectrical resistance against a three-component model to assess total body fat in children: The IDEFICS study. Int J Obes. 2013;37(4):520–6.
23. Chan DFY, Li AM, So HK, Yin J, Nelson EAS. New skinfold-thickness equation for predicting percentage body fat in Chinese obese children. Hong Kong J Paediatr. 2009;14(2):96–102.
24. Freedman DS, Horlick M, Berenson GS. A comparison of the Slaughter skinfold-thickness equations and BMI in predicting body fatness and cardiovascular disease risk factor levels in children. Am J Clin Nutr. 2013;98(6):1417–24.
25. González-Ruíz K, Medrano M, Correa-Bautista JE, García-Hermoso A, Prieto-Benavides DH, Tordecilla-Sanders A, et al. Comparison of bioelectrical impedance analysis, Slaughter skinfold-thickness equations, and dual-energy X-ray absorptiometry for estimating body fat percentage in Colombian children and adolescents with excess of adiposity. Nutrients. 2018;10(8):1–14.
26. Elberg J, McDuffie J, Sebring N, Salaita C, Keil M, Robotham D, et al. Comparison of methods to assess change in children's body composition. Am J Clin Nutr. 2004;80(1):64–9.
27. Mooney A, Kelsey L, Fellingham GW, George JD, Hager RL, Myrer JW, et al. Assessing body composition of children and adolescents using dual-energy X-ray absorptiometry, skinfolds, and electrical impedance. Meas Phys Educ Exerc Sci. 2011;15(1):2–17.
28. Stevens J, Cai J, Truesdale K, Cuttler L, Robinson T, Roberts A. Percent body fat prediction equations for 8-to 17-year-old American children. Pediatr Obes. 2014;9(4):260–71.
29. Asayama K, Dobashi K, Hayashibe H, Kodera K, Uchida N, Nakane T, et al. Threshold values of visceral fat measures and their anthropometric alternatives for metabolic derangement in Japanese obese boys. Int J Obes. 2002;26(2):208–13.
30. Ball GDC, Huang TTK, Cruz ML, Shaibi GQ, Weigensberg MJ, Goran MI. Predicting abdominal adipose tissue in overweight Latino youth. Int J Pediatr Obes. 2006;1(4):210–6.

31. Kasvis P, Cohen TR, Loiselle SÈ, Kim N, Hazell TJ, Vanstone CA, et al. Foot-to-foot bioelectrical impedance accurately tracks direction of adiposity change in overweight and obese 7- to 13-year-old children. Nutr Res. 2015;35(3):206–13.
32. Lazzer S, Bedogni G, Agosti F, De Col A, Mornati D, Sartorio A. Comparison of dual-energy X-ray absorptiometry, air displacement plethysmography and bioelectrical impedance analysis for the assessment of body composition in severely obese Caucasian children and adolescents. Br J Nutr. 2008;100(4):918–24.
33. Steinberg A, Manlhiot C, Li P, Metivier E, Pencharz PB, McCrindle BW, et al. Development and validation of bioelectrical impedance analysis equations in adolescents with severe obesity. J Nutr. 2019;149(7):1288–93.
34. Verney J, Metz L, Chaplais E, Cardenoux C, Pereira B, Thivel D. Bioelectrical impedance is an accurate method to assess body composition in obese but not severely obese adolescents. Nutr Res. 2016;36(7):663–70.
35. Shaikh MG, Crabtree NJ, Shaw NJ, Kirk JMW. Body fat estimation using bioelectrical impedance. Horm Res. 2007;68(1):8–10.
36. Vásquez F, Salazar G, Díaz E, Lera L, Anziani A, Burrows R. Comparison of body fat calculations by sex and puberty status in obese schoolchildren using two and four compartment body composition models. Nutr Hosp. 2016;33(5):1116–22.
37. Haroun D, Croker H, Viner RM, Williams JE, Darch TS, Fewtrell MS, et al. Validation of BIA in obese children and adolescents and re-evaluation in a longitudinal study. Obesity. 2009;17(12):2245–50.
38. Atherton RR, Williams JE, Wells JCK, Fewtrell MS. Use of fat mass and fat free mass standard deviation scores obtained using simple measurement methods in healthy children and patients: Comparison with the reference 4-component model. PLoS One. 2013;8(5):1–10.
39. Lazzer S, Boirie Y, Meyer M, Vermorel M. Evaluation of two foot-to-foot bioelectrical impedance analysers to assess body composition in overweight and obese adolescents. Br J Nutr. 2003;90(5):987–92.
40. Lyra A, Bonfitto AJ, Barbosa VLP, Bezerra AC, Longui CA, Monte O, et al. Comparison of methods for the measurement of body composition in overweight and obese Brazilian children and adolescents before and after a lifestyle modification program. Ann Nutr Metab. 2015;66(1):26–30.

41. Newton RL, Alfonso A, White MA, York-Crowe E, Walden H, Ryan D, et al. Percent body fat measured by BIA and DEXA in obese, African-American adolescent girls. Int J Obes. 2005;29(6):594–602.
42. Gillis L, Bar-Or O, Calvert R. Validating a practical approach to determine weight control in obese children and adolescents. Int J Obes. 2000;24(12):1648–52.
43. Resende C, Camelo Junior J, Vieira M, Perdona G, Ferriolli E, Pfrimer K, et al. Body composition in obese adolescents: Deuterium oxide dilution method, bioelectrical impedance and predictive equations. Curr Nutr Food Sci. 2013;9(10):73–81.
44. Cleary J, Daniells S, Okely AD, Batterham M, Nicholls J. Predictive validity of four bioelectrical impedance equations in determining percent fat mass in overweight and obese children. J Am Diet Assoc. 2008;108(1):136–9.
45. Hofsteenge GH, Chinapaw MJM, Weijs PJM. Fat-free mass prediction equations for bioelectric impedance analysis compared to dual energy X-ray absorptiometry in obese adolescents: A validation study. BMC Pediatr. 2015;15(1).
46. Seo YG, Kim JH, Kim YM, Lim H, Ju YS, Kang MJ, et al. Validation of body composition using bioelectrical impedance analysis in children according to the degree of obesity. Scand J Med Sci Sport. 2018;28(10):2207–15.
47. Battistini N, Brambilla P, Virgili F, Simone P, Bedogni G, Morini P, et al. The prediction of total body water from body impedance in young obese subjects. Int J Obes. 1992;16(3):207–12.
48. Ohta M, Midorikawa T, Hikihara Y, Masuo Y, Sakamoto S, Torii S, et al. Validity of segmental bioelectrical impedance analysis for estimating fat-free mass in children including overweight individuals. Appl Physiol Nutr Metab. 2017;42(2):157–65.
49. Luque V, Closa-Monasterolo R, Rubio-Torrents C, Zaragoza-Jordana M, Ferré N, Gispert-Llauradó M, et al. Bioimpedance in 7-year-old children: Validation by dual X-Ray absorptiometry - Part 1: Assessment of whole body composition. Ann Nutr Metab. 2014;64(2):113–21.
50. Luque V, Escribano J, Zaragoza-Jordana M, Rubio-Torrents C, Ferré N, Gispert-Llaurado M, et al. Bioimpedance in 7-year-old children: Validation by dual X-ray absorptiometry - Part 2: Assessment of segmental composition. Ann Nutr Metab. 2014;64(2):144–55.

51. Butcher A, Kabiri LS, Brewer W, Ortiz A. Criterion validity and sensitivity to change of a pediatric bioelectrical impedance analysis scale in adolescents. Child Obes. 2019;15(2):142–8.
52. McCarthy HD, Cole TJ, Fry T, Jebb SA, Prentice AM. Body fat reference curves for children. Int J Obes. 2006;30(4):598–602.
53. Kabiri LS, Hernandez DC, Mitchell K. Reliability, validity, and diagnostic value of a pediatric bioelectrical impedance analysis scale. Child Obes. 2015;11(5):650–5.
54. Koot BGP, Westerhout R, Bohte AE, Vinke S, Pels Rijcken TH, Nederveen AJ, et al. Ultrasonography is not more reliable than anthropometry for assessing visceral fat in obese children. Pediatr Obes. 2014;9(6):443–7.
55. Garcia-Vicencio S, Coudeyre E, Kluka V, Cardenoux C, Jegu AG, Fourot A V., et al. The bigger, the stronger? Insights from muscle architecture and nervous characteristics in obese adolescent girls. Int J Obes. 2016;40(2):245–51.
56. Wells JCK, Haroun D, Williams JE, Darch T, Eaton S, Viner R, et al. Evaluation of lean tissue density for use in air displacement plethysmography in obese children and adolescents. Eur J Clin Nutr. 2011;65(10):1094–101.
57. Gately PJ, Radley D, Cooke CB, Carroll S, Oldroyd B, Truscott JG, et al. Comparison of body composition methods in overweight and obese children. J Appl Physiol. 2003;95(5):2039–46.
58. Colantonio E, Dâmaso AR, Caranti DA, Pinheiro MM, Tufik S, De Mello MT. Clinical performance of 3-body fat measurements in obese adolescents 15 to 18 years-old. Rev Bras Med. 2015;72(3):77–82.
59. de Mello MT, Damaso AR, Antunes HKM, Siqueira KO, Castro ML, Bertolino S V., et al. Body composition evaluation in obese adolescents: The use of two different methods. Rev Bras Med do Esporte. 2005;11(5):251–4.
60. Radley D, Fields DA, Gately PJ. Validity of thoracic gas volume equations in children of varying body mass index classifications. Int J Pediatr Obes. 2007;2(3):180–7.
61. Wosje KS, Knipstein BL, Kalkwarf HJ. Measurement error of DXA: Interpretation of fat and lean mass changes in obese and non-obese children. J Clin Densitom. 2006;9(3):335–40.
62. Tsang TW, Briody J, Kohn M, Chin MC, Singh MF. Abdominal fat assessment in adolescents using dual-energy X-ray absorptiometry. J Pediatr Endocrinol Metab. 2009;22(9):781–94.

63. Wells JCK, Haroun D, Williams JE, Wilson C, Darch T, Viner RM, et al. Evaluation of DXA against the four-component model of body composition in obese children and adolescents aged 5-21 years. Int J Obes. 2010;34(4):649–55.
64. Shypailo RJ, Butte NF, Ellis KJ. DXA: Can it be used as a criterion reference for body fat measurements in children. Obesity. 2008;16(2):457–62.
65. Haroun D, Wells JCK, Williams JE, Fuller NJ, Fewtrell MS, Lawson MS. Composition of the fat-free mass in obese and nonobese children: Matched case-control analyses. Int J Obes. 2005;29(1):29–36.
66. Hui SCN, Zhang T, Shi L, Wang D, Ip CB, Chu WCW. Automated segmentation of abdominal subcutaneous adipose tissue and visceral adipose tissue in obese adolescent in MRI. Magn Reson Imaging. 2018;45(January 2017):97–104.
67. Raschpichler MC, Sorge I, Hirsch W, Mende M, Sergeyev E, Kruber D, et al. Evaluating childhood obesity: Magnetic resonance-based quantification of abdominal adipose tissue and liver fat in children. Fortschr Röntgenstr. 2012;184(4):324–32.
68. Shen W, Punyanitya M, Wang Z, Gallagher D, St-Onge M-P, Albu J, et al. Total body skeletal muscle and adipose tissue volumes: Estimation from a single abdominal cross-sectional image. J Appl Physiol. 2004;97(6):2333–8.
69. Springer F, Ehehalt S, Sommer J, Ballweg V, Machann J, Binder G, et al. Predicting volumes of metabolically important whole-body adipose tissue compartments in overweight and obese adolescents by different MRI approaches and anthropometry. Eur J Radiol. 2012;81(7):1488–94.
70. Meredith-Jones KA, Williams SM, Taylor RW. Bioelectrical impedance as a measure of change in body composition in young children. Pediatr Obes. 2015;10(4):252–9.
71. Dias KA, Ramos JS, Wallen MP, Davies PSW, Cain PA, Leong GM, et al. Accuracy of longitudinal assessment of visceral adipose tissue by dual-energy X-ray absorptiometry in children with obesity. J Obes. 2019;2019:1–12.
72. Talma H, Chinapaw MJM, Bakker B, Hirasing RA, Terwee CB, Altenburg TM. Bioelectrical impedance analysis to estimate body composition in children and adolescents: A systematic review and evidence appraisal of validity, responsiveness, reliability and measurement error. Obes Rev. 2013;14(11):895–905.

73. Lohman TG, Milliken LA. Errors in body composition measurement and assessment. In: ACSM's body composition assessment. 2020. p. 3–12.
74. Kelly AS, Kaizer AM, Bosch TA, Rudser KD, Ryder JR, Gross AC, et al. Reaching the tipping point: Identification of thresholds at which visceral adipose tissue may steeply increase in youth. Obesity. 2019;00(00):1–7.
75. Bray GA, DeLany JP, Harsha DW, Volaufova J, Champagne CC. Evaluation of body fat in fatter and leaner 10-y-old African American and white children: The Baton Rouge children's study. Am J Clin Nutr. 2001;73(4):687–702.
76. Radley D, Cooke C, Fuller N, Oldroyd B, Truscott J, Coward W, et al. Validity of foot-to-foot bio-electrical impedance analysis body composition estimates in overweight and obese children. Int J Body Compos Res. 2009;7(1):15–20.
77. Lohman TG. Assessment of body composition in children. Pediatr Exerc Sci. 1989;1(1):19–30.
78. Toro-Ramos T, Paley C, Pi-Sunyer FX, Gallagher D. Body composition during fetal development and infancy through the age of 5 years. Eur J Clin Nutr. 2015;69(12):1279–89.
79. Rolland-Cachera MF, Deheeger M, Maillot M, Bellisle F. Early adiposity rebound: Causes and consequences for obesity in children and adults. Int J Obes. 2006;30:S11–7.
80. Wong MC, Ng BK, Kennedy SF, Hwaung P, Liu EY, Kelly NN, et al. Children and adolescents' anthropometrics body composition from 3-D optical surface scans. Obesity. 2019;27(11):1738–49.
81. Heymsfield SB, Wang Z, Baumgartner RN, Ross R. Human body composition: Advances in models and methods. Annu Rev Nutr. 1997;17:527–58.
82. Hübers M, Geisler C, Bosy-Westphal A, Braun W, Pourhassan M, Sørensen TIA, et al. Association between fat mass, adipose tissue, fat fraction per adipose tissue, and metabolic risks: A cross-sectional study in normal, overweight, and obese adults. Eur J Clin Nutr. 2019;73(1):62–71.
83. Fuller NJ, Jebb SA, Laskey MA, Coward WA, Elia M. Four-component model for the assessment of body composition in humans: Comparison with alternative methods, and evaluation of the density and hydration of fat-free mass. Clin Sci. 1992;82(6):687–93.

84. Lohman TG. Applicability of body composition techniques and constants for children and youths. In: Pandolf KB, editor. Exercise and Sport Sciences Reviews. New York: Macmillan; 1986. p. 325–57.
85. Bedogni G, Bollea MR, Severi S, Trunfio O, Manzieri AM, Battistini N. The prediction of total body water and extracellular water from bioelectric impedance in obese children. Eur J Clin Nutr. 1997;51(3):129–33.
86. Goldfield GS, Cloutier P, Mallory R, Prud'homme D, Parker T, Doucet E. Validity of foot-to-foot bioelectrical impedance analysis in overweight and obese children and parents. J Sports Med Phys Fitness. 2006;46(3):447–53.
87. Lu K, Quach B, Tong TK, Lau PWC. Validation of leg-to-leg bio-impedance analysis for assessing body composition in obese Chinese children. J Exerc Sci Fit [Internet]. 2003;1(2):97–103.
88. Meredith-Jones KA, Williams SM, Taylor RW. Bioelectrical impedance as a measure of change in body composition in young children. Pediatr Obes. 2014;10(4):252–9.
89. Ohta M, Midorikawa T, Hikihara Y, Sakamoto S, Kawakami Y, Fukunaga T, et al. Body mass-to-waist ratio strongly correlates with skeletal muscle volume in children. PLoS One. 2017;12(5):1–13.
90. Thivel D, Verney J, Miguet M, Masurier J, Cardenoux C, Lambert C, et al. The accuracy of bioelectrical impedance to track body composition changes depends on the degree of obesity in adolescents with obesity. Nutr Res [Internet]. 2018;54:60–8.
91. Eisenkölbl J, Kartasurya M, Widhalm K. Underestimation of percentage fat mass measured by bioelectrical impedance analysis compared to dual energy X-ray absorptiometry method in obese children. Eur J Clin Nutr. 2001;55(6):423–9.

Chapter 4 The Relative Contribution of Adiposity and Muscularity to Metabolic Function in Children with Obesity

4.1 Preface

This chapter is part of an ongoing research project titled "A model of metabolic load-capacity in pediatric obesity: Implications for metabolic health and interactions with gut microbiota", which has received research ethics approval from the University of Alberta Research Ethics Board (No. 00082135). Within this research project, Dr. Andrea M. Haqq, Dr. Carla M. Prado, and I contributed to formulating the research questions, study design, and implementation. I was also responsible for ethics application, participant recruitment, and data collection.

This chapter includes a preliminary analysis of data collected from 31 participants who have completed the research project to date. I was responsible for the statistical analysis with continued support from Dr. Mohammadreza Pakseresht and Dr. Maria Ines Barreto Silva. I additionally interpreted the results and wrote the first draft of the manuscript with ongoing discussions with my supervisors, who were also responsible for critically reviewing the final version.

4.2 Introduction

Children with obesity are at an increased risk to develop cardiometabolic diseases (1). Despite having high body mass index (BMI), some children interestingly exhibit a metabolically healthy phenotype (2). Physical activity, diet, and inflammation were shown to play a role in disease development (2-4). Since adipose tissue and skeletal muscle are essential organs involved in homeostasis maintenance, body composition could also be a contributing factor to metabolic health (5). In fact, there is evidence indicating that excess whole-body and ectopic adiposity impairs glucose metabolism, hormonal function, and immunity (6-8). On the other hand, functional skeletal muscle (i.e. free of intramuscular fat and fibrous tissue) contributes to glucose uptake and storage, movement production, and is also a reserve of amino acids (9). Thus, adults and children with low muscle mass (or sarcopenia) also present with increased risk for metabolic dysfunction (10-11).

Body mass index has been used as a predictor of metabolic health. However, it presents with limitations at the individual level due to its inability to distinguish between different body components (12). Indeed, adults with obesity had a high variability in muscularity within similar BMI values (13). The model of metabolic-load capacity has been, therefore, proposed to explain the relative contribution of adiposity and muscularity to physiological function (14). It has been reported that adults with greater load-capacity index (LCI) have increased risk of high cholesterol and metabolic syndrome (MetS) (15, 16). Whether the model of metabolic-load capacity applies to the pediatric population is unknown. A previous study has shown that adolescents with obesity who have a phenotype of concurrent low muscle and high fat mass (FM) had higher MetS z-score, triglycerides (TG), insulin resistance (IR) and systolic blood pressure (SBP) than those with obesity or low muscle mass alone (17). Therefore, the LCI may be a useful index to distinguish metabolic health also in pediatrics (5).

Several techniques are currently available for body composition assessment in children with obesity (18). Air-displacement plethysmography (ADP) is a non-invasive technique that estimates whole-body FM and fat-free mass (FFM) based on body density. To clarify, FFM is composed of skeletal and non-skeletal muscles, bone, organs, and connective tissues (19). In contrast, ultrasound (US) can be used to assess segmental body composition and it provides direct measurements of skeletal muscle thickness and muscle cross-sectional area (mCSA) (20). Evaluation of muscle echo intensity (mEI) is also possible with some US equipment, which is

often used as a surrogate of muscle "quality". Both techniques can be used in the pediatric population to understand how different body compartments are related to metabolic risk factors.

The objectives of the present study were to evaluate the extent to which body composition, including the LCI, varied among degrees of obesity (as defined by BMI for age and sex [BMI z-score]) and metabolic health status in children with obesity. We also investigated the relationship between body composition parameters (whole-body and segmental) and markers of metabolic dysfunction. We hypothesized that children with similar BMI z-score values would exhibit a high variability in adiposity, muscularity, and LCI. Based on previous literature, ranges of fat mass index (FMI) and fat-free mass index (FFMI) would vary 40% and 20% within BMI z-score categories, respectively (12). Furthermore, we predicted that children with an unfavourable metabolic profile would have lower muscularity and a higher LCI compared to those who were metabolically healthy. As such, adiposity and LCI by ADP and US would associate with markers of metabolic dysfunction positively, while muscularity would associate negatively.

4.3 Methods

4.3.1 Study Population

This analysis includes data from 31 children who participated in the *Metabolic Load-Capacity study*, an ongoing cross-sectional study evaluating the associations between body composition phenotypes and cardiovascular risk factors in children with obesity. Participants were recruited from September 2018 to February 2020 at two sites of the Pediatric Centre for Weight & Health and pediatric community in Edmonton, AB, Canada. Children aged 10 to 16 years with a BMI at or above the 95th percentile for age and sex were eligible for this study (21). Exclusion criteria for children included diagnosis of conditions associated with impaired muscle mass, chronic diseases leading to obesity, acute infections, medication known to influence body composition (e.g. metformin, corticosteroid), or being pregnant or lactating. The study was approved by University of Alberta Health Research Ethics Board (Pro00082135). Informed consent and assent were obtained from all parents and children, respectively.

4.3.2 Experimental Design

Children accompanied by their parents attended two study visits at the University of Alberta. During the first study visit, demographic and clinical information were collected. Participants also received an accelerometer, study forms to be completed at home, and

instructions on how to adequately record study information. The second study visit was held in the morning after an overnight fast, at least seven days apart of visit 1 (median days between visits=11). Children were asked to abstain from high intensity physical activity for 24 hours and water consumption for 4 hours prior to the visit. After participants arrived in the research unit, study forms were reviewed for completeness and consistency. Then a trained researcher (CEO) assessed child's blood pressure, anthropometrics, handgrip strength (HGS), and body composition. Following these procedures, a certified phlebotomist performed a blood draw for analysis of metabolic biomarkers.

4.3.3 Demographics and Clinical Variables

Participants provided demographic information on age, sex, and race/ethnicity. For purpose of analysis, the child's race/ethnicity was categorized as White, Indigenous, and others (e.g. Latino, Black, Arabic). Parents then completed a medical history questionnaire, reporting child's gestational age and birth weight at delivery, birth mode, feeding practices during the first year of life, current medication use and health status as well as family history of diseases. Exclusive breastfeeding was defined as when the infant received only human breast milk for ≥3 months (22). Children self-reported their sexual maturation by assessing the development of genitals, breasts, and pubic hair using standard descriptions and drawings (23). Children were classified into pre-early (Tanner stages 1 and 2) and mid-late (Tanner stages 3 to 5) pubertal groups (24). Preterm birth was defined as gestational age less than 37 weeks. Size for gestational age was calculated in PediTools using the 2013 Fenton growth charts (25).

4.3.4 Anthropometrics

All anthropometric and body composition measurements were performed on the same day by the same trained researcher. Before testing, children were asked to void their bladder, wear a tight-fitting bathing suit, and remove their shoes. Weight was measured to the nearest 0.1 kg using a calibrated scale coupled to the ADP equipment. Height was measured to the nearest 0.1 cm using a wall-mounted stadiometer. Body mass index z-score was computed using the WHO Anthroplus software (v.1.0.4, Geneva, Switzerland). Waist circumference (WC) and hip circumference were included as an amendment of the original study protocol and measured in triplicate using a non-elastic flexible anthropometric tape (to nearest 0.1 cm) at the narrowest site between the xiphoid process and iliac crest and at the widest part of the hips, respectively (26). Waist percentiles and z-scores were computed using the Anthropometric Calculator for normal

children 0–19 years of age (version: 2019/01/22), based on the World Health Organization (WHO) Growth Charts for Canada. Abdominal obesity was characterized as WC ≥90th percentile for age and sex (27). Waist-to-hip ratio (WHR) and waist-to-height ratio (WHtR) were calculated as WC (in cm) divided by hip circumference (in cm) and height (in cm), respectively.

4.3.5 Air-displacement Plethysmography

Body composition was estimated using ADP (Bod Pod® 1SB-060M, Life Measurement Instruments, Concord, CA, United States) according to the manufacturer's instructions. Calibration was performed prior to each testing. Children were asked to wear an acrylic swimming cap to avoid isothermal air trapped by hair. Thoracic gas volume was predicted using a standard predictive equation based on age, sex, and height (28). From body volume measures and density calculations, percent body fat (%BF) was predicted using the Lohman equation (constants were based on age and gender) and FFM was calculated by subtracting FM from total body weight (29). Fat mass in kilograms were retrieved from the ADP analysis report. Comparison of the ADP derived %BF using the Lohman equation to a gold standard four compartment model demonstrated high agreement between methods in overweight and obese adolescents (30). The mean difference between methods was -0.04±3.6 % for body fat with standard error of estimates (SEE) of 1.81% (30). The LCI by ADP was then calculated as FM (in kg) divided by FFM (in kg).

4.3.6 Ultrasound

Children were positioned in a supine position on an exam bed for 10 minutes to allow fluid redistribution. While the participant was resting, a trained researcher landmarked the measurement site on the anterior aspect of the right thigh by locating the mid point between the anterior superior iliac spine and superior border of the patella (thigh length) (31). Only one participant had the left thigh assessed (due to injuries on the right leg occurred at a younger age). Ultrasound measurements were obtained by the same trained researcher using a B-mode US (4.2–13 MHz linear array probe, NextGen LOGIQ™ *e* US system, GE Healthcare). To achieve acoustic coupling, a water-soluble gel was applied between the US probe and skin and three sets of triplicate images were taken with minimal compression of measurement site (32). First, the probe was placed in the axial plane to capture images for mEI analysis (depth 4-9 cm). Then mCSA of the rectus femoris muscle was obtained using the panoramic mode and sliding the US probe across the thigh on the transverse plan. To acquire subcutaneous adipose tissue (SAT) and

muscle thickness, the probe was placed in the sagittal plane. Ultrasound settings were maintained consistent across participants (frequency: 12 MHz; gain: 45 dB; dynamic range: 69 Hz), except for scanning depth that was individualized due to differences in the thickness of tissues.

An image processing software (ImageJ, v.1.52A; National Institutes of Health, USA) was used to analyze the images. Muscle echo intensity was determined by manually drawing a region of interest within the rectus femoris muscle and using the histogram function (33). Echo intensity was corrected for SAT thickness (uncorrected mEI + [SAT in cm x 40.5278]) (34). Cross sectional area of the rectus femoris muscle was manually traced using the freehand selection function. Thickness of SAT was assessed by drawing a perpendicular straight-line between the skin interface and muscle interface (epimysium of rectus femoris) on the left and right sides of the image and averaging them (32, 33). The same procedure was used to assess muscle thickness; the perpendicular distance from the superior aspect of the rectus femoris to the posterior aspect of the vastus intermedius (total skeletal muscle [SM] thickness). The ratio of SAT to SM thickness was also used to calculate the LCI by US. Furthermore, SAT and SM thickness were also expressed relative to thigh length to account for differences in body size.

4.3.7 Muscular Strength

A hydraulic handgrip dynamometer (Jamar Technologies, Horsham, PA) was used to measure HGS. Children were sitting in a chair with the shoulder adducted, the elbow flexed in a 90° angle, forearm positioned on an armrest with the thumb facing upwards (35). Participants were then asked to squeeze the dynamometer as hard as possible, alternatively with their right and left hand. Three measures with each hand (right and left) were taken, and a 1-minute break between measures was given to avoid the effects of muscle fatigue. The highest score achieved by the right and left hand was recorded in kilogram.

4.3.8 Total Body Potassium

Total body potassium (TBK) was assessed using a whole-body potassium counter with a single sodium iodide crystal detector (Model 2260; Accuscan, Canberra Industries, Boston, MA, USA). Environmental background check was performed monthly during the test period, and calibration and background check were conducted within one-hour prior testing. Children were asked to lie supine on a bed, which moved automatically under the detector tower for a 45-minute counting scan to determine the activity of K^{40}. Total body potassium was then calculated using the following equation: [TBK (g) = ((((Measured activity of K^{40} x Half-life of K^{40})/Decay

Constant of K^{40}))/Avogadro's number) x Molar Mass of K^{40})/Abundance of K^{40}], where half-life of K^{40} was considered to be 1.248×10^{9} years, Avogadro's number was considered to be 6.02×10^{23}, decay constant was considered to be 1.72×10^{-17} s^{-1}, molar mass of K^{40} was considered to be 39.964 g/mol, abundance of K^{40} was considered as 0.0117%.[4]. Total body potassium was also converted to mmol {TBK (mmol) = [TBK (g)/39.098] x 1,000} and body cell mass calculated [BCM (kg) = 0.0092 x TBK (mmol)] (36). The precision of the TBK is 3.76% for repeated measures in whole-body phantom, as per manufacturer's specifications.

4.3.9 Physical Activity and Diet Assessment

Physical activity was measured using accelerometry (4MB GT3X, Actigraph, Pensacola, FL, USA), with epoch length set at 5 seconds. Children were instructed to wear the device on their right hip attached to a belt over seven consecutive days during all waking hours (except while bathing, showering, or swimming). Using the ActiLife6 software (v.6.13.4; ActiGraph, LLC, Pensacola, FL), data was downloaded and screened for compliance; those with a minimum of 10 h wear time on at least three days were retained for analysis. Accelerometry data was categorized into three intensity levels using the cut-points proposed by Evenson: sedentary behaviour, and light intensity and moderate plus vigorous physical activity (MVPA) (37). Time spent in each category was reported in minutes and as proportion of total wear time. Children with less than 60 minutes spent in MVPA was considered as not meeting the physical activity recommendations (38).

Children completed a 3-day dietary record over two weekdays and one weekend day. Participants were instructed on how to record dietary intake and measure food proportions; food records were reviewed with children and their parents upon return to ensure completeness. Average daily macronutrients intake (protein, carbohydrate, and fat) and total energy intake were determined using Food Processor SQL (v. 11.0.124, ESHA Research), with the Canadian Nutrition File database as the main source for obtaining food nutrient content. The United States Department of Agriculture Nutrient database or manufacturer's food labels were also used when food nutrient content was not available. The average daily intake of macronutrients per 1,000 kcal was used to calculate nutrient density (39). The Acceptable Macronutrient Distribution Ranges (AMDR, as percent of energy) for carbohydrate, fat and protein were 45-65%, 10-30%, and 25-35%, respectively (40). The Adequate Intake of total fiber was defined using the age and

sex appropriate dietary reference intakes (males aged 9-13 years = 31g/day; males aged 14-18 years = 38 gm/day; female aged 9-18 years = 26 g/day; Institute of Medicine, 2002) (40).

4.3.10 Metabolic Markers

Blood samples were collected in the morning after a 12-hour overnight fast into silicone-separator gel tubes (for serum) and EDTA tubes (for plasma). Plasma samples were centrifuged immediately after collection, whilst serum samples were allowed to clot for 30 minutes; supernatants were stored at -80 C until time of assay. Total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), TG, glucose, and high-sensitivity c-reactive protein (hs-CRP) were analyzed in a core laboratory using serum samples. Total cholesterol and TG were assayed using enzymatic methods on a Siemens Atellica system (CV <2% and <3%, respectively). High-density lipoprotein cholesterol was analyzed using an elimination/catalase procedure also in a Siemens Atellica system (CV <2%). Glucose and hs-CRP were analyzed using immunoassay (Abbott Architect analyzer, CV = <5%; and Siemens Atellica system, CV = <3%, respectively). Plasma concentrations of insulin, interleukin-6 (IL-6), and tumor necrosis factor alpha (TNF-α) were assessed at the University of Alberta. Plasma IL-6 (CV 10.4%, assay range: 3.1–300 pg/mL), and TNFα (CV 14.7%, assay range: 15.6–1000 pg/mL) were measured using manual ELISA kits (R&D Systems Quantikine, USA). Glucose and insulin were used to assess the homeostatic model assessment of IR (HOMA-IR = fasting insulin [mU/ml] X fasting glucose [mmol/L]/22.5) (41). Recent data on glucose and lipid profile were obtained from electronic medical records (±10 months) for those participants who did not complete the blood draw at the time of the study or had the sample analysis delayed by the core laboratory due to COVID-19.

After a 5 to 10-minute rest in a seated position, systolic (SBP) and diastolic blood pressure (DBP) were measured in triplicate on the right arm using an automated blood pressure monitor (ADView, New York, USA). Average blood pressure was then converted to percentiles for age, sex, and height (42).

4.3.11 Classification of Metabolic Risk Factors

To our knowledge, there is no established consensus on the definition of metabolic health in children with obesity (43). We therefore explored metabolic health by evaluating the presence of single (i.e. dyslipidemia, impaired fasting glucose, IR, or hypertension) and clustered (i.e. MetS) metabolic risk factors. In addition, we classified children with obesity as metabolically healthy (MHO) or metabolically unhealthy (MUO) (44).

Standard cut-point values provided in the 2012 National Heart, Lung, and Blood Institute Expert Panel Report were used to define lipid profile (45). Dyslipidemia was characterized if participant presented with abnormally high low-density lipoprotein cholesterol (LDL-C; ≥130 mg/dL) or TG levels (≥130 mg/dL), an abnormally low HDL-C level (<40 mg/dL) or was taking medication(s) for dyslipidemia. Impaired fasting glucose was defined as serum fasting glucose level equal or greater than 100 mg/dL. Children with HOMA-IR >3.16 (41) were characterized as having IR. Blood pressure levels were classified as normal, elevated, or hypertension according to the American Academic of Pediatrics guidelines (46). The definition of MetS proposed by the International Diabetes Federation (IDF) was used as a clustered metabolic risk factor (47). According to the IDF, children with abdominal obesity (WC ≥90 percentile) and two or more of the following were classified as having MetS: high TG (≥150 mg/dL), low HDL-C (<40 mg/dL), high blood pressure (systolic ≥130/diastolic ≥85 mm Hg), glucose ≥100 mg/dL.

According to Damanhoury et al., children with at least one of the following risk factors were categorized into the MUO group: HDL-C ≤40 mg/dL, TG >150 mg/dL, SBP and DBP ≥90th percentile, and abnormal measure of glycemia (glucose >100 mg/dL) (44). Children presenting with zero of these metabolic risk factors were considered as MHO.

Because there are no established cut-points or normal range for inflammatory mediators (i.e. hs-CRP, IL-6 and TNF-α) (48), we described these inflammatory biomarkers in the study population and compared individuals between study groups.

4.3.12 Statistical Analysis

Continuous data are described using median and interquartile range (IQR, 25th-75th percentile) due to the small sample size; categorical data are described using frequency and percentage. Differences between continuous variables among sex and sexual maturation groups were analyzed using the Mann Whitney U-test. The Chi-square or Fisher's exact test were used to evaluated differences between categorical variables, as appropriate. Participants were categorized into three BMI z-score categories (BMI <3SD, BMI ≥3 and <4SD, and BMI ≥4SD); the Kruskall Wallis test was used to assess differences in body composition parameters across these categories.

Data was checked for normality using the Shapiro-Wilk test, and logarithmic transformation was employed for variables not normally distributed. The Pearson (r) or Spearman (r_s) correlation tests were then used, as appropriate, to examine the correlation among

continuous variables. As there were no differences between sex for most of the body composition parameters, multivariate regression analyses were performed adjusting for sexual maturation. Muscle echo intensity was further included as a covariate in the analyses to account for the potential effects of ectopic fat deposition on muscles in the associations between variables depicting muscularity and HOMA-IR. We also investigated the effects of race/ethnicity (White vs. non-White) on these associations.

As an exploratory analysis, we additionally investigated differences in body composition and metabolic markers between children with high and low LCI by ADP and US. Sex-specific medians of LCI by ADP and US derived from the descriptive analysis were used for group stratification, and comparisons were made by employing the Mann-Whitney U test. Children with low and high LCI were further stratified by sexual maturation, and a one-way ANOVA with Bonferroni post hoc analysis or Kruskall Wallis test were used to evaluate differences in metabolic markers between subgroups, as appropriate. We also compared children with high and low mEI; median of overall group was used as a cut-point. Differences in metabolic markers were assessed using the Mann-Whitney U-test. A p-value <0.05 was considered to be statistically significant. Data was analyzed using IBM SPSS Statistics, version 24 (IBM Corp., Armonk, NY, USA).

4.4 Results

4.4.1 Overall Demographics, Clinical, and Lifestyle Characteristics

Characteristics of the 31 children (51.6% males) who have completed the study to date are summarized in **Table 4.1**. Males and females presented with similar age, sexual maturation, and race/ethnicity. Most children (87.1%) were born with gestational age ≥37 weeks; for those born preterm (12.9%), their size was appropriate for gestational age. About 32% of children presented with a history of jaundice during early infancy, and exclusively breastfed children were weaned at a median age of 13 months (IQR, 6.9-18.5). A family history of hypertension and diabetes mellitus was frequently described by participants (71.0% and 64.5%, respectively). At the time of the study, 54.8% children were taking medications. Most children were on central nervous system stimulant drugs (19.4%) for attention deficit hyperactivity disorder (ADHD) treatment; other drug classes included selective serotonin reuptake inhibitor (6.5%), aminoketone (i.e. bupropion; 3.2%), and tricyclic antidepressant (3.2%) for depression treatment or combination therapy (6.5%) for psychological disorders.

Children spent 75.6% (70.0-82.8%) of the accelerometer wear time in sedentary behaviours, 19.3% (13.3-24.7%) in light intensity physical activity, and 5.0% (3.5-6.6%) in MVPA. Although most children (90.3%) did not meet the recommendations for daily MVPA (≥60 minutes/day), males spent greater time in MVPA than females ($p = 0.014$). Accelerometer wear time was similar between sexes ($p = 1.000$). Dietary data was available for most children; only one participant did not complete the 3-day food record. Median macronutrient composition of the diet was 49.2% of energy from carbohydrates, 33.6% from fat, and 16.7% from protein. Most participants had macronutrient intake within the AMDR; however, 38.7% and 9.7% of children had macronutrient intake above the reference values for fat and carbohydrate, respectively. Macronutrient density (i.e. amount of nutrients per 1,000 kcal consumed) was comparable between males and females ($p = 0.473$-0.854). Furthermore, median total fiber intake was 16.4 g/day, and only 6.5% of the participants met the Adequate Intake recommendations for total fiber (range = 31.0-32.9 g/day).

Data on glucose and lipid profile were available for 28 children; of these, 17.9% had data obtained from medical records as children were unable to complete blood draw ($n = 2$) or analysis at a core laboratory was not possible at the time of the study ($n = 3$). For these participants, the median time between blood analysis reported on records and second study visit was 3.7 months (range 0.3 to 9.3 months). As hs-CRP data was not available from medical records, this variable was included for 23 participants.

4.4.2 Body Composition, Anthropometric, and Muscular Strength Characteristics

Children within the same BMI z-score category presented with a large variability in FMI, FFMI, and LCI by ADP (**Figure 4.1**). In fact, some children in the lowest degree of obesity had body composition similar to those in higher BMI z-score categories. Compared to children with BMI z-score <3 SD, children with the greatest obesity degree (BMI z-score ≥4 SD) had higher FMI ($p = 0.001$), FFMI (0.004), and LCI by ADP ($p = 0.005$); however, no differences were seen between those children with BMI z-score ranging from 3 SD to 4 SD.

Children with higher FM had also greater FFM ($r_s = 0.764$), SAT/thigh length ($r_s = 0.628$), mCSA ($r_s = 0.807$), mEI ($r_s = 0.629$), BMI z-score ($r_s = 0.806$), WC z-score ($r_s = 0.835$), and muscular strength (right HGS: $r_s = 0.571$; left HGS: $r_s = 0.536$), all $p \leq 0.002$. Ultrasound measures of SAT thickness were available for 25 children; SM thickness and mEI were not computed for one participant due to poor quality of the US images. Anthropometrics and body

composition (by ADP and US) did not differ between sex groups, with the exception that males presented with a greater BMI z-score (p = 0.049) than females (**Table 4.2**). Mid-late pubertal males had greater FFM (p = 0.008) and FFMI (p = 0.026) than those at pre-early puberty (**Table B1; Appendix B**), but similar levels of adiposity. In contrast, mid-late pubertal females had greater FM (p = 0.003), %BF (p = 0.038), FMI (p = 0.010), FFM (p = 0.015) than pre-early pubertal females; mCSA was the only muscle parameter assessed by US that was higher in females at more advanced pubertal stages (p = 0.005). No sex differences within each sexual maturation stage or race/ethnicity groups were found. Data on TBK and body cell mass are given on **Table 4.2**, but comparisons between sexes were not possible due to the limited number of children (n = 6, 19.4%) who have completed the test from the date the device was acquired (halfway through the study). Furthermore, muscular strength was greater in males than in females (right HGS: p = 0.045; left HGS: p = 0.027; **Table 4.2**), mid-late pubertal males than mid-late pubertal females (p = 0.036), and mid-late pubertal males versus pre-early pubertal males (p=0.050; **Table B1**).

4.4.3 Differences in Body Composition and Muscular Strength in Children With vs. Without Metabolic Dysfunction and Relationships with Metabolic Markers

4.4.3.1 Insulin Resistance

Of the included children, 54.8% had IR (**Table 4.3**). Children with IR had greater FFM (p = 0.013) and FFMI (p = 0.019) than children without IR; differences between sexes were not observed in children with IR (**Table B2**). Compared to females without IR, females with IR had greater FFM (p = 0.034) and muscular strength (right HGS: p = 0.011; left HGS: p = 0.034), but lower IL-6 concentrations (p = 0.011). In further analysis stratified by race/ethnicity among those with IR, we found that non-White children had greater FFMI, SAT/thigh length, mCSA, and mEI than White children (data not shown; all p <0.04).

Higher HOMA-IR was moderately correlated with greater FMI, FFMI, SAT/thigh length, mCSA, mEI, and muscular strength (**Table 4.4**). These associations remained significant when sexual maturation was included as a covariate, except for SAT/thigh length (**Table 4.5**). The greatest association was observed between HOMA-IR and FFMI; for each unit increase in FFMI there was a 0.49 unit increase in HOMA-IR (p = 0.002). These associations were also independent of race/ethnicity, but lost significance after further adjustment for mEI (data not shown). We additionally tested for the effects of abdominal obesity on the association between

mEI and HOMA-IR and found that including WC in the model as an additional covariate did not alter the association (R^2 = 0.49; β = 0.03; 95%CI = 0.001, 0.067; p = 0.044).

4.4.3.2 Dyslipidemia

More than 51% of children presented with dyslipidemia. Body composition and muscular strength did not differ between children with versus without dyslipidemia for the overall group, as well as dietary intake and physical activity (**Table B3**). Females with dyslipidemia had greater LCI by US (p = 0.026), and smaller mCSA (p = 0.041) than females without dyslipidemia. Among children with dyslipidemia, those who were at mid-late puberty had greater FM (p = 0.019), FFM (p = 0.013), and muscular strength than children in pre-early puberty (right HGS: p = 0.027; left HGS: p = 0.009).

Moderate and positive correlations were observed between LDL-C and LCI by US as well as mEI (**Table 4.4**). After adjusting for sexual maturation, a unit increase in LCI by US and mEI were associated with a 51.43 mg/dL and a 0.28 mg/dL higher LDL-C, respectively (**Table 4.5**). Adjusted analyses also revealed positive associations of LDL-C with LCI by ADP and SAT/thigh length; however, no relationships between HDL-C, TG and body composition indices were observed (data not shown).

4.4.3.3 Hypertension

Children with hypertension comprised of 38.7% of the sample. No differences in body composition, muscular strength, dietary intake, and physical activity between children with versus without hypertension were observed (**Table B4**). Likewise, body composition and muscular strength were similar between sexes. During mid-late puberty, children with hypertension presented with greater FM (p = 0.020), %BF (p = 0.048), FMI (p = 0.010), FFMI (p = 0.037), LCI by ADP (p = 0.030), and mCSA (p = 0.030) than children without hypertension.

Higher SBP and DBP were moderately correlated with greater FFMI, SAT/thigh length, mEI, and LCI by US (**Table 4.4**). Multivariate regression analysis revealed that DBP was positively associated with FFMI and LCI by US (**Table 4.5**). In contrast, higher SM thickness was correlated with lower DBP in unadjusted analysis only.

4.4.3.4 Metabolic Syndrome

Almost 13% of participants presented with MetS as defined by IDF. Compared to those without MetS, children with MetS had greater whole-body FM and FFM (absolute and adjusted by height; p <0.03) as well as mCSA (p = 0.035) at the midthigh (**Table B5**). Children with

MetS also showed higher LCI by ADP ($p = 0.023$) and US ($p = 0.014$) than children without MetS. Furthermore, children with MetS had greater absolute values of WC than children without MetS (112.0 [102.0-118.1] vs. 87.0 [82.5-94.8] cm; $p = 0.016$). No differences were observed for physical activity and dietary intake between the two groups. Given the small sample of participants with MetS, it was not possible to evaluate differences in sex or sexual maturation differences.

4.4.3.5 Metabolic Unhealthy Obesity

Most children were classified with MUO (83.9%). Those children with MUO had a greater LCI by US ($p = 0.012$) than children with MHO (**Table B6**). No other differences in body composition, physical activity, and dietary intake between MUO and MHO were found. Furthermore, males and females with MUO had comparable values for all these variables. In children with MUO and at mid-late puberty compared to pre-early puberty presented, respectively, with greater FM ($p = 0.001$), FMI ($p = 0.020$), FFM ($p <0.001$), FFMI ($p = 0.002$), mCSA ($p = 0.004$), muscular strength (HGS right: $p = 0.011$; HGS left: $p = 0.008$), time in sedentary behaviours ($p = 0.027$), but lower time in light intensity physical activity ($p = 0.027$).

4.4.3.6 Inflammation

Positive correlations between hs-CRP and FMI, FFMI, LCI by ADP, mCSA, SAT/thigh length and mEI were also observed (**Table 4.4**). These associations remained significant after adjusting for sexual maturation (**Table 4.5**). Body composition parameters were not associated with IL-6 or TNF-α.

4.4.4 Analysis Stratified by Load-Capacity Index

Load-capacity index by ADP was strongly correlated with LCI by US ($r_s = 0.702$, $p <0.001$), and both LCI by ADP and US were correlated with WC z-score ($r_s = 0.851$, $p <0.001$; $r_s = 0.547$, $p = 0.007$; respectively), and mEI ($r_s = 0.729$; $r_s = 0.878$; respectively, all $p <0.001$).

As expected, children with high LCI by ADP had greater FM, %BF, and FMI than children with low LCI (all $p <0.001$) (**Table 4.6**). Although FFM was also greater among those with high LCI ($p <0.001$), FFMI was similar between LCI groups ($p = 0.140$). Higher values of variables depicting abdominal obesity (i.e. WC z-score and WHtR) were also observed in children with high LCI. Regarding markers of metabolic dysfunction, children with high LCI had greater HOMA-IR (and above the reference normal range) than children with low LCI ($p = 0.041$). At the individual level, however, children with IR were found across all the LCI values

(**Figure 4.2**). Both males and females with high LCI had greater hs-CRP than children with low LCI ($p = 0.026$; $p = 0.006$, respectively), but no differences for IL-6 ($p = 0.401$) and TNF-α ($p = 0.077$) were observed. Moreover, females with high LCI had greater mEI ($p = 0.013$) than females with low LCI. On the other hand, females with low LCI spent greater time in light intensity physical activity ($p = 0.028$) than females with high LCI. Children with high LCI had also greater WC percentile than children with low LCI ($p = 0.004$).

Children with low and high LCI by ADP were further stratified by sexual maturation, and a one-way ANOVA was used to evaluate differences in metabolic markers between subgroups (**Figure 4.3**). Concentrations of HOMA-IR ($F[3, 24] = 4.26$, $p = 0.015$), hs-CRP ($F[3.19] = 7.09$, $p = 0.002$), and TNF-α ($F[3, 24] = 3.19$, $p = 0.042$) differed between subgroups; mEI was also different ($F[3,20) = 6.608$, $p = 0.003$). A Bonferroni post hoc test revealed that mid-late pubertal children with high LCI had greater HOMA-IR ($p = 0.041$) and hs-CRP ($p = 0.022$) than pre-early pubertal children with low LCI. On the other hand, children at more advance pubertal stages (but with low LCI) had lower concentrations of inflammatory markers (hs-CRP: $p = 0.041$; TNF-α: $p = 0.033$) than pre-early pubertal children with high LCI.

At the midthigh level, children with high LCI by US had higher SAT/thigh length ($p = 0.002$), SM ($p = 0.009$), and mEI ($p < 0.001$) than children with low LCI (**Table 4.6**). However, mCSA was similar between groups ($p = 0.361$). Greater muscular strength was observed in children with high LCI compared to low LCI (right HGS: $p = 0.015$; left HGS: $p = 0.007$), but no differences in physical activity and dietary intake were found. Furthermore, children with high LCI by US had higher LDL-C concentrations than children with low LCI ($p = 0.002$). Analysis further stratified by sexual maturation revealed differences in HOMA-IR ($\chi^2[3] = 9.37$, $p = 0.025$), LDL-C ($\chi^2[3] = 10.79$, $p = 0.013$), mEI ($\chi^2[3] = 14.02$, $p = 0.003$), and muscular strength ($\chi^2[3] = 8.31$-8.80, $p = 0.032$-0.040). Mid-late pubertal children with high LCI had greater HOMA-IR than pre-early pubertal children with high LCI ($p = 0.044$) as well as greater mEI than pre-early pubertal children with low LCI ($p = 0.010$) and mid-late pubertal children with low LCI ($p = 0.049$) (**Figure 4.4**). In contrast, LDL-C concentrations were higher among pre-early pubertal children with high LCI than children at more advanced pubertal stages with low LCI.

4.4.5 Analysis Stratified by Muscle Echo Intensity

We also compared markers of metabolic dysfunction among children exhibiting high vs. low mEI (using the median value from the overall sample as a cut-point), given that this muscle

parameter showed moderate correlations with several metabolic markers. Regarding metabolic health, children with high mEI had higher LDL-C ($p = 0.036$) and TNF-α ($p = 0.030$) concentrations than children with low mEI. Furthermore, differences were also observed for body composition indices and muscular strength; children with high mEI had greater FMI ($p = 0.002$), FFMI ($p = 0.028$), LCI ($p = 0.003$), and muscular strength (right HGS: $p = 0.045$).

4.5 Discussion

This study shows considerable variability in individual body composition parameters within each BMI z-score category in children with obesity. Consistent with previous literature, our findings highlight the limitation of BMI z-score in depicting fat and muscle mass (12). To our knowledge, this study is the first to test the metabolic load-capacity model in children with obesity. We found that HOMA-IR was higher (and above the reference range) in those with high versus low LCI ($p = 0.041$); however, there was a large individual variation in the range of LCI within IR status. Children with MetS and MUO also had greater LCI than healthy children ($p \leq 0.023$), but no body composition differences were found between dyslipidemia or hypertension status. These results suggest that a higher LCI may be characteristic of IR or a more detrimental metabolic condition at the group level (but not at the individual level), in which several risk factors (i.e. dyslipidemia, hypertension, and abdominal obesity) are clustered together.

Contrary to our hypothesis, children with MetS or IR had greater FFMI than healthy children. Although only 17.5% of the children and adolescents included in a study by Weber et al. had obesity, similar findings were reported (49); participants with MetS exhibited greater lean soft tissue adjusted to height (by dual-energy X-ray absorptiometry [DXA]) than those who were metabolically healthy. Despite no differences in muscularity were found across hypertension status, we observed positive associations between muscle mass and blood pressure. It is possible that greater muscles contribute to blood pressure by increasing total cardiac output, given the higher metabolic demand of skeletal muscles compared to other tissues (nearly 25% of all cardiac output) (50, 51). We also found that HOMA-IR was positively associated with muscle parameters (i.e. FFMI, mCSA, and muscular strength) to a greater extent than whole-body adiposity (i.e. FMI). As skeletal muscle is known to contribute to the maintenance of glucose homeostasis (52), we expected to observe a negative relationship between measures of muscle quantity and IR. Nevertheless, previous studies have suggested a role of muscle ectopic fat deposition in the development of IR and diabetes mellitus (53-55).

We therefore investigated the associations between muscle parameters and HOMA-IR adjusted for the effects of mEI, or functional muscle mass, and observed that these associations did not remain significant. In fact, higher mEI was associated with greater HOMA-IR, which is consistent with the literature (53, 54). For example, Lee et al. reported a negative association between intramuscular adipose tissue (by magnetic resonance imaging, MRI) and insulin sensitivity (by the euglycemic clamp technique) in males with obesity (age range = 12.4-18.1) (53). Similarly, Sinha et al. found that higher intramyocellular lipid content (assessed by ^{1}H nuclear magnetic resonance spectroscopy) was also associated with lower insulin sensitivity in the soleus muscle of children with obesity (54). Thus, children with obesity and IR had lower muscle "quality" rather than muscle "quantity", supporting the evidence that intramuscular fat is related to prediabetes (55).

The mechanisms explaining the crosstalk between fat infiltration in muscles and IR are not completely clear. It has been suggested in human and animal studies that ectopic fat, through the excess of fat-free acids release, triggers inflammation and challenge insulin signaling in muscles (56). Even in normoglycemic adolescents with obesity, the negative association between muscle insulin sensitivity and intramyocellular lipids in the soleus muscle ($r = 0.515$; $p < 0.05$) was mediated by fat-free acids concentrations ($r = -0.680$; $p < 0.001$) (57). In our study, we found that higher mEI was associated with greater hs-CRP, a surrogate of generalized inflammation, but not with TNF-α and IL-6. These former pro-inflammatory cytokines are responsible for regulating the metabolism of lipids in adipose cells and are also implicated in insulin signaling in muscles (58, 59). Despite this, Weiss et al. reported that children with obesity had similar levels of IL-6 and fat-free acids across IR status (60). Moreover, inflammation in skeletal muscle can contribute to muscle degradation, determining the sarcopenic phenotype (61). It could be argued that children in our study have not yet triggered substantial degradation in whole-body muscle mass. As revealed by the analysis stratified by LCI and sex maturation, children with high LCI by ADP and at more advanced pubertal stages had greater HOMA-IR and inflammation than pre-early pubertal children with low LCI. These findings also suggest that older children with high LCI are at an increased risk to develop diabetes than younger children with low LCI.

Despite previous studies also reported a greater visceral adiposity in children with IR compared to those with insulin sensitivity, we found similar values for the variables depicting abdominal obesity (i.e. WC absolute and adjusted for age, sex, and height) across IR status in our

study. Furthermore, WC did not affect the associations between mEI and HOMA-IR. However, the greater WC observed in children with MetS corroborates the study by Taksali et al, in which children with obesity in the highest tertile of visceral adipose tissue (by MRI) had 5.2 times greater likelihood to have MetS than those in the lowest tertile (62). Although no differences in CRP and IL-6 were found between tertiles, children in the third tertile also had lower adiponectin and leptin. Adiponectin is an insulin sensitizer hormone produced by adipocytes, and its reduced levels are related to peripheral IR in obesity (63); leptin also plays a role on energy homeostasis, and its lower concentrations contributes to obesity (64). It is noteworthy that WC was used as a surrogate of abdominal adiposity and it does not differentiate visceral from subcutaneous adiposity; thus, our findings need to be interpreted with caution.

In our study, mEI of rectus femoris was positively also associated with higher LDL-C levels, but not TG. As ectopic fat is stored in the muscles in form of TG, previous pediatric studies have shown that TG and visceral fat predicted tight signal intensity and intramuscular fat content (65, 66). One of the reasons for the lack of association could be related to the choice of muscle group assessed in our study. According to Akima et al, the quadriceps femoris (muscle group that contains the rectus femoris muscle) had the least intramuscular adiposity content compared to the other muscles in the thigh in children (67). However, abnormally high LDL-C levels are associated with increased atherogenic risk, as LDL particles accumulate in the arterial walls (68). Indeed, lower muscle density was associated with greater MetS risk score in a longitudinal study following females from pre-puberty to early adulthood (69). Although LDL-C has not been related to intramuscular adiposity in pediatric studies, changes in this body component after an exercise intervention resulted in changes in the size of LDL-C particles towards larger size with lower atherogenic potential in male adults (70). The extent to which exercise modulates intramuscular adiposity content in the pediatric obesity population has not yet been investigated. Furthermore, although increased intramuscular adiposity has been implicated in lower force production during adulthood (71), children with greater mEI had also greater muscular strength. Recently, Herda et al. investigated the firing capacity of gastrocnemius muscles and vastus lateralis in children with obesity (ages 7 to 10 years) and did not find any differences in muscle fiber recruitment rate between children with obesity and normal weight (65).

A less detailed assessment of body composition was obtained by using ADP compared to US. Air-displacement plethysmography is a two-compartment method that allows whole-body, but not segmental evaluation of fat and muscle mass. Furthermore, ADP estimates total FFM (sum of muscle, organs, and bone content) rather than the "functional muscle" mass. On the other hand, US is a non-invasive technique that measures *in vivo* adipose and muscle tissues. It is also possible to assess the distribution of body components and the "functional muscle mass" by adjusting muscle measurements to mEI (which depicts both intramuscular and fibrous tissue). Thus, these factors can partially explain the greatest associations found between LCI by US (than by ADP) and metabolic risk factors. Future analysis of the TBK data obtained in our study would contribute in investigating the associations between body cell mass, the metabolic active component of muscles, and health in pediatric obesity.

Potential methodologic limitations of this study merit discussion. Firstly, our limited sample size did not allow the use of more robust statistical methods to assess the relationships between body composition and metabolic heath. With a larger number of participants, logistic regression analysis would have informed the predictive ability of body composition parameters to determine metabolic dysfunction risk. Additionally, we were not able to stratify participants into different body composition phenotypes (e.g. high adiposity-low muscularity, high adiposity-high muscularity) (72). Secondly, the findings of this study are restricted to whole-body and midthigh body composition, and we were unable to determine detrimental roles of visceral fat as well as ectopic fat deposition in the liver. Thirdly, although HOMA-IR was used as a surrogate measure of IR, our findings were consistent with the study of Lee et al., in which more accurate tests (euglycemic clamp and oral glucose tolerance test [OGTT]) were employed (53). Lastly, the addition of a control group would have allowed us to investigate whether the LCI can be used to predict metabolic health, independent of obesity status. Furthermore, we would also have been able to investigate how body composition would differ between children with obesity and without, using the same body composition technique as there are no reference charts using ADP or US.

In conclusion, body composition parameters were not well depicted by BMI z-scores in children with obesity. Despite its preliminary character, our study does suggest that the model of load-capacity could be useful to predict MetS, IR, and low-grade systemic inflammation risk in the pediatric population (at the group level). We also showed the potential clinical application of

US to assess functional muscle, as mEI explained the positive associations between variables depicting muscularity and markers of metabolic dysfunction. Future analysis including the full study sample size will confirm the prognostic utility of the LCI and mEI with respect to metabolic dysfunction in children with obesity.

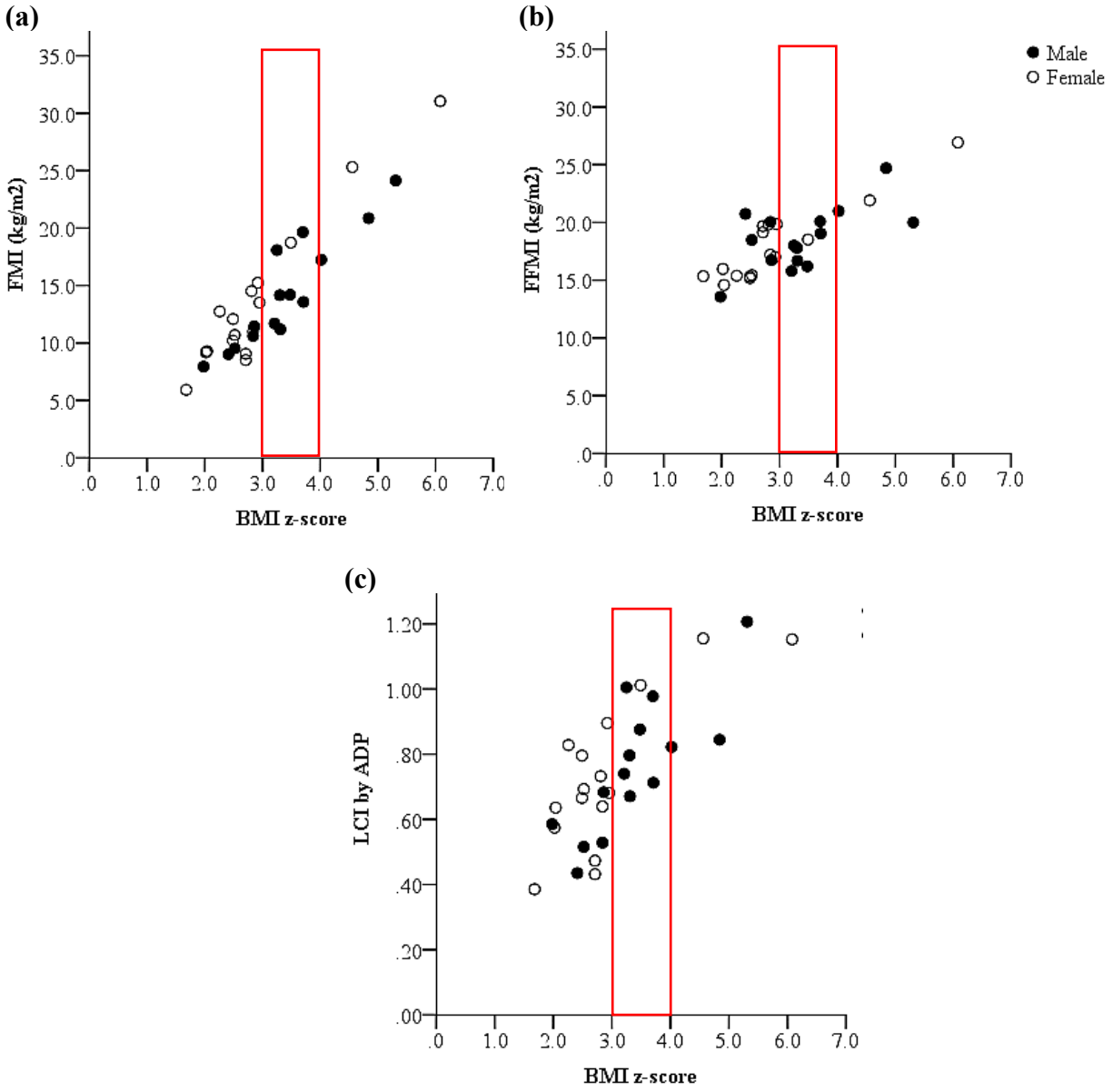


Figure 4.1 Distribution of (a) fat mass index (FMI), (b) fat-free mass index (FFMI), and (c) load-capacity index (LCI) across body mass index (BMI) z-score categories (category 1: BMI z-score <3SD, n=18; category 2: BMI z-score ≥3 SD to <4 SD, n=8; category 3: BMI z-score ≥4 SD, n=5). These graphics depict the wide range of body composition parameters in children with similar obesity degree. As highlighted by the red box, males with BMI z-score values between 3 to 4 SD had FMI ranging from 11.2 to 19.6 kg/m^2 (a 42.9% variation), FFMI ranging from 15.8 to 20.1 kg/m^2 (a 21.4% variation), and LCI by ADP ranging from 0.67 to 1.01 (a 33.7% variation). Differences between BMI z-score categories were found for FMI, FFMI, and LCI by ADP. Compared to children with the least obesity degree (category 1), children with the greatest obesity degree (category 3) had higher FMI (median [IQR]=10.7 [9.1-13.8] vs. 24.1 [19.1-28.2] kg/m^2; p=0.001), FFMI (median [IQR]=17.2 [15.4-19.8] vs. 21.9 [20.5-25.8] kg/m^2; p=0.004), and LCI by ADP (median [IQR]=0.67 [0.52-0.80] vs. 1.15 [0.83-1.18]; p=0.005).

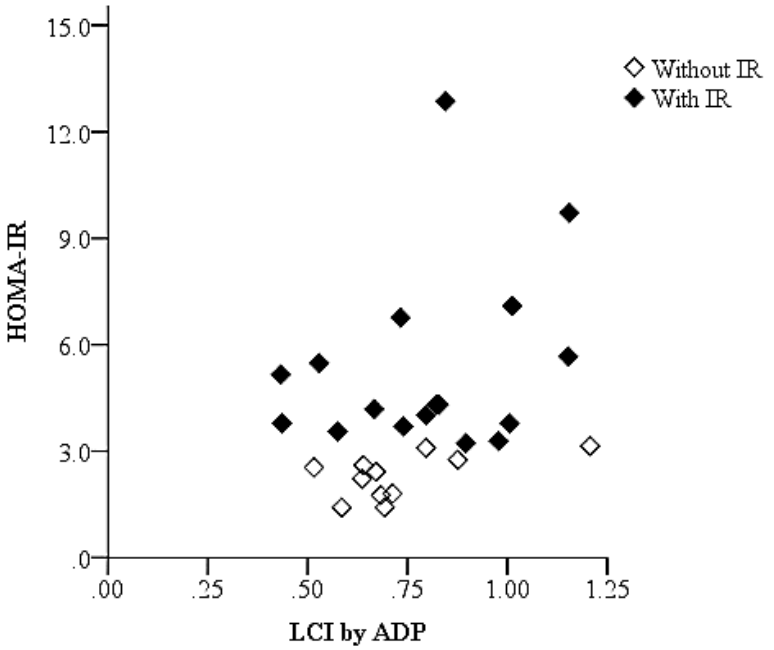


Figure 4.2 Variability in the manifestation of insulin resistance (IR) across load-capacity index (LCI) values by air-displacement plethysmography. At the individual level, the LCI ranged from 0.43 to 1.16 (a variation of 62.9%) in children with IR (n=17) and from 0.52 to 1.21 (a variation of 57.0%) in children without IR (n=11).

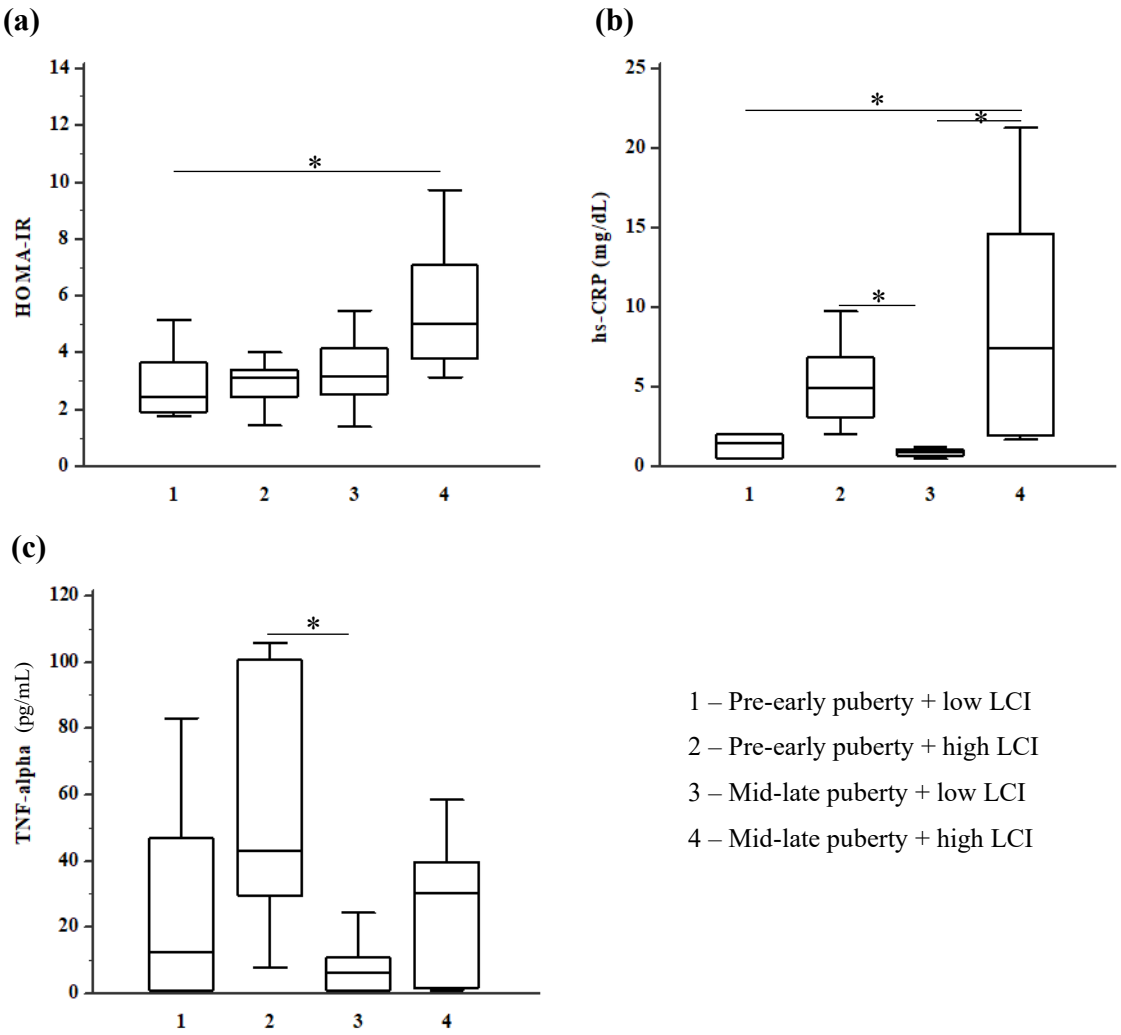


Figure 4.3 Differences in markers of insulin resistance and inflammation between children with high and low load-capacity index (LCI) by air-displacement plethysmography, stratified by sexual maturity. (a) homeostatic model assessment of insulin resistance (HOMA-IR), (b) high-sensitivity c-reactive protein (hs-CRP), and (c) tumor necrosis factor alpha (TNF-α) *P-value <0.050 using Bonferroni post hoc analysis. Sample size in (a): overall: n=28; subgroup 1: n=5; subgroup 2: n=7; subgroup 3: n=7; subgroup 4: n=9. Sample size in (b): overall: n=23; ubgroup 1: n=5; subgroup 2: n=6; subgroup 3: n=5; subgroup 4: n=7. Sample size in (c): overall: n=28; subgroup 1: n=7; subgroup 2: n=6; subgroup 3: n=7; subgroup 4: n=8.

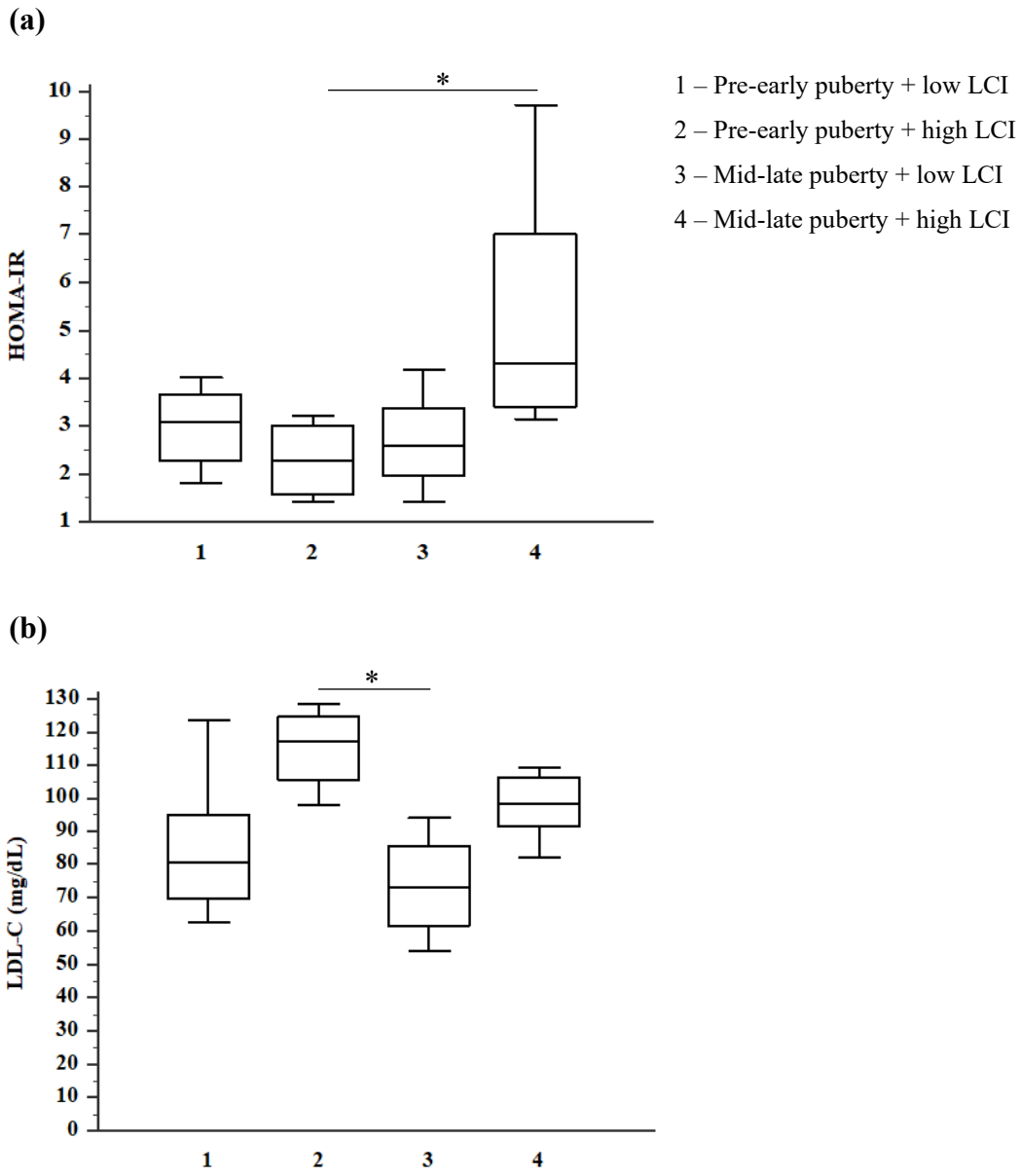


Figure 4.4 Differences in (a) homeostatic model assessment of insulin resistance (HOMA-IR), and (b) low-density lipoprotein cholesterol (LDL-C) between children with high and low load-capacity index (LCI) by ultrasound stratified by sexual maturity. *P-value <0.050 using Kruskal Wallis with post hoc analysis. Sample size in (a) and (b): overall: n=22; subgroup 1: n=7; subgroup 2: n=4; subgroup 3: n=4; subgroup 4: n=7.

Table 4.1 Demographic, clinical, and lifestyle characteristics of overall sample and stratified by sex.

	Overall sample		Males		Females		p-value[a]
	n	Median (IQR)	n	Median (IQR)	n	Median (IQR)	
Age (years)	31	12.0 (10.9-13.4)	15	12.0 (10.9-13.5)	16	11.8 (10.7-13.4)	0.892
Sexual maturation							
Pre-early puberty (%)	14	45.2	6	40.0	8	50.0	0.576[b]
Mid-late puberty (%)	17	54.8	9	60.0	8	50.0	0.576[b]
Race/Ethnicity							
White (%)	18	58.1	8	53.3	10	62.5	0.765[b]
Indigenous (%)	5	16.1	2	13.3	3	18.8	1.000[c]
Others (%)	7	22.6	4	26.7	3	18.8	0.675[c]
Birth and medical history							
Birth weight (kg)	31	3.4 (3.0-3.9)	15	3.6 (3.1-4.5)	16	3.3 (2.9-3.5)	0.110
Gestational age (weeks)	31	39.0 (38-40)	15	39.0 (38.0-40.0)	16	39.0 (38.3-40.0)	0.892
Vaginal birth (%)	20	64.5	10	66.7	10	62.5	0.809[b]
Breast-fed (%)	18	58.1	7	46.7	11	68.8	0.264[b]
Feeding difficulties (%)	5	16.1	3	20.0	2	12.5	0.654[c]
Family history of disease							
Diabetes Mellitus (%)	20	64.5	11	73.3	9	56.3	0.130[c]
Hypertension (%)	22	71.0	9	60.0	13	81.3	0.313[c]
Thyroid problems (%)	13	41.9	5	33.3	8	50.0	0.340[b]
Psychological disorders							
Depression (%)	4	13.0	1	6.7	3	18.8	0.600[c]
Anxiety (%)	5	9.7	1	6.7	4	25.0	0.333[c]
ADHD (%)	5	16.2	6	40.0	2	12.5	0.113[c]
Physical activity							
Sedentary time (min/day)	31	624.5 (533.1-695.4)	15	589.9 (533.1-672.8)	16	634.7 (532.3-697.7)	0.572
Light intensity (min/day)	31	161.4 (112.2-191.3)	15	161.7 (112.2-200.0)	16	143.5 (112.3-187.3)	0.654
MVPA (min/day)	31	39.8 (28.4-52.8)	15	48.9(40.1-55.0)	16	31.8(22.3-38.9)	**0.014**
Dietary intake							
Total energy intake (kcal/day)	30	1,870 (1,588-2,105)	14	1,870 (1,699-2,009)	16	1,807 (1,517-2,137)	0.790

	Overall sample		Males		Females		p-value[a]
	n	Median (IQR)	n	Median (IQR)	n	Median (IQR)	
Protein (g/1,000 kcal)	30	42.7 (39.9-49.2)	14	44.5(38.7-50.4)	16	41.8 (40.1-48.1)	0.498
Fat (g/1,000 kcal)	30	37.5 (35.5-42.7)	14	37.1 (34.0-40.9)	16	39.8 (35.7-43.8)	0.473
CHO (g/1,000 kcal)	30	123.8 (110.2-134.4)	14	123.8 (103.9-132.5)	16	126.6 (113.0-134.8)	0.854
Fiber (g/1,000 kcal)	30	8.7 (7.6-11.3)	14	8.7 (7.2-10.0)	16	8.7 (7.8-11.7)	0.580

Abbreviations: ADHD, attention deficit disorder; BMI, body mass index; CHO, carbohydrate; IQR, interquartile range; MVPA, moderate-to-vigorous physical activity; n, number of participants.

[a] P-values were obtained using the Mann-Witney U test unless otherwise specified. Significant differences between sexes are highlighted in bold, $p < 0.05$.

[b] P-values were obtained using the Chi-square test, $p < 0.05$.

[c] P-values were obtained using the Fisher's exact test, $p < 0.05$.

Table 4.2 Description of body composition, anthropometrics, and muscular strength in the overall sample and stratified by sex.

	Overall sample		Males		Females		p-value[a]
	n	Median (IQR)	n	Median (IQR)	n	Median (IQR)	
ADP							
FM (kg)	31	27.8 (23.0-52.8)	15	34.2 (25.3-58.4)	16	26.8 (21.5-41.5)	0.299
FM (%)	31	41.6 (36.9-46.7)	15	42.5 (36.9-46.7)	16	40.7 (37.1-46.7)	0.599
FMI (kg/m^2)	31	12.1 (9.5-17.2)	15	13.6 (10.6-18.1)	16	11.5 (9.2-15.1)	0.470
FFM (kg)	31	44.0 (35.8-58.6)	15	49.0 (39.1-61.1)	16	41.9 (35.1-52.9)	0.232
FFMI (kg/m^2)	31	18.0 (15.8-20.0)	15	18.5 (16.7-20.1)	16	17.1 (15.4-19.8)	0.264
LCI by ADP	31	0.71 (0.59-0.88)	15	0.74 (0.59-0.88)	16	0.69 (0.59-0.88)	0.599
Ultrasound							
SAT thickness	25	2.0 (1.8-2.6)	11	2.0 (1.2-2.8)	14	2.0 (1.8-2.5)	0.687
SAT/thigh length	25	0.05 (0.04-0.06)	11	0.06 (0.03-0.06)	14	0.05 (0.05-0.06)	0.767
SM thickness	24	3.8 (3.7-4.3)	11	4.0 (3.7-4.3)	13	3.7 (3.7-4.3)	0.955
SM/tight length	24	0.10 (0.09-0.11)	11	0.09 (0.10-0.11)	13	0.10 (0.08-0.10)	0.820
mCSA	25	10.3 (8.4-13.5)	11	11.7 (8.3-14.0)	14	9.4 (8.4-12.6)	0.851
mEI	24	165.6 (142.0-182.1)	10	166.7 (135.6-203.7)	14	165.6 (148.6-179.3)	0.709
LCI by US	24	0.52 (0.44-0.68)	11	0.53 (0.41-0.68)	13	0.51 (0.45-0.62)	0.691
Anthropometrics							
Weight (kg)	31	74.2 (59.8-105.0)	15	79.9 (68.4-118.5)	16	69.1 (58.6-98.5)	0.264
Height (cm)	31	156.7 (151.6-167.7)	15	161.5 (155.4-172.7)	16	154.8 (151.2-162.4)	0.101
BMI z-score	31	2.9 (2.5-3.5)	15	3.3 (2.8-3.7)	16	2.7 (2.3-2.9)	**0.049**
WC (cm)	26	87.5 (83.0-102.0)	11	87.8 (84.2-106.5)	15	83.2 (79.3-100.5)	0.330
WC percentile	26	95.5 (91.4-97.2)	11	96.3 (91.5-97.9)	15	94.8 (91.0-96.7)	0.413
WHtR	26	0.6 (0.5-0.6)	11	0.6 (0.5-0.6)	15	0.6 (0.5-0.6)	0.646
WHR	26	0.9 (0.8-0.9)	11	0.9 (0.9-1.0)	15	0.9 (0.8-0.9)	0.069
Muscular strength							
Right HGS	31	24 (18-30)	15	28 (20-34)	16	22 (18-24)	**0.045**
Left HGS	31	20 (16-26)	15	24 (19-34)	16	19 (16-22)	**0.027**
Potassium counter							
TBK (mmol)	6	1679.9-2474.4	2	1821.1-2474.4	4	1679.9-2309.8	n/a
TBK (g)	6	65.7-96.7	2	71.2-96.7	4	65.7-90.321.3	n/a
BCM (kg)	6	15.5-22.8	2	16.8-22.8	4	15.5-21.3	n/a

Abbreviations: ADP, air-displacement plethysmography; BCM, body cell mass; BMI z-score, body mass index for age and sex; FM, fat mass; FMI, fat mass index, FFM, fat-free mass, FFMI, fat-free mass index; HGS, handgrip strength; LCI, load-capacity index; mCSA, muscle cross-sectional area; mEI, muscle echo intensity; n, number of participants included in the analysis; SAT, subcutaneous adipose tissue; SM, skeletal muscle; TBK, total body potassium; US, ultrasound; WC, waist circumference; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio.
[a] P-values were obtained using the Mann-Witney U test. Significant differences between sexes are highlighted in bold, $p<0.05$.

Table 4.3 Metabolic parameters of the overall sample and stratified by sex.

	Overall sample		Males		Females		p-value
	n	Median (IQR)	n	Median (IQR)	n	Median (IQR)	
Glucose metabolism							
Glucose (mg/dL)	28	90.0 (85.1-91.8)	15	90.0 (84.6-91.8)	13	88.2 (85.5-90.0)	0.294
Insulin (pmol/L)	31	116.0 (81.3-143.1)	15	111.8 (75.0-123.0)	16	127.8 (88.7-173.1)	0.275
HOMA-IR	28	3.63 (2.56-4.94)	15	3.29 (2.42-4.01)	13	4.18 (2.85-6.21)	0.325
Lipid profile							
HDL-C (mg/dL)	28	40.41 (38.28-46.02)	15	40.22 (34.42-44.86)	13	40.60 (38.28-53.94)	0.555
LDL-C (mg/dL)	28	90.68 (77.05-102.86)	15	90.10 (76.95-104.41)	13	92.81 (77.73-102.67)	0.821
TG (mg/dL)	28	98.76 (80.16-142.38)	15	86.80 (75.28-133.74)	13	109.83 (82.37-159.87)	0.363
Inflammatory profile							
hs-CRP (mg/L)	23	2.00 (1.20-7.40)	12	2.05 (0.85-6.88)	11	2.00 (1.30-13.90)	0.566
IL-6 (pg/mL)	28	9.44 (6.10-31.74)	12	6.6 (9.5-31.6)	16	4.9 (9.4-39.5)	0.909
TNF-α (pg/mL)	28	17.74 (1.18-42.81)	12	6.9 (24.2-49.2)	16	1.0 (7.4-40.5)	0.347
Blood pressure							
SBP (mmHg)	31	119 (113 -130)	15	119 (113-128)	16	119 (113 -131)	0.984
SBP percentile	31	91 (66-96)	15	91 (65-95)	16	90 (79-99)	0.401
DBP (mmHg)	31	71 (61-76)	15	70 (59-74)	16	73 (62-78)	0.318
DBP percentile	31	78 (42-88)	15	74 (30-82)	16	84 (72-98)	0.054
Metabolic dysfunction prevalence							
IR (%)	17	54.8	8	53.3	9	56.3	0.695
Dyslipidemia (%)	16	51.6	9	60.0	7	43.8	0.588[a]
Hypertension (%)	12	38.7	3	20.0	9	56.3	0.066[b]
Mets-IDF (%)	4	12.9	2	13.3	2	12.5	1.000[b]
MUO (%)	26	83.9	13	86.7	13	81.3	1.000[b]

Abbreviations: DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment of insulin resistance; hs-CRP, high sensitivity c-reactive protein; IL-6, interleukin-6; IQR, interquartile range; IR, insulin resistance; LDL-C, low-density lipoprotein cholesterol; Mets-IDF, metabolic syndrome as defined by International Diabetes Federation; MUO, metabolically unhealthy obesity; n, number of participants; SBP, systolic blood pressure; TG, triglycerides; TNF-α, tumor necrosis factor alpha.

[a] Chi-square test

[b] Fisher's exact test

Table 4.4 Correlation coefficients between indices of body composition and metabolic markers of lipid profile, glucose metabolism, blood pressure, and inflammation.

		HOMA-IR†	LDL-C	SBP†	DBP	hs-CRP†
Body composition by ADP						
FMI†	r	**0.529***	0.271	0.212	0.245	**0.728***
	n	28	28	31	31	23
FFMI	r	**0.658***	0.001	**0.395***	**0.424***	**0.426***
	n	28	28	31	31	23
LCI by ADP	r	0.345	0.346	0.106	0.168	**0.762***
	n	28	28	31	31	23
Body composition by US						
SAT/thigh length	r	**0.466***	0.389	0.268	**0.481***	**0.579***
	n	23	23	25	25	20
SM/thigh length	r	-0.033	-0.018	**-0.405***	**-0.605***	-0.080
	n	22	22	24	24	19
mCSA	r	**0.522***	0.099	0.242	0.247	**0.586***
	n	23	23	25	25	20
LCI by US†	r	0.169	**0.546***	**0.419***	**0.464***	0.358
	n	22	22	24	24	19
mEI†	r	**0.497***	**0.426***	0.310	**0.474***	**0.592***
	n	22	22	24	24	19
Anthropometrics						
BMI z-score	r	**0.462***	0.224	0.228	0.233	**0.676***
	n	28	28	31	31	23
WC z-score	r_s	0.321	**0.415***	0.284	0.063	**0.824***
	n	23	23	26	26	19
WHtR	r	**0.456***	0.403	**0.389***	0.307	**0.740***
	n	23	23	28	26	19
WHR	r	-0.195	0.278	-0.017	-0.107	0.303
	n	23	23	26	26	19
Muscular strength						
Right HGS	r	0.324	0.139	0.123	0.077	0.172
	n	28	28	31	31	23
Left HGS	r	**0.459***	0.109	0.259	0.150	0.029
	n	28	28	31	31	23

Abbreviations: ADP, air-displacement plethysmography; BMI z-score, body mass index for age and sex; DBP, diastolic blood pressure; FMI, fat mass index, FFMI, fat-free mass index; HGS, handgrip strength; HOMA-IR, homeostatic model assessment of insulin resistance; hs-CRP, high-sensitivity C-reactive protein; LCI, load-capacity index; LDL-C, low-density lipoprotein cholesterol; mCSA, muscle cross-sectional area; mEI, muscle echo intensity; n, number of participants included in the analysis; r, Pearson correlation coefficient; r_s, Spearman correlation coefficient; SAT, subcutaneous adipose tissue; SBP, systolic blood pressure; SM, skeletal muscle; US, ultrasound; WC z-score, waist circumference for age and sex; WHtR, waist-to-height ratio; WHR, waist-to-hip ratio. * p-value <0.05; † Log-transformed variables.

Table 4.5 Associations between body composition parameters and metabolic markers using multivariate regression analysis adjusted for sexual maturation.

	R^2	β	p-value	95% CI
HOMA-IR				
FMI	0.33	0.19	**0.028**	0.02, 0.35
FFMI	0.45	0.49	**0.002**	0.20, 0.77
mCSA	0.36	0.22	**0.048**	0.00, 0.44
mEI	0.43	0.03	**0.018**	0.01, 0.05
Left HGS	0.31	0.13	**0.039**	0.01, 0.26
hs-CRP	0.42	0.17	**0.019**	0.03, 0.30
BMI z-score	0.32	0.97	**0.035**	0.08, 1.87
LDL-C (mg/dL)				
LCI by ADP	0.22	40.39	**0.027**	4.99, 75.79
LCI by US	0.34	51.43	**0.008**	15.29, 87.57
SAT/thigh length	0.25	403.78	**0.027**	51.39, 756.17
mEI	0.29	0.28	**0.018**	0.05, 0.51
WC z-score	0.27	23.59	**0.027**	2.94, 44.25
SBP (mmHg)				
FFMI	0.16	1.91	**0.030**	0.20, 3.61
LCI by US	0.21	27.63	**0.029**	3.10, 52.17
DBP (mmHg)				
FFMI	0.18	1.71	**0.04**	0.09, 3.33
SAT/thigh length	0.23	270.89	**0.027**	33.09, 508.70
SM/thigh length	0.37	-540.95	**0.002**	-867.05, -214.86
LCI by US	0.25	28.35	**0.018**	5.33, 51.37
hs-CRP (mg/L)				
FMI	0.66	0.81	**<0.001**	0.52, 1.09
FFMI	0.36	1.16	**0.007**	0.36, 1.96
LCI by ADP	0.54	18.75	**<0.001**	10.04, 27.46
LCI by US	0.36	10.85	**0.015**	2.42, 19.27
SAT/thigh length	0.57	168.78	**0.001**	84.65, 252.91
mCSA	0.41	0.90	**0.009**	0.25, 1.54
mEI	0.49	0.10	**0.004**	0.04, 0.16
BMI z-score	0.53	3.97	**<0.001**	2.10, 5.83
WC z-score	0.58	10.45	**0.001**	4.93, 15.97
WHtR	0.72	50.61	**<0.001**	31.65, 69.57

Abbreviations: ADP, air-displacement plethysmography; BMI z-score, body mass index for age and sex, CI, confidence interval; DBP, diastolic blood pressure; FMI, fat mass index, FFMI, fat-free mass index; HGS, handgrip strength; HOMA-IR, homeostatic model assessment of insulin resistance; hs-CRP, high-sensitivity C-reactive protein; LCI, load-capacity index; LDL-C, low-density lipoprotein cholesterol; mCSA, muscle cross-sectional area; mEI, muscle echo intensity; SAT, subcutaneous adipose tissue; SBP, systolic blood pressure; SM, skeletal muscle; US, ultrasound; WC z-score, waist circumference for age and sex.

Table 4.6 Comparison of the metabolic profile between children with low and high metabolic load-capacity index (LCI) by air-displacement plethysmography (ADP) and ultrasound (US).

	LCI by ADP					LCI by US				
		High LCI		**Low LCI**	p-value		**High LCI**		**Low LCI**	p-value
	n	Median (IQR)	n	Median (IQR)		n	Median (IQR)	n	Median (IQR)	
ADP										
FM (kg)	15	**52.8 (34.3-61.5)**	16	24.0 (20.9-27.6)	**<0.001**	11	**42.9 (32.1-61.5)**	13	25.3 (21.6-30.8)	**0.002**
%BF (%)	15	**46.7 (44.3-50.3)**	16	37.9 (32.6-40.4)	**<0.001**	11	**47.2 (42.3-50.3)**	13	40.0 (36.7-42.1)	**<0.001**
FMI (kg/m^2)	15	**17.2 (14.2-20.9)**	16	9.9 (9.0-11.4)	**<0.001**	11	**15.2 (12.7-19.6)**	13	11.0 (9.2-12.8)	**0.001**
FFM (kg)	15	**56.2 (39.1-61.1)**	16	41.6 (35.1-48.8)	**<0.001**	11	**52.2 (38.8-59.9)**	13	37.2 (33.8-45.8)	**0.041**
FFMI (kg/m^2)	15	18.5 (16.2-21.0)	16	17.0 (15.5-19.6)	0.140	11	18.0 (16.2-20.0)	13	16.0 (15.2-18.1)	0.055
LCI by ADP	15	**0.88 (0.80-1.01**)	16	0.61 (0.48-0.68)	**<0.001**	11	**0.90 (0.73-1.01)**	13	0.67 (0.58-0.73)	**<0.001**
Ultrasound										
SAT	13	**2.5 (2-3.2)**	12	1.9 (1.6-2.0)	**<0.001**	11	**2.5 (2.1-3.0)**	13	1.8 (1.4-1.9)	**<0.001**
SAT/thigh length	13	**0.06 (0.05-0.07)**	12	0.05 (0.04-0.06)	**0.026**	11	**0.06 (0.06-0.07)**	13	0.04 (0.04-0.05)	**0.002**
SM	12	3.8 (3.7-4.0)	12	4.1 (3.5-4.4)	0.630	11	3.7 (3.6-4.0)	13	4.0 (3.7-4.4)	0.252
SM/thigh length	12	0.09 (0.08-0.10)	12	0.10 (0.09-0.12)	0.101	11	0.09 (0.08-0.09)	13	**0.10 (0.10-0.11)**	**0.009**
mCSA	13	11.4 (8.9-15.4)	12	8.8 (7.2-11.8)	0.137	11	11.3 (8.5-14)	13	9.1 (7.4-12.4)	0.361
mEI	12	**180.7 (164.6-220.6)**	12	151.1 (138.1-167.5)	**0.006**	10	**180.7 (169.2-213.0)**	13	148.5 (136.6-161.1)	**<0.001**
LCI by US	12	**0.66 (0.54-0.71)**	12	0.44 (0.42-0.51)	**0.002**	11	**0.68 (0.57-0.71)**	13	0.44 (0.42-0.48)	**<0.001**
Muscular strength										
Right HGS	15	24 (22-30)	16	21 (18-26.8)	0.163	11	**28 (22-33)**	13	18 (17-26)	**<0.001**
Left HGS	15	22 (20-31)	16	19 (15-24)	0.086	11	**22 (20-31)**	13	16 (15-21)	**<0.001**
Physical activity										
Sedentary time (min/day)	15	629.6 (546.9-699.5)	16	589.1 (504.4-662.5)	0.247	11	624.5 (533.1-699.5)	13	609.5 (507.7-656.7)	0.691

	LCI by ADP					LCI by US				
	High LCI		Low LCI		p-value	High LCI		Low LCI		p-value
	n	Median (IQR)	n	Median (IQR)		n	Median (IQR)	n	Median (IQR)	
Light intensity (min/day)	15	129.5 (87.6-200.0)	16	162.2 (125.8-183.0)	0.281	11	129.5 (87.6-191.3)	13	161.7 (129.2-187.0)	0.569
MVPA (min/day)	15	34.2 (21.0-55.5)	16	40.0 (29.3-49.0)	0.800	11	34.2 (21.0-57.4)	13	40.1 (28.4-49.0)	1.000
Dietary intake										
TEI (kcal/day)	15	1803 (1548-2127)	15	1908 (1601-2017)	0.744	10	1767 (1635-2143)	13	2000 (1813-2134)	0.208
Fat (g/1,000 kcal)	15	37.3 (29.8-42.5)	15	37.8 (35.9-44.0)	0.486	10	36.6 (29.7-44.6)	13	40.1 (37.1-42.9)	0.343
Protein (g/1,000 kcal)	15	43.4 (36.2-51.1)	15	42.3 (41.1-46.2)	0.935	10	42.6 (36.1-49.9)	13	42.0 (39.2-47.7)	0.976
CHO (g/1,000 kcal)	15	129.0 (103.7-136.8)	15	122.6 (113.0-134.3)	0.744	10	129.7 (102.5-138.9)	13	116.9 (112.7-131.3)	0.648
Fiber (g/1,000 kcal)	15	8.9 (7.8-10.6)	15	8.6 (7.3-11.8)	0.870	10	8.4 (7.6-9.9)	13	8.9 (7.6-11.7)	0.410
Metabolic markers										
Glucose (mg/dL)	15	90.0 (84.6-91.8)	13	88.2 (85.5-90.9)	0.413	11	90.0 (84.6-90.0)	11	86.4 (84.6-88.2)	0.401
Insulin (pmol/L)	15	122.9 (102.8-209.0)	16	99.0 (68.2-130.8)	0.072	11	111.8 (81.3-209.0)	13	84.7 (69.1-123.0)	0.252
HOMA-IR	15	**4.01 (3.15-6.76)**	13	2.60 (2.01-3.98)	**0.041**	11	3.29 (2.76-6.76)	11	2.60 (2.22-3.70)	0.171
HDL-C (mg/dL)	15	40.2 (34.0-46.4)	13	41.0 (39.3-46.4)	0.413	11	39.4 (34.0-46.4)	11	41.8 (40.2-44.9)	0.133
LDL-C (mg/dL)	15	97.1 (82.4-107.1)	13	78.5 (71.9-95.3)	0.170	11	**104.4 (97.1-113.7)**	11	78.5 (66.9-94)	**0.002**
TG (mg/dL)	15	114. 3 (83.3-160.3)	13	94.8 (77.1-129.8)	0.235	11	132.9 (83.3-160.3)	11	79.7 (75.3-133.7)	0.243

	LCI by ADP					LCI by US				
	High LCI		Low LCI		p-value	High LCI		Low LCI		p-value
	n	Median (IQR)	n	Median (IQR)		n	Median (IQR)	n	Median (IQR)	
hs-CRP (mg/dL)	13	**5.9 (2.05-11.8)**	10	1.1 (0.5-1.78)	**<0.001**	10	4.7 (1.9-9.1)	9	1.3 (0.9-5.1)	0.113
TNF-α (pg/mL)	14	33.7 (6.4-54.0)	14	6.8 (1.0-28.8)	0.077	11	35.3 (7.9-52.5)	11	6.8 (1.0-43.0)	0.332
IL-6 (pg/mL)	14	12.0 (7.1-37.7)	14	9.3 (3.5-26.3)	0.401	11	18.2 (7.4-35.1)	11	9.6 (6.2-62.2)	0.847
SBP (mmHg)	15	118 (116.3-128)	16	120 (111-131)	0.861	11	118 (117-131)	13	113 (110-126)	0.150
SBP percentile	15	85 (66-95)	16	93 (69-99)	0.470	11	83 (66-96)	13	85 (65-97)	0.955
DBP (mmHg)	15	72 (62-76)	16	71 (58-77)	0.770	11	74 (62-76)	13	61 (57-74)	0.134
DBP percentile	15	78 (48-95)	16	77 (34-86)	0.572	11	83 (74-98)	13	48 (29-81)	0.082

Abbreviations: %BF, percent body fat; CHO, carbohydrate; ADP, air-displacement plethysmography; DBP, diastolic blood pressure; FFM, fat-free mass; FFMI, fat-free mass index; FM, fat mass; FMI, fat mass index; HDL-C, high-density lipoprotein cholesterol; HGS, handgrip strength; HOMA-IR, homeostatic model assessment of insulin resistance; hs-CRP, high sensitivity c-reactive protein; IL-6, interleukin-6; IQR, interquartile range; LCI, load-capacity index; LDL-C, low-density lipoprotein cholesterol; mCSA, muscle cross-sectional area; mEI, muscle echo intensity; MVPA, moderate-to-vigorous physical activity; n, number of participants included in the analysis; SAT, subcutaneous adipose tissue; SBP, systolic blood pressure; SM, skeletal muscle; TEI, total energy intake; TG, triglycerides; TNF-α, tumor necrosis factor alpha; US, ultrasound

Statistically significant difference between LCI groups (high vs. low) by Mann-Whitney U test is highlighted in bold, $p < 0.05$.

4.6 References

1. Friedemann C, Heneghan C, Mahtani K, Thompson M, Perera R, Ward AM. Cardiovascular disease risk in healthy children and its association with body mass index: Systematic review and meta-analysis. BMJ. 2012;345(7876):1–16.
2. Elmaogullari S, Demirel F, Hatipoglu N. Risk factors that affect metabolic health status in obese children. J Pediatr Endocrinol Metab. 2017;30(1):49–55.
3. Higgins V, Adeli K. Pediatric metabolic syndrome: Pathophysiology and laboratory assessment. eJIFCC. 2017;28(1):25–42.
4. Blüher S, Schwarz P. Metabolically healthy obesity from childhood to adulthood - Does weight status alone matter? Metabolism. 2014;63(9):1084–92.
5. Wells JCK. Using body composition assessment to evaluate the double burden of malnutrition. Ann Nutr Metab. 2019;75(2):103–8.
6. Kindler JM, Lobene AJ, Vogel KA, Martin BR, McCabe LD, Peacock M, et al. Adiposity, insulin resistance, and bone mass in children and adolescents. J Clin Endocrinol Metab. 2018;104(3):892–9.
7. Marginean CO, Melit LE, Ghica D V., Mărginean MO. Early inflammatory status related to pediatric obesity. Front Pediatr. 2019;7:1–7.
8. Nieuwenhuis D, Pujol-Gualdo N, Arnoldussen IA, Kiliaan AJ. Adipokines: A gear shift in puberty. Obes Rev. 2020;(January):1–10.
9. Frontera WR, Ochala J. Skeletal muscle: A brief review of structure and function. Calcif Tissue Int. 2015;96(3):183–95.
10. Wannamethee SG, Atkins JL. Muscle loss and obesity: The health implications of sarcopenia and sarcopenic obesity. Proc Nutr Soc. 2015;74(4):405–12.
11. Burrows R, Correa-Burrows P, Reyes M, Blanco E, Albala C, Gahagan S. Low muscle mass is associated with cardiometabolic risk regardless of nutritional status in adolescents: A cross-sectional study in a Chilean birth cohort. Pediatr Diabetes. 2017;18:895–902.
12. Wells JCK. Toward body composition reference data for infants, children, and adolescents. Adv Nutr. 2014;5(June):320S-329S.
13. Stoklossa CAJ, Sharma AM, Forhan M, Siervo M, Padwal RS, Prado CM. Prevalence of sarcopenic obesity in adults with class II/ III obesity using different diagnostic criteria. J Nutr Metab. 2017;2017.

14. Siervo M, Prado CM, Mire E, Broyles S, Wells JC, Heymsfield S, et al. Body composition indices of a load-capacity model: Gender-and BMI-specific reference curves. Public Health Nutr. 2014;18(7):1245–54.
15. Xiao J, Cain A, Purcell SA, Ormsbee MJ, Contreras RJ, Kim JS, et al. Sarcopenic obesity and health outcomes in patients seeking weight loss treatment. Clin Nutr ESPEN. 2018;23:79–83.
16. Kang S-Y, Lim GE, Kim YK, Kim HW, Lee K, Park T-J, et al. Association between sarcopenic obesity and metabolic syndrome in postmenopausal women: A cross-sectional study based on the Korean National Health and Nutritional Examination Surveys from 2008 to 2011. J Bone Metab. 2017;24(1):9–14.
17. Burrows R, Correa-Burrows P, Reyes M, Blanco E, Albala C, Gahagan S. Low muscle mass is associated with cardiometabolic risk regardless of nutritional status in adolescents: A cross-sectional study in a Chilean birth cohort. Pediatr Diabetes. 2017;18:895–902.
18. Orsso CE, Rubin DA, Silva MIB, Heymsfield SB, Gonzalez MC, Prado CM, et al. Assessment of body composition in pediatric overweight and obesity: A systematic review of the reliability and validity of common techniques. Obes Rev. 2020;1–18. *In press*.
19. Prado CMM, Heymsfield SB. Lean tissue imaging: A new era for nutritional assessment and intervention. J Parenter Enter Nutr. 2014;38(8):940–53.
20. Pillen S. Skeletal muscle ultrasound. Eur J Transl Myol 2010; 2010;1(4):145–55.
21. Kuczmarski RJ, Ogden CL, Grummer-Strawn LM, Flegal KM, Guo SS, Wei R, et al. CDC growth charts: United States. Hyattsville, MD; 2000.
22. Subhan FB, Shulman L, Yuan Y, McCargar LJ, Kong L, Bell RC, et al. Association of pre-pregnancy BMI and gestational weight gain with fat mass distribution and accretion during pregnancy and early postpartum: A prospective study of Albertan women. BMJ Open. 2019;9(7).
23. Rasmussen AR, Wohlfahrt-Veje C, Tefre de Renzy-Martin K, Hagen CP, Tinggaard J, Mouritsen A, et al. Validity of self-assessment of pubertal maturation. Pediatrics. 2015;135(1):86–93.
24. Gheller BJ, Gheller M, Li A, Nunes F, Anini Y, Glanville NT, et al. Effect of dairy and nondairy snacks on postprandial blood glucose regulation in 9–14-year-old children. Appl Physiol Nutr Metab. 2019;44(10):1073–80.

25. Chou JH, Roumiantsev S, Singh R. PediTools electronic growth chart calculators: Applications in clinical care, research, and quality improvement. J Med Internet Res. 2020;22(1):1–17.
26. Johnson ST, Kuk JL, Mackenzie KA, Huang TT, Rosychuk RJ, Ball GDC. Metabolic risk varies according to waist circumference measurement site in overweight boys and girls. J Pediatr. 2010;156(2):247-252.e1.
27. Xi B, Zong X, Kelishadi R, Litwin M, Hong YM, Poh BK, et al. International waist circumference percentile cutoffs for central obesity in children and adolescents aged 6 to 18 years. J Clin Endocrinol Metab. 2020;105(4):1–15.
28. Fields DA, Goran MI, McCrory MA. Body-composition assessment via air-displacement plethysmography in adults and children: A review. Am J Clin Nutr. 2002;75(3):453–67.
29. Lohman TG. Assessment of body composition in children. Pediatr Exerc Sci. 1989;1(1):19–30.
30. Gately PJ, Radley D, Cooke CB, Carroll S, Oldroyd B, Truscott JG, et al. Comparison of body composition methods in overweight and obese children. J Appl Physiol. 2003;95(5):2039–46.
31. Jacobs J, Jansen M, Janssen H, Raijmann W, Van Alfen N, Pillen S. Quantitative muscle ultrasound and muscle force in healthy children: A 4-year follow-up study. Muscle and Nerve. 2013;47(6):856–63.
32. Caresio C, Molinari F, Emanuel G, Minetto MA. Muscle echo intensity: Reliability and conditioning factors. Clin Physiol Funct Imaging. 2015;35(5):393–403.
33. Oranchuk DJ, Stock MS, Nelson AR, Storey AG, Cronin JB. Variability of regional quadriceps echo intensity in active young men with and without subcutaneous fat correction. Appl Physiol Nutr Metab. 2020;1–24.
34. Young HJ, Jenkins NT, Zhao Q, Mccully KK. Measurement of intramuscular fat by muscle echo intensity. Muscle and Nerve. 2015;52(6):963–71.
35. Roberts HC, Denison HJ, Martin HJ, Patel HP, Syddall H, Cooper C, et al. A review of the measurement of grip strength in clinical and epidemiological studies: Towards a standardised approach. Age Ageing. 2011;40(4):423–9.

36. Wang Z, St-Onge M-P, Lecumberri B, Pi-Sunyer FX, Heshka S, Wang J, et al. Body cell mass: Model development and validation at the cellular level of body composition. Am J Physiol Endocrinol Metab. 2004;286(1):E123–8.
37. Evenson KR, Catellier DJ, Gill K, Ondrak KS, McMurray RG. Calibration of two objective measures of physical activity for children. J Sports Sci. 2008;26(14):1557–65.
38. Tremblay MS, Chaput JP, Adamo KB, Aubert S, Barnes JD, Choquette L, et al. Canadian 24-Hour Movement Guidelines for the Early Years (0-4 years): An Integration of physical activity, sedentary behaviour, and sleep. BMC Public Health. 2016;41:S311–27.
39. Subar AF, Freedman LS, Tooze JA, Kirkpatrick SI, Boushey C, Neuhouser ML, et al. Addressing current criticism regarding the value of self-report dietary data. J Nutr. 2015;145(12):2639–45.
40. Lupton J, Brooks J, Butte N, Caballero B, Flatt J, Fried S. Dietary reference intakes for energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein, and amino acids. Washington, DC; 2002.
41. Keskin M, Kurtoglu S, Kendirci M, Atabek ME, Yazici C. Homeostasis model assessment is more reliable than the fasting glucose/insulin ratio and quantitative insulin sensitivity check index for assessing insulin resistance among obese children and adolescents. Pediatrics. 2005;115(4):e500–3.
42. Rosner B, Cook N, Portman R, Daniels S, Falkner B. Determination of blood pressure percentiles in normal-weight children: Some methodological issues. Am J Epidemiol. 2008;167(6):653–66.
43. Magge SN, Goodman E, Armstrong SC, Daniels S, Corkins M, De Ferranti S, et al. The metabolic syndrome in children and adolescents: Shifting the focus to cardiometabolic risk factor clustering. Pediatrics. 2017;140(2):e20171603.
44. Damanhoury S, Newton AS, Rashid M, Hartling L, Byrne JLS, Ball GDC. Defining metabolically healthy obesity in children: A scoping review. Obes Rev. 2018;(November):1476–91.
45. U.S. Department of Health and Human Services. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: Summary report. National Institutes of Health: Bethesda, MD. 2012; 12-7486.

46. Flynn JT, Kaelber DC, Baker-Smith CM, Blowey D, Carroll AE, Daniels SR, et al. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. Pediatrics. 2017;140(3):e20171904.
47. Alberti SG, Zimmet P, Kaufman F, Tajima N, Silink M, Arslanian S, et al. The IDF consensus definition of the metablic syndrome in children and adolescents. International Diabetes Federation. 2007.
48. Levy E, Saenger AK, Steffes MW, Delvin E. Pediatric obesity and cardiometabolic disorders: Risk factors and biomarkers. eJIFCC. 2017;28(1):6–24.
49. Weber DR, Leonard MB, Shults J, Zemel BS. A comparison of fat and lean body mass index to BMI for the identification of metabolic syndrome in children and adolescents. J Clin Endocrinol Metab. 2014;99(9):3208–16.
50. Daniels SR, Kimball TR, Khoury P, Witt S, Morrison JA. Correlates of the hemodynamic determinants of blood pressure. Hypertension. 1996;28(1):37–41.
51. Korthuis RJ. Skeletal muscle circulation. In Colloquium Series on Integrated Systems Physiology: From Molecule to Function. Morgan & Claypool Life Sciences. 2011;3(4):1-144.
52. DeFronzo RA, Jacot E, Jequier E, Maeder E, Wahren J, Felber JP. The effect of insulin on the disposal of intravenous glucose: Results from indirect calorimetry and hepatic and femoral venous catheterization. Diabetes. 1981;30(12):1000–7.
53. Lee S, Kim Y, White DA, Kuk JL, Arslanian S. Relationships between insulin sensitivity, skeletal muscle mass and muscle quality in obese adolescent boys. Eur J Clin Nutr. 2012;66(12):1366–8.
54. Sinha R, Dufour S, Petersen KF, LeBon V, Enoksson S, Ma Y, et al. Assessment of skeletal muscle triglyceride content by ^{1}H nuclear magnetic resonance spectroscopy in lean and obese adolescents. Diabetes. 2002;51:1022–7.
55. Weiss R, Dufour S, Taksali SE, Tamborlane WV., Petersen KF, Bonadonna RC, et al. Prediabetes in obese youth: A syndrome of impaired glucose tolerance, severe insulin resistance, and altered myocellular and abdominal fat partitioning. Lancet. 2003;362(9388):951–7.
56. Ertunc ME, Hotamisligil GS. Lipid signaling and lipotoxicity in metaflammation: Indications for metabolic disease pathogenesis and treatment. J Lipid Res. 2016;57(12):2099–114.

57. Cree-Green M, Wiromrat P, Stuppy JJ, Thurston J, Bergman BC, Baumgartner AD, et al. Muscle insulin resistance in youth with obesity and normoglycemia is associated with altered fat metabolism. Obesity. 2019;27(12):2046–54.
58. Kim HJ, Higashimori T, Park SY, Choi H, Dong J, Kim YJ, et al. Differential effects of interleukin-6 and -10 on skeletal muscle and liver insulin action in vivo. Diabetes. 2004;53(4):1060–7.
59. Kawakami M, Murase T, Ogama H, Ishibashi S, Mori N, Takaku F, et al. Human recombinant TNF suppresses lipoprotein lipase activity and stimulates lipolysis in 3T3-L1 cells. J Biochem. 1987;101(2):331–8.
60. Weiss R, Taksali SE, Dufour S, Yeckel CW, Papademetris X, Cline G, et al. The "obese insulin-sensitive" adolescent: Importance of adiponectin and lipid partitioning. J Clin Endocrinol Metab. 2005;90(6):3731–7.
61. Rolland Y, Czerwinski S, Van Kan GA, Morley JE, Cesari M, Onder G, et al. Sarcopenia: Its assessment, etiology, pathogenesis, consequences and future perspectives. J Nutr Heal Aging. 2008;12(7):433–50.
62. Taksali SE, Caprio S, Dziura J, Dufour S, Calı AMG, Goodman TR, et al. High visceral and low abdominal subcutaneous fat stores in the obese adolescent: A determinant of an adverse metabolic phenotype. Diabetes. 2008;57(February):367–71.
63. Ruan H, Dong LQ. Adiponectin signaling and function in insulin target tissues. J Mol Cell Biol. 2016;8(2):101–9.
64. Timper K, Brü Ning JC. Hypothalamic circuits regulating appetite and energy homeostasis: Pathways to obesity. Disease models & mechanisms. 2017;10(6):679-89
65. Herda TJ, Ryan ED, Kohlmeier M, Trevino MA, Gerstner GR, Roelofs EJ, et al. Muscle cross-sectional area and motor unit properties of the medial gastrocnemius and vastus lateralis in normal weight and overfat children. Exp Physiol. 2020;105(2):335–46.
66. Brumbaugh DE, Crume TL, Nadeau K, Scherzinger A, Dabelea D. Intramyocellular lipid is associated with visceral adiposity, markers of insulin resistance, and cardiovascular risk in prepubertal children: The EPOCH study. J Clin Endocrinol Metab. 2012;97(7):1099–105.
67. Akima H, Kainuma K, Togashi K. Abdominal and thigh muscle attenuation is associated with visceral fat and age inchildren and adolescents with obesity. Glob Pediatr Heal. 2018;5:1–9.

68. Weber C, Noels H. Atherosclerosis: Current pathogenesis and therapeutic options. Nat Med. 2011;17(11):1410–22.
69. Cheng S, Wiklund P. The effects of muscle mass and muscle quality on cardio-metabolic risk in peripubertal girls: A longitudinal study from childhood to early adulthood. Int J Obes. 2018 Oct 30;42:648.
70. Durheim MT, Slentz CA, Bateman LA, Mabe SK, Kraus WE. Relationships between exercise-induced reductions in thigh intermuscular adipose tissue, changes in lipoprotein particle size, and visceral adiposity. Am J Physiol - Endocrinol Metab. 2008;295(2):407–12.
71. Addison O, Marcus RL, Lastayo PC, Ryan AS. Intermuscular fat: A review of the consequences and causes. Int J Endocrinol. 2014;2014:1–11.
72. Prado CMM, Siervo M, Mire E, Heymsfield SB, Stephan BCM, Broyles S, et al. A population-based approach to define body-composition phenotypes. Am J Clin Nutr. 2014;99(6):1369–77.

Chapter 5 Conclusions and Discussion

5.1 Introduction

Adipose tissue (AT) and skeletal muscle have important metabolic roles. Evidence has shown that body composition might be altered in the presence of obesity and potentially associated with metabolic dysfunction across the lifespan (1-3). In children with obesity, I aimed to characterize their body composition and investigate the relationships of adiposity and muscularity with metabolic risk factors. In Chapter 3, I hypothesized that laboratory techniques would have a greater reliability and validity to assess body composition compared to field techniques (4). Skinfolds and ultrasound (US; field techniques) as well as air-displacement plethysmography (ADP) and dual-energy X-ray absorptiometry (DXA; laboratory techniques) had high repeatability and reproducibility; but the reliability of bioelectrical impedance analysis (BIA) was inferior for estimating percent body fat (%BF), fat mass (FM), and fat-free mass (FFM). Analysis of Bland-Altman plots assessing the agreement between these body composition techniques against multicompartment models revealed that laboratory techniques (i.e. DXA, ADP, and isotope dilution) had the smallest bias and acceptable limits of agreement (LoA) for %BF evaluation. On the other hand, skinfolds and BIA showed large bias with wide LoA for %BF; compared to these techniques, US overestimated %BF in females and underestimate it in males to a much smaller degree. In Chapter 4, I hypothesized and demonstrated, through preliminary analysis of study findings, that children with obesity would exhibit a wide range of adiposity (e.g. 40% variation in fat mass index [FMI]) and muscularity (e.g. 20% variation in fat-free mass index [FFMI]) within similar body mass index for age and sex (BMI z-score) values. I also tested the hypothesis that those children with metabolic dysfunction (i.e. insulin resistance [IR], dyslipidemia, hypertension, metabolic syndrome [MetS], or metabolically unhealthy obesity [MUO]) would have lower muscularity and greater load-capacity index (LCI) than metabolically healthy children. Along these lines, greater adiposity and lower muscularity would be associated with higher values of markers depicting metabolic dysfunction. Contrary to my hypothesis, children with MetS or IR had greater FFMI than healthy children; but those with MetS and MUO had also higher LCI. Analysis stratified by LCI (high vs. low using sex-specific medians) revealed that children with high LCI had greater concentration of markers of low-grade inflammation (i.e. high-sensitivity c-reactive protein [hs-CRP]) and IR (i.e. homeostatic model assessment of IR [HOMA-IR]). We also found that

HOMA-IR was positively associated with muscle parameters to a greater extent than adiposity measures. However, the associations were lost after adjusting for the effects of muscle echo intensity (mEI; a surrogate of intramuscular AT [IMAT]; hence, muscle "quality"). In fact, greater mEI independently predicted HOMA-IR and hs-CRP. Taken together, these findings suggest that children with obesity had lower muscle "quality" rather than muscle "quantity". The implications and limitations of these results will be discussed in the following sections. Considerations for future research will also be presented.

5.2 Inaccuracies of Body Composition Assessment in Children with Excess Body Weight

Body mass index (BMI) has been widely used as a surrogate of adiposity and to identify metabolic risk factors associated with excess body weight (5, 6). In a sample of children with obesity, we confirmed a large variability in the range of FMI and FFMI among those with similar BMI z-score values (Chapter 4). Sex-specific changes in FM and FFM particularly occur during growth and maturation, and cannot be identified by simply measuring weight (7). Corroborating with the literature reviewed in Chapter 2, we indeed found differences in body composition across sexual maturation status (Chapter 4). For example, compared to pre-early pubertal children, males at more advanced pubertal stages had greater FFMI and females had higher values for variables depicting both adiposity and muscularity. Our results therefore support previous studies discussing on the limitations of BMI to be used in clinical and research settings and raising awareness of the importance of employing body composition techniques to accurately assess metabolic risk and the effectiveness of obesity interventions (8, 9).

Several techniques are currently available for body composition assessment. Choosing a technique that have both high repeatability and validity is crucial for an accurate characterization of adiposity and muscularity in pediatric obesity studies (10). In light of this and through a comprehensive systematic review, we showed that laboratory body composition techniques (i.e. ADP, DXA, isotope dilution) should not be replaced by field techniques, such as anthropometrics, skinfolds, and BIA (4). Explanations for this recommendation are given below.

The first reason is that these field techniques are based on anthropometric measures (i.e. body weight, length, circumferences, and skinfolds) and do not reflect body composition adequately. Secondly, using an equation to estimate adiposity and muscularity that is not population- or device-specific can introduce errors (10, 11). In fact, equations that have been developed in populations with similar characteristics (e.g. sexual maturation, sex, race/ethnicity,

and obesity degree) to the one being studied are not always available; validating the chosen equation prior to its application for body composition assessment may also not be feasible. A third reason is that tissue hydration differs across levels of obesity during childhood and adolescence (12). This factor is particularly important when employing the BIA technique, as it estimates body composition based on the impedance and reactance to an electrical current that passes through the body water pool (11). Hydration status should therefore be closely controlled for an accurate body composition assessment, a procedure that is rarely followed. For example, we showed in Chapter 3 that 59.4% of the reviewed BIA studies did not provide a clear description on pretest procedures or test administration (including controlling of hydration status), whilst these studies were validating the use of BIA equations (4).

We noticed that recent studies in pediatric obesity have employed anthropometric measures (including skinfolds) as an indicator of body composition (13-17). It is noteworthy that despite our findings, future studies may still use the above-mentioned field techniques, given their feasibility in large-scale studies, unavailability of other body composition techniques, and lack of knowledge on their limitations. That being the case, caution will be needed when interpreting these studies' findings; specially those using a longitudinal design, as measurement errors might conceal actual changes in body composition and clinical outcomes.

One field technique with potential application in pediatric obesity is the US. We found high coefficients of reliability for assessment of several body components, including subcutaneous AT (SAT), visceral AT (VAT), and skeletal muscle (Chapter 3) (4). Although the validity of this technique has only been evaluated for whole-body fat estimation, we suggested further investigation on its validity as it offers several advantages over other laboratory techniques. For instance, many US devices are portable, easy to use at the bedside, and readily available in clinical practice (18). With reduced costs, US probes can be coupled to smartphones or tablets and easily transported across research and hospital facilities. Another feature of the US technique is that it allows evaluation of whole-body composition (using prediction equations) and segmental adiposity and muscularity. As discussed in Chapter 4, assessing segmental rather than whole-body composition (by a two-compartment model) may be more clinically relevant in children with obesity due to the ability of the former to depict muscle "quality" (19). In our study, we used the midthigh because it is an accessible measurement site with clear boundaries (SAT-muscle interface) (20); however, we did not evaluate the pennation angle from muscle

images, which could have provided further information about the capacity of locomotor muscles to produce force (21). Pennation angle is the angle (or orientation) in which muscle fibers are placed within the muscle belly, and the greater its value the stronger is the muscle (21). In addition to these measurements, we could have assessed ectopic fat accumulation in visceral depots and in the liver by US with no additional costs, although experience would be required (22).

It is important to emphasize that image resolution obtained by a brightness modulation (B-mode) US is greater than an amplitude modulation (A-mode). Furthermore, not all US devices have the same features (e.g. panoramic mode for assessment of muscle cross-sectional area is only available in specific devices) and maintaining similar US parameters across patients is necessary for comparability between measurements. Other limitations of using the US technique for body composition assessment can be discussed. First, experience and anatomical knowledge of the structures being assessed are assets. Second, presence of scars on the measurement site or excess SAT thickness can challenge the evaluation of mEI and muscle structure as these factors create a barrier for the US sound waves to penetrate, reflect, and form the gray-scale images (23). To overcome this limitation, a correction factor that accounts for differences in SAT has been proposed and used by several studies (24-26). Last, tissue compression can significantly vary between evaluators. In our study, all the US measurements were obtained by the same trained researcher using a minimal pressure protocol, excluding this inter-rater limitation. Thus, a device that can be coupled with the US probe would help to standardize probe pressure, improving inter-rater reliability and validity as well as promoting the widespread use in clinical and research settings.

Besides US, other imaging techniques that depict ectopic fat and fibrous tissue within skeletal muscles are also available for “functional” muscle mass assessment. Computerized tomography (CT) and magnetic resonance imaging (MRI) are examples, in which the IMAT is quantified based on tissues densities or their chemical properties, respectively (27). As discussed in Chapter 2, radiation exposure makes CT a less preferred method to be used in the pediatric population (28). On the other hand, assessment of body composition by MRI is time-consuming, expensive, and often challenged by irregularities in the region of interest; given these factors, inclusion of MRI as technique to measure body composition in our study was not feasible. Previous studies have also assessed the lipid content stored within the muscle cells (termed

intramyocellular lipids) using the proton (^{1}H) magnetic resonance spectroscopy, which evaluates body composition at the molecular level (29, 30). With reduced costs, another option would be the non-invasive D_3Creatine dilution method. As about 98% of creatine is found in the skeletal muscle, functional muscle mass can be quantified in a sample of urine using the ratio of labeled D_3-creatinine to unlabeled endogenous creatinine (31).

5.3 The Combined and Individual Contribution of Adiposity and Muscularity

The LCI has been proposed as the ratio of adiposity to muscularity and used to integrate the physiological effects of abnormal body composition on health outcomes in diverse adult populations (32, 33). Given the roles of adiposity and muscularity on homeostasis, these body compartments are identified as risk and protective factors, respectively (33). As such, high LCI values may reflect large differences between adiposity and muscularity and, consequently, greater risks for metabolic dysfunction. In other words, the capacity of skeletal muscle to overcome the physiological load posed by adiposity is reduced when there is a disparity in the proportions between these two body compartments. Additionally, it is notable that the proportions of adiposity to muscularity are highly variable across individuals and not depicted by BMI (33). In view of this, the LCI has also been proposed to identify abnormal body composition, including the sarcopenic obesity phenotype in which a high ratio mirrors the characteristic high adiposity and low muscularity (33, 34). Therefore, the LCI may be a more sensitive approach for disease risk prediction and identification of body composition phenotypes at the individual and group levels.

In Chapter 2, several factors were shown to affect adiposity and skeletal muscle development during childhood and adolescence. It is therefore likely that some children with obesity could also exhibit a high LCI (or concomitant sarcopenia) and associated metabolic dysfunction. To our knowledge, only one study including 660 participants explored the metabolic implications of having concurrent high FM and low muscle mass in adolescents with obesity and demonstrated a more detrimental health for those with the sarcopenic-like phenotype (35). However, the authors did not investigate whether the ratio of adiposity to muscularity (or LCI) would predict disease risk or differ between metabolically healthy and unhealthy adolescents. Thus, this is the first study to test the LCI in children with obesity using techniques that depict whole (ADP) and segmental body composition (US at the midthigh level).

We reported in Chapter 4 that children with high LCI had greater values of markers depicting low-grade systemic inflammation (i.e. hs-CRP; $p < 0.001$) and IR (i.e. HOMA-IR; above the reference normal range; $p=0.041$). Furthermore, children with MetS or MUO had a greater LCI than healthy children ($p \leq 0.023$). Despite this, we found a considerable variability in LCI by ADP values within IR status (62.9% in children with IR, and 57.0% in children without IR). These findings suggest that the LCI may be a valuable tool for assessing metabolic dysfunction risk at the group level, but not at the individual level. Nevertheless, it is important to note that differences in LCI were mainly driven by greater adiposity rather than muscularity, implying that a higher load may be more detrimental to metabolic health during childhood. Given the preliminary character of this study, we were unable to test whether the LCI or adiposity alone predicted disease risk. Therefore, the clinical utility of LCI to identify health outcomes in this population remains to be confirmed in future analysis using a larger sample size.

Although some participants in our study presented with high LCI values (Chapter 4), we were unable to identify the sarcopenic obesity phenotype for some reasons, including: the lack of criteria for diagnosing sarcopenia in children, and the small sample size included in this preliminary analysis. These reasons are briefly explained below.

First, there is no clear definition (or established cut-points) of what constitutes sarcopenia in the pediatric population. Reference curves to identify the low muscularity phenotype are limited and have not been developed for Canadian children and adolescents using the ADP technique. Thus, children in our study could have a high LCI even with normal values for FFMI. In addition to muscle wasting, low muscular strength is also a key characteristic of sarcopenia in aging (36) and has been associated with metabolic dysfunction risk in the pediatric population (37-39). Cut-points for handgrip strength adjusted for body weight have been indeed established to diagnose metabolic risk in Colombian children (40). However, the prevalence of obesity in the study sample ranged from 5.7 to 10.9% and are population-specific; it is unknown whether the reference cut-points are applicable to children with excess adiposity and of other race/ethnicities. In our study, we noted that children with high LCI also had greater muscular strength (LCI by US; or similar using LCI by ADP). It could be argued that excess adiposity also poses a greater mechanical load to the body and, consequently, drives muscle mass development (41). Although we found that children with high LCI also had more ectopic fat in muscle, evidence has shown

that IMAT does not affect the contractile capacity of muscles to produce force in children with obesity (26). Thus, incorporating a measurement of muscular strength may not be fully adequate for the discrimination of metabolic risks associated with abnormal body composition in children.

Second, a larger sample size would be required to stratify children into different body composition phenotypes. A study including more than 13,000 adults (aged ≥18 years) identified that only 15.2% of men and 10.3% of women presented with the high adiposity-low muscularity phenotype (or sarcopenic obesity) (42); as such, it is possible that only a small prevalence of this phenotype would also be observed in children. Future large-scale studies should be conducted to evaluate the prevalence of sarcopenic obesity in the pediatric population.

We also explored the single contribution of adiposity and muscularity to metabolic health. As expected, children with metabolic dysfunction had greater whole-body and segmental adiposity, confirming the metabolic load that excess adiposity poses to the body (43, 44). But contrary to our hypothesis and previous studies (45, 46), children with metabolic dysfunction also had greater values for variables depicting muscularity. We further explored this hypothesis by analyzing the mEI data, and demonstrated that children with obesity had lower muscle "quality". This finding is in line with the literature investigating the role of adiposity distribution on IR and prediabetes risk (44, 47, 48), as discussed in Chapter 4. Thus, it seems that the roles of adiposity and muscularity on health cannot be studied separately.

The pathways explaining the relationship between ectopic fat accumulation in muscles and IR have been elegantly reviewed by Hong et al (49). Briefly, fat cells composed of lipids (mainly triacylglycerol, diacylglycerol, and ceramides) are stored in muscles when the inflow of fatty acids is greater than their oxidative capacity. These lipids impair glucose utilization and fat oxidation in the mitochondria by blocking the glucose transporter type 4 translocation, leading to skeletal muscle IR. It is also suggested that reduced mitochondria respiration is associated with reactive oxygen species formation, myocyte toxicity, and consequent sarcopenia development. Nevertheless, no differences were found in calf-muscle mitochondrial function across weight status in adolescents after an exercise intervention (isometric plantar flexion), although children with obesity had higher intramyocellular lipid content than children with normal weight (50). Thus, I speculate that children in our study might not yet have manifested the end-stage of mitochondrial dysfunction, which would have led to muscle wasting.

Ectopic fat in muscle also stimulates inflammatory pathways. Adipose tissue and skeletal muscles are endocrine tissues with specific secretion profiles. Cytokines released by each tissue (or by both [i.e. adipo-myokines]) may contribute in promoting the crosstalk between AT and skeletal muscle triggering IR (51). The most studied adipo-myokines are interleukin-6 (IL-6), irisin, and myostatin and they have unique effects on each tissue (51). For example, IL-6 has an anti-inflammatory role on skeletal muscle (promotes muscle hypertrophy, glucose uptake), while it has a pro-inflammatory effect on AT (increase lipolysis and free fatty acid oxidation).

Irisin plays an anti-inflammatory role on both adipose and muscle tissues, and also promotes glycogenesis, lipolysis, and muscle development. On the other hand, myostatin inhibits muscle hypertrophy and adipocyte lipolysis. Thus, increased secretion of pro-inflammatory and decreased secretion of anti-inflammatory adipo-myokines can lead to sarcopenia and comorbidities associated with ectopic fat accumulation on muscles. Interestingly, a recent work by Kumar and colleagues found that reductions in irisin and myostatin were associated with improved metabolic health in youth with severe obesity who underwent bariatric surgery (52). The authors also speculated that decreases in myostatin could be related to prevention of muscle loss. Additionally, imbalances between pro- and anti-inflammatory cytokines was also shown to determine white AT expansion in diet-induced lean and obese mice (53) and IR development (54).

It has been suggested that skeletal muscle IR is the main determinant of type 2 diabetes mellitus, as muscle is responsible for 80-90% of postprandial glucose uptake (55). However, recent work from Cree-Green et al. demonstrated that adolescents with obesity (ages 12 to 21 years) had reduced insulin sensitivity not only in muscle, but also in adipose and liver tissues (50). Although we did not evaluate visceral adiposity using direct measures or fatty liver, a more comprehensive analysis of diverse body compartments (including whole and segmental body composition and adiposity distribution) would have a greater utility in clinical and research settings in both cross-sectional and longitudinal evaluations, as health care professionals would be able to identify whether treatment is resulting in changes at the tissue level. Therefore, body composition assessment using two-compartment methods (e.g. ADP, DXA, BIA) may have limited value in children with obesity. It is also worth mentioning that there are insufficient reference curves allowing comparison of body composition among the pediatric population across different race/ethnicity, sexual maturation, and body composition techniques (8, 28). As

highlighted in Chapter 3, none of the studied body composition techniques presented with bias close to zero or very narrow LoA, which can lead to inaccurate interpretation of the results if children are evaluated using a technique different from the one employed in the development of the reference data (4).

5.4 Limitations

Some limitations of this research not discussed above or in Chapters 3 and 4 must be considered. First, our research scope was restricted to the pediatric overweight and obesity populations. It is unknown whether agreement between index tests and reference standards is inferior in children with obesity compared to children of normal weight. Furthermore, as the metabolically unhealthy phenotype has also been described in the absence of obesity (56), we were not able to explore the implications of body composition on the metabolic health of children with normal weight.

A second limitation is that children were mostly recruited from two sites of a regional pediatric obesity clinic, in which children and their families were attending a multidisciplinary program with personalized care. Although lifestyle modifications are the cornerstone of weight management in this program, data from our study showed that most of the included children did not meet the recommendations for moderate and vigorous physical activity; almost 40% of them had carbohydrate intake above the Acceptable Macronutrient Distribution Range; and less than 7% met the recommendations for fiber intake (Chapter 4) (57). Despite this, findings of this study cannot be generalized to children with obesity who are not enrolled in weight management programs.

Third, we reported associations between body composition and markers of metabolic dysfunction, but causality could not be determined given the cross-sectional nature of this study. As discussed above, we did not evaluate associations of metabolic markers with measurements of visceral and liver adiposity, which could have explained IR to a greater extent than mEI.

Fourth, we stratified children into LCI groups (high vs. low LCI) based on sex-specific medians. Although a common approach, using the median split may result in loss of information at the individual level (58). For example, those individuals with LCI slightly above the median were classified at the same level of those children with the highest values for LCI. A more appropriate procedure for studies with exploratory character is the use of sex-specific tertiles;

however, taking this approach would have led to reductions of experimental power given the small sample size included in this preliminary analysis.

A final notable limitation is the definition of metabolically healthy obesity (MHO). It could be argued that those children with a metabolically healthy phenotype will be transitioning into a more detrimental phenotype as they age (59); thus, stratifying metabolic risk in children with obesity should be done with caution, especially if this is would be further informing treatment choice. Furthermore, there is not a firm definition for MetS in the pediatric population. Several criteria have been proposed from adaptations of the adult definition with distinct cut-points for each risk factor, limiting comparisons across studies (60). We used the definition proposed by the International Diabetes Federation (IDF), which was created during a consensus workshop with experts on the topic and used worldwide since its establishment (61).

5.5 Translation and Considerations for Future Research

Our study was the first to investigate the applicability of the metabolic load-capacity model in children with obesity. Given its preliminary nature, future analysis with a greater sample size should test the LCI validity to identify presence of metabolic dysfunction as well as to establish cut-points using the receiver operator curve analysis that maximizes sensitivity and specificity. Additionally, including a measurement of muscle "quality" in the model may increase its clinical utility, as we observed independent associations between IR and mEI.

We also demonstrated the potential clinical utility of an US device to assess body composition in children with obesity (Chapters 3 and 4). However, further work is required to establish the validity of the technique against gold standard imaging methods (e.g. MRI) in children with obesity, and to standardize protocols that can be used across research and clinical settings. In addition, longitudinal studies should further explore how changes in ectopic fat accumulation determine the transition from a metabolically healthy to an unhealthy phenotype in the presence of obesity in children.

With the ultimate goal of improving metabolic health in children with obesity, interventional studies with diet and exercise modification aiming to improve muscle quality should be undertaken. Along these lines, incorporating body composition analysis into the routine assessment will improve care. With a perspective of patient-oriented research, it should be noted that findings from this study can be translatable to local patients and aid health care providers to understand the limitations of anthropometric measurements. In fact, patients who

participated in this study have already received their individual study results (see form in Appendix C) and were encouraged to share this information with the pediatric obesity clinic. At the completion of the study, we will create an infographic and a video animation to share the study findings with patients seeking treatment at these local obesity clinics and their health care providers. Furthermore, a large body composition database can be created and reviewed retrospectively (through analysis of medical electronic records) to further explore longitudinal associations between different body compartments and disease risk or progression.

In future studies, it would be beneficial to add a measurement of cardiorespiratory fitness in the definition of MHO because this variable has been shown as an important marker of metabolic health (62). Moreover, evaluation of adipo-myokines might help to illustrate whether an imbalance of inflammatory markers is mediating the associations between IR and measures of adiposity and muscularity. As previous research has identified the implications of gut microbiota on immune and metabolic function (63-65), it would be interesting to explore the interplay between microbiota composition and function with body composition. Fecal samples from participants enrolled in this study have been collected and will be analyzed in the future to develop a deeper understanding about the interplay between gut microbiota, body composition, and metabolic dysfunction in pediatric obesity.

Findings from Chapter 3 suggest that laboratory techniques should not be replaced by field techniques. As discussed above, future large-scale studies might still use skinfolds, anthropometrics, and BIA to estimate body composition in children with obesity given their higher feasibility compared to laboratory techniques. One approach to further explore the sarcopenic obesity phenotype during childhood (and limit the effects of inherent measurement errors on study results) would be to use cut-points for handgrip strength that identifies the sarcopenic obesity phenotype, as handgrip test is a simple and low-cost method. To our knowledge, two studies have indeed defined reference cut-points for children aged 4 to 14 years old based on measurements of body composition obtained by a multi-frequency, hand-to-foot BIA (InBody 720, Biospace Co., Korea). Given the limitations of this technique to assess body composition in the pediatric obesity population, there is a need to develop and validate newer reference data using more accurate laboratory techniques (66).

Another important issue identified in Chapter 3 that should be addressed by future research is the lack of evidence on the validity of techniques to detect longitudinal changes in

body composition. To advance the field and expand the use of body composition analysis in obesity interventions, research investigating the smallest detectable differences obtained by each laboratory technique is timely.

5.6 Conclusions

The major finding of this research was that compared to children with obesity alone, those with obesity and metabolic dysfunction had lower muscle "quality" (or functional muscles) rather than lower muscle "quantity". As BMI and two-compartment body composition models cannot distinguish ectopic fat and functional muscles from whole-body adiposity and muscularity, respectively, the US technique may have a greater clinical utility to identify children with MUO. However, future studies should evaluate the agreement between US and imaging techniques in depicting segmental body composition in pediatric obesity populations. These findings will contribute to advance the field of pediatric body composition assessment, design of trials investigating obesity intervention effectiveness, and improve care of children living with obesity.

5.7 References

1. Kang S-Y, Lim GE, Kim YK, Kim HW, Lee K, Park T-J, et al. Association between sarcopenic obesity and metabolic syndrome in postmenopausal women: A cross-sectional study based on the Korean National Health and Nutritional Examination Surveys from 2008 to 2011. J Bone Metab. 2017;24(1):9–14.
2. Van Aller C, Lara J, Stephan BCM, Donini LM, Heymsfield S, Katzmarzyk PT, et al. Sarcopenic obesity and overall mortality: Results from the application of novel models of body composition phenotypes to the National Health and Nutrition Examination Survey 1999–2004. Clin Nutr. 2018; 38(1):264-70.
3. Orsso CE, Tibaes JRB, Rubin DA, Field CJ, Heymsfield SB, Prado CM, et al. Metabolic implications of low muscle mass in the pediatric population: A critical review. Metabolism. 2019;99:102–12.
4. Orsso CE, Rubin DA, Silva MIB, Heymsfield SB, Gonzalez MC, Prado CM, et al. Assessment of body composition in pediatric overweight and obesity: A systematic review of the reliability and validity of common techniques. Obes Rev. 2020;1–18. *In press.*
5. Hall DMB, Cole TJ. What use is the BMI? Arch Dis Child. 2006;91(4):283–6.
6. Friedemann C, Heneghan C, Mahtani K, Thompson M, Perera R, Ward AM. Cardiovascular disease risk in healthy children and its association with body mass index: Systematic review and meta-analysis. BMJ. 2012;345(7876):1–16.
7. McCarthy HD, Cole TJ, Fry T, Jebb SA, Prentice AM. Body fat reference curves for children. Int J Obes. 2006;30(4):598–602.
8. Wells JCK. Toward body composition reference data for infants, children, and adolescents. Adv Nutr. 2014;5(June):320S-329S.
9. Vanderwall C, Eickhoff J, Randall Clark R, Carrel AL. BMI z-score in obese children is a poor predictor of adiposity changes over time. BMC Pediatr. 2018;18(1):1–6.
10. Earthman CP. Body composition tools for assessment of adult malnutrition at the bedside: A tutorial on research considerations and clinical applications. J Parenter Enter Nutr. 2015;39(7):787–822.
11. Gonzalez MC. Using bioelectrical impedance analysis for body composition assessment: Sorting out some misunderstandings. J Parenter Enter Nutr. 2019;43(8):954–5.

12. Williams JE, Wells JCK, Wilson CM, Haroun D, Lucas A, Fewtrell MS. Evaluation of Lunar Prodigy dual-energy X-ray absorptiometry for assessing body composition in healthy persons and patients by comparison with the criterion 4-component model. Am J Clin Nutr. 2006;83(5):1047–54.
13. Sanchez-Escobedo S, Azcorra H, Bogin B, Hoogesteijn AL, Sámano R, Varela-Silva MI, et al. Birth weight, birth order, and age at first solid food introduction influence child growth and body composition in 6- to 8-year-old Maya children: The importance of the first 1000 days of life. Am J Hum Biol. 2020;(e23385):1–11.
14. Patni N, Li X, Adams-Huet B, Vasandani C, Gomez-Diaz RA, Garg A. Regional body fat changes and metabolic complications in children with dunnigan lipodystrophy-causing LMNA variants. J Clin Endocrinol Metab. 2019;104(4):1099–108.
15. Kryst Ł, Żegleń M, Das S, Dasgupta P, Saha R, Das R. Intergenerational changes in adiposity and fat distribution from 1982 to 2011 in male children and adolescents from Kolkata (India). Pediatr Obes. 2020;15(e12585).
16. Isacco L, Roche J, Quinart S, Thivel D, Gillet V, Nègre V, et al. Cardiometabolic risk is associated with the severity of sleep-disordered breathing in children with obesity. Physiol Behav. 2017;170:62–7.
17. Flynn AC, Thompson JMD, Dalrymple K V., Wall C, Begum S, Pallippadan Johny J, et al. Childhood dietary patterns and body composition at age 6 years: The Children of SCOPE study. Br J Nutr. 2020;1–21.
18. Teigen LM, Kuchnia AJ, Mourtzakis M, Earthman CP. The use of technology for estimating body composition: Strengths and weaknesses of common modalities in a clinical setting. Nutr Clin Pract. 2017;32(1):20–9.
19. Caresio C, Molinari F, Emanuel G, Minetto MA. Muscle echo intensity: Reliability and conditioning factors. Clin Physiol Funct Imaging. 2015;35(5):393–403.
20. Paris MT, Mourtzakis M, Day A, Leung R, Watharkar S, Kozar R, et al. Validation of bedside ultrasound of muscle layer thickness of the quadriceps in the critically ill patient (VALIDUM Study). J Parenter Enter Nutr. 2017;41(2):171–80.
21. Kawakami Y, Abe T, Fukunaga T. Muscle-fiber pennation angles are greater in hypertrophied than in normal muscles. J Appl Physiol. 1993;74(6):2740–4.

22. Bazzocchi A, Filonzi G, Ponti F, Amadori M, Sassi C, Salizzoni E, et al. The role of ultrasonography in the evaluation of abdominal fat: Analysis of technical and methodological issues. Acad Radiol. 2013;20(10):1278–85.
23. Wattjes MP, Kley RA, Fischer D. Neuromuscular imaging in inherited muscle diseases. Eur Radiol. 2010;20(10):2447–60.
24. Young HJ, Jenkins NT, Zhao Q, Mccully KK. Measurement of intramuscular fat by muscle echo intensity. Muscle and Nerve. 2015;52(6):963–71.
25. Oranchuk DJ, Stock MS, Nelson AR, Storey AG, Cronin JB. Variability of regional quadriceps echo intensity in active young men with and without subcutaneous fat correction. Appl Physiol Nutr Metab. 2020;1–24.
26. Herda TJ, Ryan ED, Kohlmeier M, Trevino MA, Gerstner GR, Roelofs EJ, et al. Muscle cross-sectional area and motor unit properties of the medial gastrocnemius and vastus lateralis in normal weight and overfat children. Exp Physiol. 2020;105(2):335–46.
27. Addison O, Marcus RL, Lastayo PC, Ryan AS. Intermuscular fat: A review of the consequences and causes. Int J Endocrinol. 2014;2014:1–11.
28. Orsso CE, Tibaes JRB, Oliveira CLP, Rubin DA, Field CJ, Heymsfield SB, et al. Low muscle mass and strength in pediatrics patients: Why should we care? Clin Nutr. 2019;38(5):2002-15.
29. Hu HH. Assessment of abdominal adiposity and organ fat with magnetic resonance imaging. In: Body and organ fat quantification - Advances in CT and MRI Techniques: Preconference-workshop of The Obesity Society 2011 Meeting [Internet]. 2011. Available from: http://www.obesity.org/education/body-and-organ-fat-quantification-preconference-course.htm
30. Brumbaugh DE, Crume TL, Nadeau K, Scherzinger A, Dabelea D. Intramyocellular lipid is associated with visceral adiposity, markers of insulin resistance, and cardiovascular risk in prepubertal children: The EPOCH study. J Clin Endocrinol Metab. 2012;97(7):1099–105.
31. Evans WJ, Hellerstein M, Orwoll E, Cummings S, Cawthon PM. D3-Creatine dilution and the importance of accuracy in the assessment of skeletal muscle mass. J Cachexia Sarcopenia Muscle. 2019;10(1):14–21.
32. Siervo M, Prado CM, Mire E, Broyles S, Wells JC, Heymsfield S, et al. Body composition indices of a load-capacity model: Gender-and BMI-specific reference curves. Public Health Nutr. 2014;18(7):1245–54.

33. Xiao J, Cain A, Purcell SA, Ormsbee MJ, Contreras RJ, Kim JS, et al. Sarcopenic obesity and health outcomes in patients seeking weight loss treatment. Clin Nutr ESPEN. 2018;23:79–83.
34. Xiao J, Purcell SA, Prado CM, Gonzalez MC. Fat mass to fat-free mass ratio reference values from NHANES III using bioelectrical impedance analysis. Clin Nutr. 2018;37(6):2284–7.
35. Burrows R, Correa-Burrows P, Reyes M, Blanco E, Albala C, Gahagan S. Low muscle mass is associated with cardiometabolic risk regardless of nutritional status in adolescents: A cross-sectional study in a Chilean birth cohort. Pediatr Diabetes. 2017;18:895–902.
36. Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyère O, Cederholm T, et al. Sarcopenia: Revised European consensus on definition and diagnosis. Age Ageing. 2018;0(1):1–16.
37. Cohen DD, Gómez-Arbeláez D, Camacho PA, Pinzon S, Hormiga C, Trejos-Suarez J, et al. Low muscle strength is associated with metabolic risk factors in Colombian children: The ACFIES study. PLoS One. 2014;9(4):1–10.
38. Artero EG, Ruiz JR, Ortega FB, España-Romero V, Vicente-Rodríguez G, Molnar D, et al. Muscular and cardiorespiratory fitness are independently associated with metabolic risk in adolescents: The HELENA study. Pediatr Diabetes. 2011;12(8):704–12.
39. Peterson MD, Zhang P, Saltarelli WA, Visich PS, Gordon PM. Low muscle strength thresholds for the detection of cardiometabolic risk in adolescents. Am J Prev Med. 2016;50(5):593–9.
40. Ramírez-Vélez R, Peña-Ibagon JC, Martínez-Torres J, Tordecilla-Sanders A, Correa-Bautista JE, Lobelo F, et al. Handgrip strength cutoff for cardiometabolic risk index among Colombian children and adolescents: The FUPRECOL Study. Sci Rep. 2017;7(February):1–7.
41. Garcia-Vicencio S, Coudeyre E, Kluka V, Cardenoux C, Jegu AG, Fourot A V., et al. The bigger, the stronger? Insights from muscle architecture and nervous characteristics in obese adolescent girls. Int J Obes. 2016;40(2):245–51.
42. Prado CMM, Siervo M, Mire E, Heymsfield SB, Stephan BCM, Broyles S, et al. A population-based approach to define body-composition phenotypes. Am J Clin Nutr. 2014;99(6):1369–77.
43. Kindler JM, Lobene AJ, Vogel KA, Martin BR, McCabe LD, Peacock M, et al. Adiposity, insulin resistance, and bone mass in children and adolescents. J Clin Endocrinol Metab. 2018;104(3):892–9.

44. Sinha R, Dufour S, Petersen KF, LeBon V, Enoksson S, Ma Y, et al. Assessment of skeletal muscle triglyceride content by ^{1}H nuclear magnetic resonance spectroscopy in lean and obese adolescents. Diabetes. 2002;51:1022–7.
45. Kim JH, Park YS. Low muscle mass is associated with metabolic syndrome in Korean adolescents: The Korea National Health and Nutrition Examination Survey 2009-2011. Nutr Res. 2016;36(12):1423–8.
46. Weber DR, Leonard MB, Shults J, Zemel BS. A comparison of fat and lean body mass index to BMI for the identification of metabolic syndrome in children and adolescents. J Clin Endocrinol Metab. 2014;99(9):3208–16.
47. Lee S, Kim Y, White DA, Kuk JL, Arslanian S. Relationships between insulin sensitivity, skeletal muscle mass and muscle quality in obese adolescent boys. Eur J Clin Nutr. 2012;66(12):1366–8.
48. Weiss R, Dufour S, Taksali SE, Tamborlane W V., Petersen KF, Bonadonna RC, et al. Prediabetes in obese youth: A syndrome of impaired glucose tolerance, severe insulin resistance, and altered myocellular and abdominal fat partitioning. Lancet. 2003;362(9388):951–7.
49. Hong SH, Choi KM. Sarcopenic obesity, insulin resistance, and their implications in cardiovascular and metabolic consequences. Int J Mol Sci. 2020;21(2).
50. Cree-Green M, Wiromrat P, Stuppy JJ, Thurston J, Bergman BC, Baumgartner AD, et al. Muscle insulin resistance in youth with obesity and normoglycemia is associated with altered fat metabolism. Obesity. 2019;27(12):2046–54.
51. Graf C, Ferrari N. Metabolic health — The role of adipo-myokines. 2019;1–21.
52. Kumar S, Hossain J, Inge T, Balagopal PB. Changes in myokines in youths with severe obesity following Roux-en-Y gastric bypass surgery. JAMA Surg. 2019;154(7):668–9.
53. Lee JH, Zhang Y, Zhao Z, Ye X, Zhang X, Wang H, et al. Intracellular ATP in balance of pro- and anti-inflammatory cytokines in adipose tissue with and without tissue expansion. Int J Obes. 2017;41(4):645–51.
54. Rehman K, Akash MSH. Mechanisms of inflammatory responses and development of insulin resistance: How are they interlinked? J Biomed Sci. 2016;23(1):1–18.
55. DeFronzo RA, Tripathy D. Skeletal muscle insulin resistance is the primary defect in type 2 diabetes. Diabetes Care. 2009;32(Suppl 2):S157-63.

56. Stefan N, Schick F, Häring HU. Causes, characteristics, and consequences of metabolically unhealthy normal weight in humans. Cell Metab. 2017;26(2):292–300.
57. Lupton J, Brooks J, Butte N, Caballero B, Flatt J, Fried S. Dietary reference intakes for energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein, and amino acids. Washington, DC; 2002.
58. Iacobucci D, Posavac SS, Kardes FR, Schneider MJ, Popovich DL. Toward a more nuanced understanding of the statistical properties of a median split. J Consum Psychol. 2015;25(4):652–65.
59. Smith GI, Mittendorfer B, Klein S. Metabolically healthy obesity: Facts and fantasies. J Clin Invest. 2019;129(10):3978–89.
60. Weiss R, Bremer AA, Lustig RH. What is metabolic syndrome, and why are children getting it? Ann N Y Acad Sci. 2013;1281(1):123–40.
61. Alberti SG, Zimmet P, Kaufman F, Tajima N, Silink M, Arslanian S, et al. The IDF consensus definition of the metablic syndrome in children and adolescents. International Diabetes Federation. 2007.
62. Blüher S, Schwarz P. Metabolically healthy obesity from childhood to adulthood - Does weight status alone matter? Metabolism. 2014;63(9):1084–92.
63. Caesar R, Tremaroli V, Kovatcheva-Datchary P, Cani PD, Bäckhed F. Crosstalk between gut microbiota and dietary lipids aggravates WAT inflammation through TLR signaling. Cell Metab. 2015;22(4):658–68.
64. Boulangé CL, Neves AL, Chilloux J, Nicholson JK, Dumas ME. Impact of the gut microbiota on inflammation, obesity, and metabolic disease. Genome Med. 2016;8(1):1–12.
65. Karlsson F, Tremaroli V, Nielsen J, Backhed F. Assessing the human gut microbiota in metabolic diseases. Diabetes. 2013;62(10):3341–9.
66. Steffl M, Chrudimsky J, Tufano JJ. Using relative handgrip strength to identify children at risk of sarcopenic obesity. PLoS One. 2017;12(5):1–9.

Alphabetical Bibliography

Abera M, Tesfaye M, Admassu B, Hanlon C, Ritz C, Wibaek R, et al. Body composition during early infancy and developmental progression from 1 to 5 years of age: The Infant Anthropometry and Body Composition (iABC) cohort study among Ethiopian children. Br J Nutr. 2018;119(11):1263–73.

Abera M, Tesfaye M, Girma T, Hanlon C, Andersen GS, Wells JC, et al. Relation between body composition at birth and child development at 2 years of age: A prospective cohort study among Ethiopian children. Eur J Clin Nutr. 2017;71(12):1411–7.

Abera M, Tesfaye M, Hanlon C, Admassu B, Girma T, Wells JC, et al. Body composition during early infancy and mental health outcomes at 5 years of age: A prospective cohort study of Ethiopian children. J Pediatr. 2018;200:225–31.

Adamo KB, Colley RC, Hadjiyannakis S, Goldfield GS. Physical activity and sedentary behavior in obese youth. J Pediatr. 2015;166(5):1270–5.

Adamo KB, Prince SA, Tricco AC, Connor-Gorber S, Tremblay M. A comparison of indirect versus direct measures for assessing physical activity in the pediatric population: A systematic review. Int J Pediatr Obes. 2009;4(1):2–27.

Addison O, Marcus RL, Lastayo PC, Ryan AS. Intermuscular fat: A review of the consequences and causes. Int J Endocrinol. 2014;2014:1–11.

Admassu B, Ritz C, Wells JCK, Girma T, Andersen GS, Belachew T, et al. Accretion of fat-free mass rather than fat mass in infancy is positively associated with linear growth in childhood. J Nutr. 2018;148(4):607–15.

Aguilera CM, Gomez-Llorente C, Tofe I, Gil-campos M, Canete R, Gil A. Genome-wide expression in visceral adipose tissue from obese prepubertal children. Int J Mol Sci. 2015;16:7723–37.

Aguirre CA, Salazar GDC, Lopez De Romaña DV, Kain JA, Corvalán CL, Uauy RE. Evaluation of simple body composition methods: Assessment of validity in prepubertal Chilean children. Eur J Clin Nutr. 2015;69(2):269–73.

Akhmedov D, Berdeaux R. The effects of obesity on skeletal muscle regeneration. Front Physiol. 2013;4 DEC(December):1–12.

Akima H, Kainuma K, Togashi K. Abdominal and thigh muscle attenuation is associated with visceral fat and age inchildren and adolescents with obesity. Glob Pediatr Heal. 2018;5:1–9.

Akyol B, Boyraz M, Aysoy C. Relationship of epicardial adipose tissue thickness with early indicators of atherosclerosis and cardiac functional changes in obese adolescents with metabolic syndrome. J Clin Res Pediatr Endocrinol. 2013;5(3):156–63.

Alberga AS, Prud'homme D, Sigal RJ, Goldfield GS, Hadjiyannakis S, Phillips P, et al. Effects of aerobic training, resistance training, or both on cardiorespiratory and musculoskeletal fitness in adolescents with obesity: the HEARTY trial. Appl Physiol Nutr Metab. 2016;41(3):255–65.

Alberti SG, Zimmet P, Kaufman F, Tajima N, Silink M, Arslanian S, et al. The IDF consensus definition of the metablic syndrome in children and adolescents. International Diabetes Federation. 2007.

Alves AC, Silva NMG De, Karhunen V, Sovio U, Das S, Taal HR, et al. GWAS on longitudinal growth traits reveals different genetic factors influencing infant, child, and adult BMI. Sci Adv. 2019;5:1–18.

Andersen GS, Girma T, Wells JCK, Kastel P, Michaelsen KF, Friis H. Fat and fat-free mass at birth: Air displacement plethysmography measurements on 350 Ethiopian newborns. Pediatr Res. 2011;70(5):501–6.

Andersen LB, Harro M, Sardinha LB, Froberg K, Ekelund U, Brage S, et al. Physical activity and clustered cardiovascular risk in children: a cross-sectional study (The European Youth Heart Study). Lancet. 2006;368(9532):299–304.

Anderson SE, Whitaker RC. Prevalence of obesity among US preschool children in different racial and ethnic groups. Arch Pediatr Adolesc Med. 2009;163(4):344–8.

Appelhans BM. Neurobehavioral inhibition of reward-driven feeding: Implications for dieting and obesity. Obesity. 2009;17(4):640–7.

Araújo AJS, Santos ACO, Prado WL. Body composition of obese adolescents: association between adiposity indicators and cardiometabolic risk factors. J Hum Nutr Diet. 2017;30(2):193–202.

Arfai K, Pitukcheewanont PD, Goran MI, Tavare CJ, Heller L, Gilsanz V. Bone, muscle, and fat: sex-related differences in prepubertal children. Radiology. 2002;224(2):338–44.

Arslanian S, Suprasongsin C. Testosterone treatment in adolescents with delayed puberty: Changes in body composition, protein, fat, and glucose metabolism. J Clin Endocrinol Metab. 1997;82(10):3213–20.

Artero EG, Ruiz JR, Ortega FB, España-Romero V, Vicente-Rodríguez G, Molnar D, et al. Muscular and cardiorespiratory fitness are independently associated with metabolic risk in adolescents: The HELENA study. Pediatr Diabetes. 2011;12(8):704–12.

Asayama K, Dobashi K, Hayashibe H, Kodera K, Uchida N, Nakane T, et al. Threshold values of visceral fat measures and their anthropometric alternatives for metabolic derangement in Japanese obese boys. Int J Obes. 2002;26(2):208–13.

Assmann KE, Joslowski G, Buyken AE, Cheng G, Remer T, Kroke A, et al. Prospective association of protein intake during puberty with body composition in young adulthood. Obesity. 2013;21(12):782–9.

Atherton RR, Williams JE, Wells JCK, Fewtrell MS. Use of fat mass and fat free mass standard deviation scores obtained using simple measurement methods in healthy children and patients: Comparison with the reference 4-component model. PLoS One. 2013;8(5):1–10.

Bäckhed F, Roswall J, Peng Y, Feng Q, Jia H, Kovatcheva-Datchary P, et al. Dynamics and stabilization of the human gut microbiome during the first year of life. Cell Host Microbe. 2015;17(5):690–703.

Baker J, Workman M, Bedrick E, Frey MA, Hurtado M, Pearson O. Brains versus brawn: An empirical test of barkers brain sparing model. Am J Hum Biol. 2010;22(2):206–15.

Ball GDC, Huang TTK, Cruz ML, Shaibi GQ, Weigensberg MJ, Goran MI. Predicting abdominal adipose tissue in overweight Latino youth. Int J Pediatr Obes. 2006;1(4):210–6.

Bammann K, Huybrechts I, Vicente-Rodriguez G, Easton C, De Vriendt T, Marild S, et al. Validation of anthropometry and foot-to-foot bioelectrical resistance against a three-component model to assess total body fat in children: The IDEFICS study. Int J Obes. 2013;37(4):520–6.

Barbour-Tuck E, Erlandson M, Muhajarine N, Foulds H, Baxter-Jones A. Influence of childhood and adolescent fat development on fat mass accrual during emerging adulthood: a 20-year longitudinal study. Obesity. 2018;26(3):613–20.

Barnes MJ, Lynch MK, Lisenby MD, Jester T, Maclin J, Knight T, et al. Conceptual model of lean body mass in pediatric inflammatory bowel disease. J Pediatr Gastroenterol Nutr. 2019;68(3):301–5.

Bassols J, Martínez-Calcerrada JM, Prats-Puig A, Carreras-Badosa G, Xargay-Torrent S, Lizarraga-Mollinedo E, et al. Perirenal fat is related to carotid intima-media thickness in children. Int J Obes. 2018;42(4):641–7.

Battistini N, Brambilla P, Virgili F, Simone P, Bedogni G, Morini P, et al. The prediction of total body water from body impedance in young obese subjects. Int J Obes. 1992;16(3):207–12.

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(8):755–63.

Bazzocchi A, Filonzi G, Ponti F, Amadori M, Sassi C, Salizzoni E, et al. The role of ultrasonography in the evaluation of abdominal fat: Analysis of technical and methodological issues. Acad Radiol. 2013;20(10):1278–85.

Bedogni G, Bollea MR, Severi S, Trunfio O, Manzieri AM, Battistini N. The prediction of total body water and extracellular water from bioelectric impedance in obese children. Eur J Clin Nutr. 1997;51(3):129–33.

Behm DG, Faigenbaum AD, Falk B, Klentrou P. Canadian Society for Exercise Physiology position paper: Resistance training in children and adolescents. Appl Physiol Nutr Metab. 2008;33(3):547–61.

Bell KA, Wagner CL, Feldman HA, Shypailo RJ, Belfort MB. Associations of infant feeding with trajectories of body composition and growth. Am J Clin Nutr. 2017;106(2):491–8.

Berger-Kulemann V, Brugger PC, Reisegger M, Klein K, Hachemian N, Koelblinger C, et al. Quantification of the subcutaneous fat layer with MRI in fetuses of healthy mothers with no underlying metabolic disease vs. fetuses of diabetic and obese mothers. J Perinat Med. 2012;40(2):179–84.

Bhatia R, Lesser DJ, Oliveira FGSA, Tran WH, Keens TG, Khoo MCK, et al. Body fat composition: A predictive factor for sleep related breathing disorder in obese children. J Clin Sleep Med. 2015;11(9):1039–45.

Bielemann RM, Gigante DP, Horta BL. Birth weight, intrauterine growth restriction and nutritional status in childhood in relation to grip strength in adults: From the 1982 Pelotas (Brazil) birth cohort. Nutrition. 2016;32(2):228–35.

Billon N, Monteiro MC, Dani C. Developmental origin of adipocytes: new insights into a pending question. Biol Cell. 2008;100(10):583–575.

Bispham J, Gopalakrishnan GS, Dandrea J, Wilson V, Budge H, Keisler DH, et al. Maternal endocrine adaptation throughout pregnancy to nutritional manipulation: Consequences for maternal plasma leptin and cortisol and the programming of fetal adipose tissue development. Endocrinology. 2003;144(8):3575–85.

Black PMM, Walker PSP, Fernald LCH, Andersen CT, Digirolamo AM, Lu C, et al. Advancing early childhood development: From science to scale 1: Early childhood development coming of age: science through the life course. Lancet. 2017;389(10064):77–90.

Blackett PR, Wilson DP, McNeal CJ. Secondary hypertriglyceridemia in children and adolescents. J Clin Lipidol. 2015;9(5):S29–40.

Blakeley CE, Van Rompay MI, Schultz NS, Sacheck JM. Relationship between muscle strength and dyslipidemia, serum 25(OH)D, and weight status among diverse schoolchildren: A cross-sectional analysis. BMC Pediatr. 2018;18(1):23.

Blimkie CJR, Sale DG, Bar-Or O. Voluntary strength, evoked twitch contractile properties and motor unit activation of knee extensors in obese and non-obese adolescent males. Eur J Appl Physiol Occup Physiol. 1990;61(3–4):313–8.

Blüher S, Schwarz P. Metabolically healthy obesity from childhood to adulthood - Does weight status alone matter? Metabolism. 2014;63(9):1084–92.

Boisseau N, Delamarche P. Metabolic and hormonal responses to exercise in children and adolescents. Sport Med. 2000;30(6):405–22.

Borgo F, Verduci E, Riva A, Lassandro C, Riva E, Morace G, et al. Relative abundance in bacterial and fungal gut microbes in obese children: a case control study. Child Obes. 2017;13(1):78–84.

Boswell N, Byrne R, Davies PSW. Aetiology of eating behaviours: a possible mechanism to understand obesity development in early childhood. Neurosci Biobehav Rev. 2018;95(November):438–48.

Bouchard C, Tremblay A, Despres J-P, Nadeau A, Lupien PJ, Theriault G, et al. The response to long-term overfeeding in identical twins. N Engl J Med. 1990;332(21):1477–82.

Boulangé CL, Neves AL, Chilloux J, Nicholson JK, Dumas ME. Impact of the gut microbiota on inflammation, obesity, and metabolic disease. Genome Med. 2016;8(1):1–12.

Boulet SL, Schieve LA, Boyle CA. Birth weight and health and developmental outcomes in US children, 1997-2005. Matern Child Health J. 2011;15(7):836–44.

Boyle KE, Patinkin ZW, Shapiro ALB, Baker PR, Dabelea D, Friedman JE. Mesenchymal stem cells from infants born to obese mothers exhibit greater potential for adipogenesis: The healthy start babybump project. Diabetes. 2016;65(3):647–59.

Brand-Saberi B. Genetic and epigenetic control of skeletal muscle development. Ann Anat. 2005;187(3):199–207.

Bray GA, DeLany JP, Harsha DW, Volaufova J, Champagne CC. Evaluation of body fat in fatter and leaner 10-y-old African American and white children: The Baton Rouge children's study. Am J Clin Nutr. 2001;73(4):687–702.

Bray GA, DeLany JP, Volaufova J, Harsha DW, Champagne C. Prediction of body fat in 12-y-old African American and white children: Evaluation of methods. Am J Clin Nutr. 2002;76(5):980–90.

Breij LM, Abrahamse-Berkeveld M, Acton D, De Lucia Rolfe E, Ong KK, Hokken-Koelega ACS. Impact of early infant growth, duration of breastfeeding and maternal factors on total body fat mass and visceral fat at 3 and 6 months of age. Ann Nutr Metab. 2017;71(3–4):203–10.

Brion MA, Ness AR, Davey Smith G, Leary SD. Association between body composition and blood pressure in a contemporary cohort of 9-year-old children. J Hum Hypertens. 2007;21(4):283–90.

Brown AW, Altman DG, Baranowski T, Bland JM, Dawson JA, Dhurandhar NV, et al. Childhood obesity intervention studies: A narrative review and guide for investigators, authors, editors, reviewers, journalists, and readers to guard against exaggerated effectiveness claims. Obes Rev. 2019;20(11):1523–41.

Brown L, Clegg D. Central effects of estradiol in the regulation of adiposity. J Steroid Biochem Mol Biol. 2010;122(1–3):65–73.

Brumbaugh DE, Crume TL, Nadeau K, Scherzinger A, Dabelea D. Intramyocellular lipid is associated with visceral adiposity, markers of insulin resistance, and cardiovascular risk in prepubertal children: The EPOCH study. J Clin Endocrinol Metab. 2012;97(7):1099–105.

Burrows R, Correa-Burrows P, Reyes M, Blanco E, Albala C, Gahagan S. High cardiometabolic risk in healthy Chilean adolescents: Associations with anthropometric, biological and lifestyle factors. Public Health Nutr. 2015;19(3):486–93.

Burrows R, Correa-Burrows P, Reyes M, Blanco E, Albala C, Gahagan S. Low muscle mass is associated with cardiometabolic risk regardless of nutritional status in adolescents: A cross-sectional study in a Chilean birth cohort. Pediatr Diabetes. 2017;18:895–902.

Butcher A, Kabiri LS, Brewer W, Ortiz A. Criterion validity and sensitivity to change of a pediatric bioelectrical impedance analysis scale in adolescents. Child Obes. 2019;15(2):142–8.

Cabeço LC, Budri PE, Baroni M, Castan EP, Carani FR, De Souza PAT, et al. Maternal protein restriction induce skeletal muscle changes without altering the MRFs MyoD and myogenin expression in offspring. J Mol Histol. 2012;43(5):461–71.

Caesar R, Tremaroli V, Kovatcheva-Datchary P, Cani PD, Bäckhed F. Crosstalk between gut microbiota and dietary lipids aggravates WAT inflammation through TLR signaling. Cell Metab. 2015;22(4):658–68.

Cameron JD, Sigal RJ, Kenny GP, Alberga AS, Prud'homme D, Phillips P, et al. Body composition and energy intake — skeletal muscle mass is the strongest predictor of food intake in obese adolescents: The HEARTY trial. Appl Physiol Nutr Metab. 2016;41(6):611–7.

Campbell KJ, Crawford DA, Salmon J, Carver A, Garnett SP, Baur LA. Associations between the home food environment and obesity-promoting eating behaviors in adolescence. Obesity. 2007;15(3):719–30.

Canapari CA, Hoppin AG, Kinane TB, Thomas BJ, Torriani M, Katz ES. Relationship between sleep apnea, fat distribution, and insulin resistance in obese children. J Clin Sleep Med. 2011;7(3):268–73.

Cani PD, Amar J, Iglesias MA, Poggi M, Knauf C, Bastelica D, et al. Metabolic endotoxemia initiates obesity and insulin resistance. Diabetes. 2007;56(5):1232–42.

Caresio C, Molinari F, Emanuel G, Minetto MA. Muscle echo intensity: Reliability and conditioning factors. Clin Physiol Funct Imaging. 2015;35(5):393–403.

Carvennec M Le, Fagour C, Adenis-lamarre E, Perlemoine C, Gin H, Rigalleau V. Body composition of obese subjects by air displacement plethysmography: The influence of hydration. Obesity. 2007;15(1):78–84.

Cassidy SB, Schwartz S, Miller JL, Driscoll DJ. Prader-Willi syndrome. Genet Med. 2012;14(1):10–26.

Cauley JA. An Overview of Sarcopenic Obesity. J Clin Densitom. 2015;18(4):499–505.

Cejas CP, Serra MM, Galvez DFG, Cavassa EA, Taratuto AL, Vazquez GA, et al. Muscle MRI in pediatrics: Clinical, pathological and genetic correlation. Pediatr Radiol. 2017;47:724–35.

Chambers ES, Viardot A, Psichas A, Morrison DJ, Murphy KG, Zac-Varghese SEK, et al. Effects of targeted delivery of propionate to the human colon on appetite regulation, body weight maintenance and adiposity in overweight adults. Gut. 2015;64(11):1744–54.

Chan DCC, Lee WTK, Lo DHS, Leung JCS, Kwok AWL, Leung PC. Relationship between grip strength and bone mineral density in healthy Hong Kong adolescents. Osteoporos Int. 2008;19(10):1485–95.

Chan DFY, Li AM, So HK, Yin J, Nelson EAS. New skinfold-thickness equation for predicting percentage body fat in Chinese obese children. Hong Kong J Paediatr. 2009;14(2):96–102.

Chen X, Wang Y. Tracking of blood pressure from childhood to adulthood: A systematic review and meta-regression analysis. Circulation. 2008;117(25):3171–80.

Cheng S, Wiklund P. The effects of muscle mass and muscle quality on cardio-metabolic risk in peripubertal girls: A longitudinal study from childhood to early adulthood. Int J Obes. 2018 Oct 30;42:648.

Chomtho S, Wells JCK, Williams JE, Davies PSW, Lucas A, Fewtrell MS. Infant growth and later body composition: evidence from the 4-component model. Am J Clin Nutr. 2008;87(6):1776–84.

Chomtho S, Wells JCK, Williams JE, Lucas A, Fewtrell MS. Associations between birth weight and later body composition: Evidence from the 4-component model. Am J Clin Nutr. 2008;88(4):1040–8.

Chou JH, Roumiantsev S, Singh R. PediTools electronic growth chart calculators: Applications in clinical care, research, and quality improvement. J Med Internet Res. 2020;22(1):1–17.

Chung ST, Ha J, Onuzuruike AU, Kasturi K, Galvan-De La Cruz, M. Bingham BA, Sumner AE. Time to glucose peak during an oral glucose tolerance test identifies prediabetes risk. Clin Endocrinol (Oxf). 2017;87(5):484–91.

Cleary J, Daniells S, Okely AD, Batterham M, Nicholls J. Predictive validity of four bioelectrical impedance equations in determining percent fat mass in overweight and obese children. J Am Diet Assoc. 2008;108(1):136–9.

Cleasby ME, Jamieson PM, Atherton PJ. Insulin resistance and sarcopenia: Mechanistic links between common co-morbidities. J Endocrinol. 2016;229(2):R67–81.

Cohen DD, Gómez-Arbeláez D, Camacho PA, Pinzon S, Hormiga C, Trejos-Suarez J, et al. Low muscle strength is associated with metabolic risk factors in Colombian children: The ACFIES study. PLoS One. 2014;9(4):1–10.

Colantonio E, Dâmaso AR, Caranti DA, Pinheiro MM, Tufik S, De Mello MT. Clinical performance of 3-body fat measurements in obese adolescents 15 to 18 years-old. Rev Bras Med. 2015;72(3):77–82.

Cole TJ, Ahmed ML, Preece MA, Hindmarsh P, Dunger DB. The relationship between insulin-like growth factor 1, sex steroids and timing of the pubertal growth spurt. Clin Endocrinol (Oxf). 2015;82(6):862–9.

Cole TJ. Weight/heightp compared to weight/height2 for assessing adiposity in childhood: Influence of age and bone age on p during puberty. Ann Hum Biol. 1986;13(5):433–51.

Colley RC, Carson V, Garriguet D, Janssen I, Roberts KC, Tremblay MS. Physical activity of Canadian children and youth, 2007 to 2015. Heal Reports. 2017;28(10):8–16.

Cortés-Castell E, Juste M, Palazón-Bru A, Monge L, Sánchez-Ferrer F, Rizo-Baeza MM. A simple equation to estimate body fat percentage in children with overweightness or obesity: A retrospective study. PeerJ. 2017;2017(4):1–14.

Costa-Orvay JA, Figueras-Aloy J, Romera G, Closa-Monasterolo R, Carbonell-Estrany X. The effects of varying protein and energy intakes on the growth and body composition of very low birth weight infants. Nutr J. 2011;10(1):1–9.

Cote AT, Harris KC, Panagiotopoulos C, Sandor GGS, Devlin AM. Childhood obesity and cardiovascular dysfunction. J Am Coll Cardiol. 2013;62(15):1309–19.

Cree-Green M, Wiromrat P, Stuppy JJ, Thurston J, Bergman BC, Baumgartner AD, et al. Muscle insulin resistance in youth with obesity and normoglycemia is associated with altered fat metabolism. Obesity. 2019;27(12):2046–54.

Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyère O, Cederholm T, et al. Sarcopenia: Revised European consensus on definition and diagnosis. Age Ageing. 2018;0(1):1–16.

Currie C, Ahluwalia N, Godeau E, Nic Gabhainn S, Due P, Currie DB. Is obesity at individual and national level associated with lower age at menarche? Evidence from 34 countries in the health behaviour in school-aged children study. J Adolesc Heal. 2012;50(6):621–6.

Dalrymple K V., Thompson JMD, Begum S, Godfrey KM, Poston L, Seed PT, et al. Relationships of maternal body mass index and plasma biomarkers with childhood body mass index and adiposity at 6 years: The Children of SCOPE study. Pediatr Obes. 2019;14(10):1–12.

Damanhoury S, Newton AS, Rashid M, Hartling L, Byrne JLS, Ball GDC. Defining metabolically healthy obesity in children: A scoping review. Obes Rev. 2018;(November):1476–91.

Daniels SR, Kimball TR, Khoury P, Witt S, Morrison JA. Correlates of the hemodynamic determinants of blood pressure. Hypertension. 1996;28(1):37–41.

Darabian S, Hormuz M, Latif MA, Pahlevan S, Budoff MJ. The role of carotid intimal thickness testing and risk prediction in the development of coronary atherosclerosis. Curr Atheroscler Rep. 2013;15(3):1–6.

de Mello MT, Damaso AR, Antunes HKM, Siqueira KO, Castro ML, Bertolino S V., et al. Body composition evaluation in obese adolescents: The use of two different methods. Rev Bras Med do Esporte. 2005;11(5):251–4.

DeFronzo RA, Jacot E, Jequier E, Maeder E, Wahren J, Felber JP. The effect of insulin on the disposal of intravenous glucose: Results from indirect calorimetry and hepatic and femoral venous catheterization. Diabetes. 1981;30(12):1000–7.

DeFronzo RA, Tripathy D. Skeletal muscle insulin resistance is the primary defect in type 2 diabetes. Diabetes Care. 2009;32(Suppl 2):S157-63.

Deillon E, Hauschild M, Faouzi M, Stoppa-Vaucher S, Elowe-Gruau E, Dwyer A, et al. Natural history of growth hormone deficiency in a pediatric cohort. Horm Res Paediatr. 2015;83(4):252–61.

Delezie J, Handschin C. Endocrine crosstalk between skeletal muscle and the brain. Front Neurol. 2018;9:698.

Devonshire AL, Hager ER, Black MM, Diener-West M, Tilton N, Snitker S. Elevated blood pressure in adolescent girls: Correlation to body size and composition. BMC Public Health. 2016;16(1):1–7.

Dhuper S, Sakowitz S, Daniels J, Buddhe S, Cohen HW. Association of lipid abnormalities with measures and severity of adiposity and insulin resistance among overweight children and adolescents. J Clin Hypertens. 2009;11(10):594–600.

Di Cesare M, Sorić M, Bovet P, Miranda JJ, Bhutta Z, Stevens GA, et al. The epidemiological burden of obesity in childhood: A worldwide epidemic requiring urgent action. BMC Med. 2019;17(1):212.

Dias KA, Ingul CB, Tjønna AE, Keating SE, Gomersall SR, Follestad T, et al. Effect of high-intensity interval training on fitness, fat mass and cardiometabolic biomarkers in children with obesity: a randomised controlled trial. Sport Med. 2018;48(3):733–46.

Dias KA, Ramos JS, Wallen MP, Davies PSW, Cain PA, Leong GM, et al. Accuracy of longitudinal assessment of visceral adipose tissue by dual-energy X-ray absorptiometry in children with obesity. J Obes. 2019;2019:1–12.

Dodds R, Denison HJ, Ntani G, Cooper R, Cooper C, Sayer a a, et al. Birth weight and muscle strength: A systematic review and meta-analysis. J Nutr Health Aging. 2012;16(7):609–15.

Donin AS, Nightingale CM, Owen C, Rudnicka AR, McNamara M, Prynne CJ, et al. Ethnic differences in blood lipids and dietary intake between UK children of black African, black Caribbean, South Asian, and white European origin: The Child Heart and Health Study in England (CHASE). Am J Clin Nutr. 2010;92(4):776–83.

Dorsey KB, Thornton JC, Heymsfield SB, Gallagher D. Greater lean tissue and skeletal muscle mass are associated with higher bone mineral content in children. Nutr Metab (Lond). 2010;7(1):41.

Dotan R, Mitchell C, Cohen R, Klentrou P, Gabriel D, Bareket F. Child-adult differences in muscle activation - A review. Pediatr Exerc Sci. 2012;24(1):2–21.

Dulloo AG, Jacquet J, Seydoux J, Montani JP. The thrifty 'catch-up fat' phenotype: Its impact on insulin sensitivity during growth trajectories to obesity and metabolic syndrome. Int J Obes. 2006;30:S23–35.

Duran I, Martakis K, Hamacher S, Stark C, Semler O, Schoenau E. Are there effects of age, gender, height, and body fat on the functional muscle-bone unit in children and adults? Osteoporos Int. 2018;29(5):1069–79.

Durheim MT, Slentz CA, Bateman LA, Mabe SK, Kraus WE. Relationships between exercise-induced reductions in thigh intermuscular adipose tissue, changes in lipoprotein particle size, and visceral adiposity. Am J Physiol - Endocrinol Metab. 2008;295(2):407–12.

Earthman CP. Body composition tools for assessment of adult malnutrition at the bedside: A tutorial on research considerations and clinical applications. J Parenter Enter Nutr. 2015;39(7):787–822.

Eckel J. Adipose tissue: A major secretory organ. In: The Cellular Secretome and Organ Crosstalk. Academic Press; 2018. p. 9–63.

Eisenkölbl J, Kartasurya M, Widhalm K. Underestimation of percentage fat mass measured by bioelectrical impedance analysis compared to dual energy X-ray absorptiometry method in obese children. Eur J Clin Nutr. 2001;55(6):423–9

Elberg J, McDuffie J, Sebring N, Salaita C, Keil M, Robotham D, et al. Comparison of methods to assess change in children's body composition. Am J Clin Nutr. 2004;80(1):64–9.

Elmaogullari S, Demirel F, Hatipoglu N. Risk factors that affect metabolic health status in obese children. J Pediatr Endocrinol Metab. 2017;30(1):49–55.

Ertunc ME, Hotamisligil GS. Lipid signaling and lipotoxicity in metaflammation: Indications for metabolic disease pathogenesis and treatment. J Lipid Res. 2016;57(12):2099–114.

Evans WJ, Hellerstein M, Orwoll E, Cummings S, Cawthon PM. D3-Creatine dilution and the importance of accuracy in the assessment of skeletal muscle mass. J Cachexia Sarcopenia Muscle. 2019;10(1):14–21.

Evenson KR, Catellier DJ, Gill K, Ondrak KS, McMurray RG. Calibration of two objective measures of physical activity for children. J Sports Sci. 2008;26(14):1557–65.

Fields DA, Goran MI. Body composition techniques and the four-compartment model in children. J Appl Physiol. 2000;89(2):613–20.

Fields DA, Allison DB. Air-displacement plethysmography pediatric option in 2–6 years old using the 4-compartment model as a criterion method. Obes (Silver Spring). 2012;20(8):1732–7.

Fields DA, Goran MI, McCrory MA. Body-composition assessment via air-displacement plethysmography in adults and children: A review. Am J Clin Nutr. 2002;75(3):453–67.

Flynn AC, Thompson JMD, Dalrymple K V., Wall C, Begum S, Pallippadan Johny J, et al. Childhood dietary patterns and body composition at age 6 years: The Children of SCOPE study. Br J Nutr. 2020;1–21.

Flynn JT, Kaelber DC, Baker-Smith CM, Blowey D, Carroll AE, Daniels SR, et al. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. Pediatrics. 2017;140(3):e20171904.

Forbes JD, Azad MB, Vehling L, Tun HM, Konya TB, Guttman DS, et al. Association of exposure to formula in the hospital and subsequent infant feeding practices with gut microbiota and risk of overweight in the first year of life. JAMA Pediatr. 2018;172(7):e181161.

Freedman DS, Horlick M, Berenson GS. A comparison of the Slaughter skinfold-thickness equations and BMI in predicting body fatness and cardiovascular disease risk factor levels in children. Am J Clin Nutr. 2013;98(6):1417–24.

Freedman DS, Wang J, Thornton JC, Mei Z, Pierson Jr RN, Dietz WH, et al. Racial/ethnic differences in body fatness among children and adolescents. Obesity. 2008;16(5):1105–11.

Fricke O, Schoenau E. The "Functional Muscle-Bone Unit": Probing the relevance of mechanical signals for bone development in children and adolescents. Growth Horm IGF Res. 2007;17(1):1–9.

Friedemann C, Heneghan C, Mahtani K, Thompson M, Perera R, Ward AM. Cardiovascular disease risk in healthy children and its association with body mass index: Systematic review and meta-analysis. BMJ. 2012;345(7876):1–16.

Frontera WR, Ochala J. Skeletal muscle: A brief review of structure and function. Calcif Tissue Int. 2015;96(3):183–95.

Fuemmeler BF, Sheng Y, Schechter JC, Do E, Zucker N, Majors A, et al. Associations between attention deficit hyperactivity disorder symptoms and eating behaviors in early childhood. Pediatr Obes. 2020;e12631:1–10.

Fukada SI. The roles of muscle stem cells in muscle injury, atrophy and hypertrophy. J Biochem. 2018;163(5):353–8.

Fuller NJ, Jebb SA, Laskey MA, Coward WA, Elia M. Four-component model for the assessment of body composition in humans: Comparison with alternative methods, and evaluation of the density and hydration of fat-free mass. Clin Sci. 1992;82(6):687–93.

Füssenich LM, Boddy LM, Green DJ, Graves LEF, Foweather L, Dagger RM, et al. Physical activity guidelines and cardiovascular risk in children: A cross sectional analysis to determine whether 60 minutes is enough. BMC Public Health. 2016;16(1):1–7.

Gaines J, Vgontzas AN, Fernandez-Mendoza J, Calhoun SL, He F, Liao D, et al. Inflammation mediates the association between visceral adiposity and obstructive sleep apnea in adolescents. Am J Physiol - Endocrinol Metab. 2016;311:E851–8.

Garcia-Vicencio S, Coudeyre E, Kluka V, Cardenoux C, Jegu AG, Fourot A V., et al. The bigger, the stronger? Insights from muscle architecture and nervous characteristics in obese adolescent girls. Int J Obes. 2016;40(2):245–51.

Garcia-Vicencio S, Martin V, Kluka V, Cardenoux C, Jegu AG, Fourot AV, et al. Obesity-related differences in neuromuscular fatigue in adolescent girls. Eur J Appl Physiol. 2015;115(11):2421–32.

Garlick PJ. Protein requirements of infants and children. Nestle Nutr Work Ser Pediatr Progr. 2006;58:39–50.

Gately PJ, Radley D, Cooke CB, Carroll S, Oldroyd B, Truscott JG, et al. Comparison of body composition methods in overweight and obese children. J Appl Physiol. 2003;95(5):2039–46.

Gawlik KI. At the crossroads of clinical and preclinical research for muscular dystrophy-are we closer to effective treatment for patients? Int J Mol Sci. 2018;19(5).

Gepstein V, Weiss R. Obesity as the main risk factor for metabolic syndrome in children. Front Endocrinol (Lausanne). 2019;10(August):1–7.

Gheller BJ, Gheller M, Li A, Nunes F, Anini Y, Glanville NT, et al. Effect of dairy and nondairy snacks on postprandial blood glucose regulation in 9–14-year-old children. Appl Physiol Nutr Metab. 2019;44(10):1073–80.

Gillis L, Bar-Or O, Calvert R. Validating a practical approach to determine weight control in obese children and adolescents. Int J Obes. 2000;24(12):1648–52.

Gingras V, Aris IM, Rifas-Shiman SL, Switkowski KM, Oken E, Hivert MF. Timing of complementary feeding introduction and adiposity throughout childhood. Pediatrics. 2019;144(6):e20191320.

Gishti O, Gaillard R, Durmus B, Abrahamse M, Van Der Beek EM, Hofman A, et al. BMI, total and abdominal fat distribution, and cardiovascular risk factors in school-age children. Pediatr Res. 2015;77(5):710–8.

Glass NA, Torner JC, Letuchy EM, Burns TL, Janz KF, Eichenberger Gilmore JM, et al. Does visceral or subcutaneous fat influence peripheral cortical bone strength during adolescence? A longitudinal study. J Bone Miner Res. 2018;33(4):580–8.

Goldfield GS, Cloutier P, Mallory R, Prud'homme D, Parker T, Doucet E. Validity of foot-to-foot bioelectrical impedance analysis in overweight and obese children and parents. J Sports Med Phys Fitness. 2006;46(3):447–53.

Gonzalez MC. Using bioelectrical impedance analysis for body composition assessment: Sorting out some misunderstandings. J Parenter Enter Nutr. 2019;43(8):954–5.

González-Ruíz K, Medrano M, Correa-Bautista JE, García-Hermoso A, Prieto-Benavides DH, Tordecilla-Sanders A, et al. Comparison of bioelectrical impedance analysis, Slaughter skinfold-thickness equations, and dual-energy X-ray absorptiometry for estimating body fat percentage in Colombian children and adolescents with excess of adiposity. Nutrients. 2018;10(8):1–14.

Goodpaster BH, Wolf D. Skeletal muscle lipid accumulation in obesity, insulin resistance, and type 2 diabetes. Pediatr Diabetes. 2004;5(4):219–26.

Goran MI. Measurement issues related to studies of childhood obesity: Assessment of body composition, body fat distribution, physical activity, and food intake. Pediatrics. 1998;101(Supplement 2):505–18.

Gracia-Marco L, Moreno LA, Ruiz JR, Ortega FB, de Moraes ACF, Gottrand F, et al. Body composition indices and single and clustered cardiovascular disease risk factors in adolescents: Providing clinical-based cut-points. Prog Cardiovasc Dis. 2016;58(5):555–64.

Graf C, Ferrari N. Metabolic health — The role of adipo-myokines. 2019;1–21.

Granacher U, Goesele A, Roggo K, Wischer T, Fischer S, Zuerny C, et al. Effects and mechanisms of strength training in children. Int J Sport Med. 2011;32:357–64.

Gregory JW, Greene SA, Thompson J, Scrlmgeour CM, Rennle MJ. Effects of oral testosterone undecanoate on growth, body composition, strength and energy expenditure of adolescent boys. Clin Endocrinol (Oxf). 1992;37(3):207–13.

Gridneva Z, Rea A, Tie WJ, Lai CT, Kugananthan S, Ward LC, et al. Carbohydrates in human milk and body composition of term infants during the first 12 months of lactation. Nutrients. 2019;11(1472):1–24.

Griffin IJ, Cooke RJ. Development of whole body adiposity in preterm infants. Early Hum Dev. 2012;88:S19–24.

Gulotta G, Iannella G, Vicini C, Polimeni A, Greco A, de Vincentiis M, et al. Risk factors for obstructive sleep apnea syndrome in children: State of the art. Int J Environ Res Public Health. 2019;16(3235):1–20.

Gunther AL, Remer T, Kroke A, Buyken AE. Early protein intake and later obesity risk: Which protein sources at which time points throughout infancy and childhood are important for body mass index and body fat percentage at 7 y of age ? Am J Clin Nutr. 2007;(86):1765–72.

Haapala EA, Väistö J, Lintu N, Tompuri T, Brage S, Westgate K, et al. Adiposity, physical activity, and neuromuscular performance in children. J Sports Sci. 2016;34(18):1699–706.

Hall DMB, Cole TJ. What use is the BMI? Arch Dis Child. 2006;91(4):283–6.

Hao G, Wang X, Treiber FA, Harshfield G, Kapuku G, Su S. Body mass index trajectories in childhood is predictive of cardiovascular risk: Results from the 23-year longitudinal Georgia Stress and Heart study. Int J Obes. 2018;42(4):923–5.

Harding J, Johnston B. Nutrition and fetal growth. Reprod Fertil Dev. 1995;7(3):539–47.

Haroun D, Croker H, Viner RM, Williams JE, Darch TS, Fewtrell MS, et al. Validation of BIA in obese children and adolescents and re-evaluation in a longitudinal study. Obesity. 2009;17(12):2245–50.

Haroun D, Wells JCK, Williams JE, Fuller NJ, Fewtrell MS, Lawson MS. Composition of the fat-free mass in obese and nonobese children: Matched case-control analyses. Int J Obes. 2005;29(1):29–36.

Harris C, Buyken A, Von Berg A, Berdel D, Lehmann I, Hoffmann B, et al. Prospective associations of meat consumption during childhood with measures of body composition during adolescence: Results from the GINIplus and LISAplus birth cohorts. Nutr J. 2016;15(1).

Haylett WL, Ferris WF. Adipocyte–progenitor cell communication that influences adipogenesis. Cell Mol Life Sci. 2020;77(1):115–28.

He J, Cai Z, Fan X. Prevalence of binge and loss of control eating among children and adolescents with overweight and obesity: An exploratory meta-analysis. Int J Eat Disord. 2017;50(2):91–103.

He Q, Horlick M, Fedun B, Wang J, Pierson RN, Heshka S, et al. Trunk fat and blood pressure in children through puberty. Circulation. 2002;105(9):1093–8.

Heinonen S, Jokinen R, Rissanen A, Pietiläinen KH. White adipose tissue mitochondrial metabolism in health and in obesity. Obes Rev. 2019;21(2):1–23.

Helgeland Ø, Vaudel M, Juliusson PB, Holmen OL, Juodakis J, Bacelis J, et al. Genome-wide association study reveals dynamic role of genetic variation in infant and early childhood growth. Nat Commun. 2019;10(4448).

Herda TJ, Ryan ED, Kohlmeier M, Trevino MA, Gerstner GR, Roelofs EJ, et al. Muscle cross-sectional area and motor unit properties of the medial gastrocnemius and vastus lateralis in normal weight and overfat children. Exp Physiol. 2020;105(2):335–46.

Herman KM, Sabiston CM, Mathieu ME, Tremblay A, Paradis G. Sedentary behavior in a cohort of 8- to 10-year-old children at elevated risk of obesity. Prev Med (Baltim). 2014;60:115–20.

Hetherington-Rauth M, Bea JW, Blew RM, Funk JL, Hingle MD, Lee VR, et al. Relative contributions of lean and fat mass to bone strength in young Hispanic and non-Hispanic girls. Bone. 2018;113:144–50.

Heymsfield SB, Wang Z, Baumgartner RN, Ross R. Human body composition: Advances in models and methods. Annu Rev Nutr. 1997;17:527–58.

Higgins V, Adeli K. Pediatric metabolic syndrome: Pathophysiology and laboratory assessment. eJIFCC. 2017;28(1):25–42.

Hill DC, Moss RH, Sykes-Muskett B, Conner M, O'Connor DB. Stress and eating behaviors in children and adolescents: Systematic review and meta-analysis. Appetite. 2018;123:14–22.

Hinney A, Giuranna J. Polygenic obesity. In: Freemark MS, editor. Pediatric Obesity: Etiology, Pathogenesis and Treatment. Second edition. New York: Springer International Publishing; 2018. p. 183–204.

Hockett CW, Harrall KK, Moore BF, Starling AP, Bellatorre A, Sauder KA, et al. Persistent effects of in utero overnutrition on offspring adiposity: The Exploring Perinatal Outcomes among Children (EPOCH) study. Diabetologia. 2019;62(11):2017–24.

Hoepner LA. Bisphenol A: A narrative review of prenatal exposure effects on adipogenesis and childhood obesity via peroxisome proliferator-activated receptor gamma. Environ Res. 2019;173(March):54–68.

Hofsteenge GH, Chinapaw MJM, Weijs PJM. Fat-free mass prediction equations for bioelectric impedance analysis compared to dual energy X-ray absorptiometry in obese adolescents: A validation study. BMC Pediatr. 2015;15(1).

Hong SH, Choi KM. Sarcopenic obesity, insulin resistance, and their implications in cardiovascular and metabolic consequences. Int J Mol Sci. 2020;21(2).

Horan M, Gibney E, Molloy E, McAuliffe F. Methodologies to assess paediatric adiposity. Irish Journal of Medical Science. 2015.

Hou WW, Tse MA, Lam TH, Leung GM, Schooling CM. Adolescent testosterone, muscle mass and glucose metabolism: Evidence from the "Children of 1997" birth cohort in Hong Kong. Diabet Med. 2015;32(4):505–12.

Hu HH. Assessment of abdominal adiposity and organ fat with magnetic resonance imaging. In: Body and organ fat quantification - Advances in CT and MRI Techniques: Preconference-

workshop of The Obesity Society 2011 Meeting [Internet]. 2011. Available from: http://www.obesity.org/education/body-and-organ-fat-quantification-preconference-course.htm

Hübers M, Geisler C, Bosy-Westphal A, Braun W, Pourhassan M, Sørensen TIA, et al. Association between fat mass, adipose tissue, fat fraction per adipose tissue, and metabolic risks: A cross-sectional study in normal, overweight, and obese adults. Eur J Clin Nutr. 2019;73(1):62–71.

Hübers M, Geisler C, Plachta-Danielzik S, Müller MJ. Association between individual fat depots and cardio-metabolic traits in normal- and overweight children, adolescents and adults. Nutr Diabetes. 2017;7(5):1–8.

Hui SCN, Zhang T, Shi L, Wang D, Ip CB, Chu WCW. Automated segmentation of abdominal subcutaneous adipose tissue and visceral adipose tissue in obese adolescent in MRI. Magn Reson Imaging. 2018;45(January 2017):97–104.

Hui W, Slorach C, Guerra V, Parekh RS, Hamilton J, Messiha S, et al. Effect of obstructive sleep apnea on cardiovascular function in obese youth. Am J Cardiol. 2019;123(2):341–7.

Hulthén L, Bengtsson BÅ, Sunnerhagen KS, Hallberg L, Grimby G, Johannsson G. GH is needed for the maturation of muscle mass and strength in adolescents. J Clin Endocrinol Metab. 2001;86(10):4765–70.

Hurtado-López EF, Vásquez-Garibay EM, Trujillo X, Larrosa-Haro A. Body composition predicts growth in infants and toddlers with chronic liver disease. J Pediatr Gastroenterol Nutr. 2017;65(6):e117–9.

Iacobucci D, Posavac SS, Kardes FR, Schneider MJ, Popovich DL. Toward a more nuanced understanding of the statistical properties of a median split. J Consum Psychol. 2015;25(4):652–65.

Illner K, Brinkmann G, Heller M, Bosy-Westphal A, Muller MJ. Metabolically active components of fat free mass and resting energy expenditure in nonobese adults. Am J Physiol Endocrinol Metab. 2000;278(2):E308-15.

Indiani CMDSP, Rizzardi KF, Castelo PM, Ferraz LFC, Darrieux M, Parisotto TM. Childhood obesity and Firmicutes/Bacteroidetes ratio in the gut microbiota: A systematic review. Child Obes. 2018;14(8):501–9.

Irizarry KA, Haqq AM. Syndromic obesity. In: Freemark MS, editor. Pediatric Obesity: Etiology, Pathogenesis and Treatment. Second edition. New York: Springer International Publishing; 2018. p. 153–82.

Isacco L, Roche J, Quinart S, Thivel D, Gillet V, Nègre V, et al. Cardiometabolic risk is associated with the severity of sleep-disordered breathing in children with obesity. Physiol Behav. 2017;170:62–7.

Isong IA, Rao SR, Bind M-A, Avendaño M, Kawachi I, Richmond TK. Racial and ethnic disparities in early childhood obesity. Pediatrics. 2018;141(1):1–11.

Jacobs J, Jansen M, Janssen H, Raijmann W, Van Alfen N, Pillen S. Quantitative muscle ultrasound and muscle force in healthy children: A 4-year follow-up study. Muscle and Nerve. 2013;47(6):856–63.

Jeffery E, Church CD, Holtrup B, Colman L, Rodeheffer MS. Rapid depot-specific activation of adipocyte precursor cells at the onset of obesity. Nat Cell Biol. 2015;17(4):376–85.

Jelicic Kadic A, Vucic K, Dosenovic S, Sapunar D, Puljak L. Extracting data from figures with software was faster, with higher interrater reliability than manual extraction. J Clin Epidemiol. 2016;74:119–23.

Jen V, Karagounis LG, Jaddoe VWV, Franco OH, Voortman T. Dietary protein intake in school-age children and detailed measures of body composition: The Generation R Study. Int J Obes. 2018;

Johansson E, Lubberink M, Heurling K, Eriksson JW, Skrtic S, Ahlström H, et al. Whole-body imaging of tissue-specific insulin sensitivity and body composition by using an integrated PET/MR system: A feasibility study. Radiology. 2018;286(1):271–8.

Johnson ST, Kuk JL, Mackenzie KA, Huang TT, Rosychuk RJ, Ball GDC. Metabolic risk varies according to waist circumference measurement site in overweight boys and girls. J Pediatr. 2010;156(2):247-252.e1.

Joint WHO/FAO/UNU Expert Consultation. Protein and amino acid requirements in human nutrition. Vol. 935, World Health Organization Technical Report Series. 2007.

Joosten SA, Landry SA, Terrill PI. Statistical uncertainty of the apnea-hypopnea index is another reason to question the utility of this metric. Sleep Med. 2020;65:159–60.

Jung SM, Sanchez-Gurmaches J, Guertin DA. Brown adipose tissue development and metabolism. In: Brown Adipose Tissue. Springer, Cham; 2018. p. 3–36.

Kâ K, Rousseau M, Lambert M, O'Loughlin J, Henderson M, Tremblay A, et al. Association between lean and fat mass and indicators of bone health in prepubertal caucasian children. Horm Res Paediatr. 2013;80(3):154–62.

Kabiri LS, Hernandez DC, Mitchell K. Reliability, validity, and diagnostic value of a pediatric bioelectrical impedance analysis scale. Child Obes. 2015;11(5):650–5.

Kalhan SC. Optimal protein intake in healthy infants. Am J Clin Nutr. 2009;89:1719–20.

Kamijo K, Khan NA, Pontifex MB, Scudder MR, Eric S, Raine LB, et al. The relation of adiposity to cognitive control and scholastic achievement in preadolescent children. Obes (Silver Spring). 2012;20(12):2406–11.

Kang S-Y, Lim GE, Kim YK, Kim HW, Lee K, Park T-J, et al. Association between sarcopenic obesity and metabolic syndrome in postmenopausal women: A cross-sectional study based on the Korean National Health and Nutritional Examination Surveys from 2008 to 2011. J Bone Metab. 2017;24(1):9–14.

Kaplan HS, Lancaster JB. An evolutionary and ecological analysis of human fertility, mating patterns, and parental investment. In: Wachter K., Bulatao R., editors. Offspring: Human fertility behavior in biodemographic perspective panel. National Academy of Sciences; 2003. p. 170–223.

Karlsson F, Tremaroli V, Nielsen J, Backhed F. Assessing the human gut microbiota in metabolic diseases. Diabetes. 2013;62(10):3341–9.

Kasvis P, Cohen TR, Loiselle SÈ, Kim N, Hazell TJ, Vanstone CA, et al. Foot-to-foot bioelectrical impedance accurately tracks direction of adiposity change in overweight and obese 7- to 13-year-old children. Nutr Res. 2015;35(3):206–13.

Kavey REW. Combined dyslipidemia in childhood. J Clin Lipidol. 2015;9(5):S41–56.

Kawakami M, Murase T, Ogama H, Ishibashi S, Mori N, Takaku F, et al. Human recombinant TNF suppresses lipoprotein lipase activity and stimulates lipolysis in 3T3-L1 cells. J Biochem. 1987;101(2):331–8.

Kawakami Y, Abe T, Fukunaga T. Muscle-fiber pennation angles are greater in hypertrophied than in normal muscles. J Appl Physiol. 1993;74(6):2740–4.

Kelly AS, Fox CK, Rudser KD, Gross AC, Ryder JR. Pediatric obesity pharmacotherapy: Current state of the field, review of the literature and clinical trial considerations. Int J Obes. 2016;40(7):1043–50.

Kelly AS, Kaizer AM, Bosch TA, Rudser KD, Ryder JR, Gross AC, et al. Reaching the tipping point: Identification of thresholds at which visceral adipose tissue may steeply increase in youth. Obesity. 2019;00(00):1–7.

Keskin M, Kurtoglu S, Kendirci M, Atabek ME, Yazici C. Homeostasis model assessment is more reliable than the fasting glucose/insulin ratio and quantitative insulin sensitivity check index for assessing insulin resistance among obese children and adolescents. Pediatrics. 2005;115(4):e500–3.

Khanal P, Pandey D, Binti Ahmad S, Safayi S, Kadarmideen HN, Olaf Nielsen M. Differential impacts of late gestational over-and undernutrition on adipose tissue traits and associated visceral obesity risk upon exposure to a postnatal high-fat diet in adolescent sheep. Physiol Rep. 2020;8(3):e14359.

Kheirandish-Gozal L, Bhattacharjee R, Bandla HPR, Gozal D. Antiinflammatory therapy outcomes for mild OSA in children. Chest. 2014;146(1):88–95.

Kim HJ, Higashimori T, Park SY, Choi H, Dong J, Kim YJ, et al. Differential effects of interleukin-6 and -10 on skeletal muscle and liver insulin action in vivo. Diabetes. 2004;53(4):1060–7.

Kim HY, Jung HW, Hong H, Kim JH, Shin CH, Yang SW, et al. The role of overweight and obesity on bone health in Korean adolescents with a focus on lean and fat mass. J Korean Med Sci. 2017;32(10):1633–41.

Kim J, Bang H. Three common misuses of P values. Dent Hypotheses. 2016;7(3):73–80.

Kim JH, Park YS. Low muscle mass is associated with metabolic syndrome in Korean adolescents: The Korea National Health and Nutrition Examination Survey 2009-2011. Nutr Res. 2016;36(12):1423–8.

Kim JY, Bacha F, Tfayli H, Michaliszyn SF, Yousuf S, Arslanian S. Adipose tissue insulin resistance in youth on the spectrum from normal weight to obese and from normal glucose tolerance to impaired glucose tolerance to type 2 diabetes. Diabetes Care. 2019;42(2):265–72.

Kim JY, Tfayli H, Bacha F, Lee SJ, Michaliszyn SF, Yousuf S, et al. β-cell function, incretin response, and insulin sensitivity of glucose and fat metabolism in obese youth: relationship to OGTT-time-to-glucose-peak. Pediatr Diabetes. 2020;21(1):18–27.

Kim S, Valdez R. Metabolic risk factors in U.S. youth with low relative muscle mass. Obes Res Clin Pract. 2015;9(2):125–32.

Kincaid HJ, Nagpal R, Yadav H. Microbiome-immune-metabolic axis in the epidemic of childhood obesity: Evidence and opportunities. Obes Rev. 2019;(July):1–13.

Kindler JM, Lobene AJ, Vogel KA, Martin BR, McCabe LD, Peacock M, et al. Adiposity, insulin resistance, and bone mass in children and adolescents. J Clin Endocrinol Metab. 2018;104(3):892–9.

Kjellberg E, Roswall J, Andersson J, Bergman S, Karlsson AK, Svensson PA, et al. Metabolic risk factors associated with visceral and subcutaneous adipose tissue in a sex-specific manner in seven-year-olds. Obesity. 2019;27(6):982–8.

Knittle JL, Timmers K, Ginsberg-Fellner F, Brown RE, Katz DP. The growth of adipose tissue in children and adolescents: cross-sectional and longitudinal studies of adipose cell number and size. J Clin Invest. 1979;63(2):239–46.

Koletzko B, Broekaert I, Demmelmair H, Franke J, Hannibal I, Oberle D, et al. Early nutrition and its later consequences: New opportunities. In: Advances in Experimental Medicine and Biology. Dordrecht: Springer; 2005. p. 69–79.

Koontz MB, Gunzler DD, Presley L, Catalano PM. Longitudinal changes in infant body composition: association with childhood obesity. Pediatr Obes. 2014;9(6):e141–4.

Koot BGP, Westerhout R, Bohte AE, Vinke S, Pels Rijcken TH, Nederveen AJ, et al. Ultrasonography is not more reliable than anthropometry for assessing visceral fat in obese children. Pediatr Obes. 2014;9(6):443–7.

Korthuis RJ. Skeletal muscle circulation. In Colloquium Series on Integrated Systems Physiology: From Molecule to Function. Morgan & Claypool Life Sciences. 2011;3(4):1-144

Kristinsson J, Valdimarsson O, Steingrimsdottir L, Sigurdsson G. Relation between calcium intake, grip strength and bone mineral density in the forearms of girls aged 13 and 15. J Intern Med. 1994;236(4):385–90.

Kryst Ł, Żegleń M, Das S, Dasgupta P, Saha R, Das R. Intergenerational changes in adiposity and fat distribution from 1982 to 2011 in male children and adolescents from Kolkata (India). Pediatr Obes. 2020;15(e12585).

Kuczmarski RJ, Ogden CL, Grummer-Strawn LM, Flegal KM, Guo SS, Wei R, et al. CDC growth charts: United States. Hyattsville, MD; 2000.

Kumar S, Hossain J, Inge T, Balagopal PB. Changes in myokines in youths with severe obesity following Roux-en-Y gastric bypass surgery. JAMA Surg. 2019;154(7):668–9.

Kuppens RJ, Bakker NE, Siemensma EPC, Tummers-De Lind Van Wijngaarden RFA, Donze SH, Festen DAM, et al. Beneficial effects of GH in young adults with Prader-Willi syndrome: A 2-year crossover trial. J Clin Endocrinol Metab. 2016;101(11):4110–6.

Kwon EJ, Kim YJ. What is fetal programming?: A lifetime health is under the control of in utero health. Obs Gynecol Sci. 2017;60(6):506–19.

Kyle UG, Earthman CP, Pichard C, Coss-Bu JA. Body composition during growth in children: Limitations and perspectives of bioelectrical impedance analysis. Eur J Clin Nutr. 2015;

Laddu DR, Farr JN, Lee VR, Blew RM, Stump C, Houtkooper L, et al. Muscle density predicts changes in bone density and strength: A prospective study in girls. J Musculoskelet Neuronal Interact. 2014;14(2):195–204.

Laharrague P, Casteilla L. The emergence of adipocytes. In: Levy-Marchal C, Pénicaud L, editors. Adipose tissue sevelopment: From animal models to clinical conditions. Karger Medical and Scientific Publishers; 2010. p. 21–30.

Landgraf K, Rockstroh D, Wagner I V, Weise S, Tauscher R, Schwartze JT, et al. Evidence of early alterations in adipose tissue biology and function and its association with obesity-related inflammation and insulin resistance in children. Diabetes. 2015;64(April):1249–61.

Lapillonne A, Braillon P, Claris O, Chatelain PG, Delmas PD, Salle BL. Body composition in appropriate and in small for gestational age infants. Acta Paediatr. 1997;86(2):196–200.

Larraufie P, Martin-Gallausiaux C, Lapaque N, Dore J, Gribble FM, Reimann F, et al. SCFAs strongly stimulate PYY production in human enteroendocrine cells. Sci Rep. 2018;8(1):74.

Lawrence AE, Adler BH, Minneci PC. Response to: Evaluation of sarcopenia in children. J Surg Res. 2018;2–3.

Lazzer S, Bedogni G, Agosti F, De Col A, Mornati D, Sartorio A. Comparison of dual-energy X-ray absorptiometry, air displacement plethysmography and bioelectrical impedance analysis for the assessment of body composition in severely obese Caucasian children and adolescents. Br J Nutr. 2008;100(4):918–24.

Lazzer S, Boirie Y, Meyer M, Vermorel M. Evaluation of two foot-to-foot bioelectrical impedance analysers to assess body composition in overweight and obese adolescents. Br J Nutr. 2003;90(5):987–92.

Lecoutre S, Petrus P, Rydén M, Breton C. Transgenerational epigenetic mechanisms in adipose tissue development. Trends Endocrinol Metab. 2018;29(10):675–85.

Lee DY, Wetzsteon RJ, Zemek BS, Shults J, Organ JM, Foster BJ, et al. Muscle torque relative to cross-sectional area and the functional muscle-bone unit in children and adolescents with chronic disease. J Bone Min Res. 2015;30(3):575–83.

Lee JH, Zhang Y, Zhao Z, Ye X, Zhang X, Wang H, et al. Intracellular ATP in balance of pro- and anti-inflammatory cytokines in adipose tissue with and without tissue expansion. Int J Obes. 2017;41(4):645–51.

Lee S, Bountziouka V, Lum S, Stocks J, Bonner R, Naik M, et al. Ethnic variability in body size, proportions and composition in children aged 5 to 11 years: Is ethnic-specific calibration of bioelectrical impedance required? PLoS One. 2014;9(12):1–17.

Lee S, Kim Y, White DA, Kuk JL, Arslanian S. Relationships between insulin sensitivity, skeletal muscle mass and muscle quality in obese adolescent boys. Eur J Clin Nutr. 2012;66(12):1366–8.

Lee SJ, Arslanian SA. Cardiorespiratory fitness and abdominal adiposity in youth. Eur J Clin Nutr. 2007;61(4):561–5.

Lee SJ, Guerra N, Arslanian S. Skeletal muscle lipid content and insulin sensitivity in black versus white obese adolescents: Is there a race differential? J Clin Endocrinol Metab. 2010;95(5):2426–32.

Levy E, Saenger AK, Steffes MW, Delvin E. Pediatric obesity and cardiometabolic disorders: Risk factors and biomarkers. eJIFCC. 2017;28(1):6–24.

Levy-Marchal C, Arslanian S, Cutfield W, Sinaiko A, Druet C, Marcovecchio ML, et al. Insulin resistance in children: Consensus, perspective, and future directions. J Clin Endocrinol Metab. 2010;95(12):5189–98.

Li AM, Chan D, Wong E, Yin J, Nelson EAS, Fok TF. The effects of obesity on pulmonary function. Arch Dis Child. 2003;88(1):361–3.

Li H, Huang T, Liu J, Yan Y, Zhao X, Xiao P, et al. Body fat indicators perform better than body mass index in identifying abnormal lipid profiles in boys but not in girls. Pediatr Res. 2019;85(5):617–24.

Lohman TG, Milliken LA. Errors in body composition measurement and assessment. In: ACSM's body composition assessment. 2020. p. 3–12.

Lohman TG. Applicability of body composition techniques and constants for children and youths. In: Pandolf KB, editor. Exercise and Sport Sciences Reviews. New York: Macmillan; 1986. p. 325–57.

Lohman TG. Assessment of body composition in children. Pediatr Exerc Sci. 1989;1(1):19–30.

López-Contreras BE, Morán-Ramos S, Villarruel-Vázquez R, Macías-Kauffer L, Villamil-Ramírez H, León-Mimila P, et al. Composition of gut microbiota in obese and normal-weight Mexican school-age children and its association with metabolic traits. Pediatr Obes. 2018;13(6):381–8.

Loprinzi PD, Cardinal BJ. Measuring children's physical activity and sedentary behaviors. J Exerc Sci Fit. 2011;9(1):15–23.

Loureiro C, Campino C, Martinez-Aguayo A, Godoy I, Aglony M, Bancalari R, et al. Positive association between aldosterone-renin ratio and carotid intima-media thickness in hypertensive children. Clin Endocrinol (Oxf). 2013;78(3):352–7.

Lowe Jr WL, Lowe LP, Kuang A, Catalano PM, Nodzenski M, Talbot O, et al. Maternal glucose levels during pregnancy and childhood adiposity in the Hyperglycemia and Adverse Pregnancy Outcome Follow-up Study. Diabetologia. 2019;62(4):598–610.

Lu K, Quach B, Tong TK, Lau PWC. Validation of leg-to-leg bio-impedance analysis for assessing body composition in obese Chinese children. J Exerc Sci Fit [Internet]. 2003;1(2):97–103.

Lupton J, Brooks J, Butte N, Caballero B, Flatt J, Fried S. Dietary reference intakes for energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein, and amino acids. Washington, DC; 2002.

Luque V, Closa-Monasterolo R, Rubio-Torrents C, Zaragoza-Jordana M, Ferré N, Gispert-Llauradó M, et al. Bioimpedance in 7-year-old children: Validation by dual X-Ray absorptiometry - Part 1: Assessment of whole body composition. Ann Nutr Metab. 2014;64(2):113–21.

Luque V, Escribano J, Zaragoza-Jordana M, Rubio-Torrents C, Ferré N, Gispert-Llaurado M, et al. Bioimpedance in 7-year-old children: Validation by dual X-ray absorptiometry - Part 2: Assessment of segmental composition. Ann Nutr Metab. 2014;64(2):144–55.

Lyra A, Bonfitto AJ, Barbosa VLP, Bezerra AC, Longui CA, Monte O, et al. Comparison of methods for the measurement of body composition in overweight and obese Brazilian children and adolescents before and after a lifestyle modification program. Ann Nutr Metab. 2015;66(1):26–30.

Mackenzie ML, Triador L, Gill JK, Pakseresht M, Mager D, Field CJ, et al. Dietary intake in youth with prader-willi syndrome. Am J Med Genet Part A. 2018;(In press).

MacLean JE, DeHaan K, Chowdhury T, Nehme J, Bendiak GN, Hoey L, et al. The scope of sleep problems in Canadian children and adolescents with obesity. Sleep Med. 2018;47:44–50.

Mager DR, Carroll MW, Wine E, Siminoski K, MacDonald K, Kluthe CL, et al. Vitamin D status and risk for sarcopenia in youth with inflammatory bowel diseases. Eur J Clin Nutr. 2018;72(4):623–6.

Magge SN, Goodman E, Armstrong SC, Daniels S, Corkins M, De Ferranti S, et al. The metabolic syndrome in children and adolescents: Shifting the focus to cardiometabolic risk factor clustering. Pediatrics. 2017;140(2):e20171603.

Mahaffey R, Morrison SC, Bassett P, Drechsler WI, Cramp MC. Biomechanical characteristics of lower limb gait waveforms: Associations with body fat in children. Gait Posture. 2018;61(January):220–5.

Malfatti E, Romero NB. Diseases of the skeletal muscle. 1st ed. Vol. 145, Handbook of Clinical Neurology. Elsevier B.V.; 2017. 429–451 p.

Maratova K, Soucek O, Matyskova J, Hlavka Z, Lenka P, Obermannova B, et al. Muscle functions and bone strength are impaired in adolescents with type 1 diabetes. Bone. 2018;106:22–7.

Marginean CO, Melit LE, Ghica D V., Mărginean MO. Early inflammatory status related to pediatric obesity. Front Pediatr. 2019;7:1–7.

Marriott CJC, Beaumont LF, Farncombe TH, Cranston AN, Athale UH, Yakemchuk VN, et al. Body composition in long-term survivors of acute lymphoblastic leukemia diagnosed in childhood and adolescence: A focus on sarcopenic obesity. Cancer. 2018;124(6):1225–31.

Martin CK, Johnson WD, Myers CA, Apolzan JW, Earnest CP, Thomas DM, et al. Effect of different doses of supervised exercise on food intake, metabolism, and non-exercise physical activity: The E-MECHANIC randomized controlled trial. Am J Clin Nutr. 2019;110(3):583–92.

Martinez EE, Smallwood CD, Quinn NL, Ariagno K, Bechard LJ, Duggan CP, et al. Body composition in children with chronic illness: Accuracy of bedside assessment techniques. J Pediatr. 2017;190:56–62.

Mazahery H, von Hurst PR, McKinlay CJD, Cormack BE, Conlon CA. Air displacement plethysmography (Pea Pod) in full-term and pre-term infants: A comprehensive review of accuracy, reproducibility, and practical challenges. Matern Heal Neonatol Perinatol. 2018;4(1):12.

McCarthy HD, Cole TJ, Fry T, Jebb SA, Prentice AM. Body fat reference curves for children. Int J Obes. 2006;30(4):598–602.

McCarthy HD, Samani-Radia D, Jebb SA, Prentice AM. Skeletal muscle mass reference curves for children and adolescents. Pediatr Obes. 2014;9(4):249–59.

McConnell-Nzunga J, Patti-Jean N, Macdonald HM, Rhodes RE, Hofer SM, McKay HA. Body fat accrual trajectories for a sample of Asian-Canadian and Caucasian-Canadian children and youth: A longitudinal DXA-based study. Pediatr Obes. 2020;15:e12570.

Meng T, Thayer S, Venn A, Wu F, Cicuttini F, March L, et al. Association of childhood adiposity measures with adulthood knee cartilage defects and bone marrow lesions: A 25-year cohort study. Osteoarthr Cartil. 2018;26(8):1055–62.

Meredith-Jones KA, Williams SM, Taylor RW. Bioelectrical impedance as a measure of change in body composition in young children. Pediatr Obes. 2015;10(4):252–9.

Meyer C, Dostou JM, Welle SL, Gerich JE. Role of human liver, kidney, and skeletal muscle in postprandial glucose homeostasis. Am J Physiol - Endocrinol Metab. 2002;282(2):E419–27.

Miller JD, Sterczala AJ, Trevino MA, Herda TJ. Examination of muscle composition and motor unit behavior of the first dorsal interosseous of normal and overweight children. J Neurophysiol. 2018;119(5):1902–11.

Miller SA, Wu RKS, Oremus M. The association between antibiotic use in infancy and childhood overweight or obesity: A systematic review and meta-analysis. Obes Rev. 2018;19(11):1463–75.

Min SY, Desai A, Yang Z, Sharma A, DeSouza T, Genga RMJ, et al. Diverse repertoire of human adipocyte subtypes develops from transcriptionally distinct mesenchymal progenitor cells. Proc Natl Acad Sci U S A. 2019;116(36):17970–9.

Mitchell WK, Wilkinson DJ, Phillips BE, Lund JN, Smith K, Atherton PJ. Human skeletal muscle protein metabolism responses to amino acid nutrition. Adv Nutr. 2016;7(Suppl):828S-838S.

Moliner-Urdiales D, Ruiz JR, Vicente-Rodriguez G, Ortega FB, Rey-Lopez JP, España-Romero V, et al. Associations of muscular and cardiorespiratory fitness with total and central body fat in adolescents: The HELENA study. Br J Sports Med. 2011;45(2):101–8.

Mooney A, Kelsey L, Fellingham GW, George JD, Hager RL, Myrer JW, et al. Assessing body composition of children and adolescents using dual-energy X-ray absorptiometry, skinfolds, and electrical impedance. Meas Phys Educ Exerc Sci. 2011;15(1):2–17.

Moore FD, Boyden CM. Body Cell mass and limits of hydration of the fat-free body: Their relation to estimated skeletal weight. Ann N Y Acad Sci. 1963;110(1):62–71.

Moulton CR. Age and chemical development in mammals. J Biol Chem. 1923;57:79–97.

Mueller NT, Whyatt R, Hoepner L, Oberfield S, Dominguez-Bello MG, Widen EM, et al. Prenatal exposure to antibiotics, cesarean section and risk of childhood obesity. Int J Obes. 2015;39(4):665–70.

Mueller WH, Chan W, Meininger JC. Utility of different body composition indicators: Demographic influences and associations with blood pressures and heart rates in adolescents (Heartfelt Study). Ann Hum Biol. 2003;30(6):714–27.

Muniyappa R, Lee S, Chen H, Quon MJ. Current approaches for assessing insulin sensitivity and resistance in vivo: advantages, limitations, and appropriate usage. AJP Endocrinol Metab. 2007;294(1):E15–26.

Murphy AJ, Ellis KJ, Kurpad A V., Preston T, Slater C. Total body potassium revisited. Eur J Clin Nutr. 2014;68(2):153–4.

Murphy MJ, Metcalf BS, Jeffery AN, Voss LD, Wilkin TJ. Does lean rather than fat mass provide the link between birth weight, BMI, and metabolic risk? EarlyBird 23. Pediatr Diabetes. 2006;7(4):211–4.

Naggara O, Raymond J, Guilbert F, Roy D, Weill A, Altman DG. Analysis by categorizing or dichotomizing continuous variables is inadvisable: An example from the natural history of unruptured aneurysms. Am J Neuroradiol. 2011;32(3):437–40.

Nagy TR, Gower BA, Trowbridge CA, Dezenberg C, Shewchuk RM, Goran MI. Effects of gender, ethnicity, body composition, and fat distribution on serum leptin concentrations in children. J Clin Endocrinol Metab. 1997;82(7):2148–52.

Näslund U, Lundgren A, Vanoli D, Norberg M. Is intima-media thickness a predictor for cardiovascular risk? – Authors' reply. Lancet. 2019;394(10196):381.

NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: A pooled analysis of 2416 population-based measurement studies in 128·9 million children, adolescents, and adults. Lancet. 2017;390(10113):2627–42.

Nettle H, Sprogis E. Pediatric Exercise : Truth and/or consequences. Sport Med Arthrosc Rev. 2011;19(1):75–80.

Neu CM, Rauch F, Rittweger J, Manz F, Schoenau E. Influence of puberty on muscle development at the forearm. Am J Physiol - Endocrinol Metab. 2002;283(1):E103–7.

Newton RL, Alfonso A, White MA, York-Crowe E, Walden H, Ryan D, et al. Percent body fat measured by BIA and DEXA in obese, African-American adolescent girls. Int J Obes. 2005;29(6):594–602.

Ng JM, Bertoldo A, Minhas DS, Helbling NL, Coen PM, Price JC, et al. Dynamic PET imaging reveals heterogeneity of skeletal muscle insulin resistance. J Clin Endocrinol Metab. 2014;99(1):102–6.

Ng M, Fleming T, Robinson M, Thomson B, Graetz N. Global, regional and national prevalence of overweight and obesity in children and adults 1980-2013: A systematic analysis. Lancet. 2014;384(9945):766–81.

Nguyen-Rodriguez ST, Gallo LC, Isasi CR, Buxton OM, Thomas KS, Sotres-Alvarez D, et al. Adiposity, depression symptoms and inflammation in Hispanic/Latino youth: Results from HCHS/SOL youth. Ann Behav Med. 2020;1–6.

Nicolucci AC, Hume MP, Martínez I, Mayengbam S, Walter J, Reimer RA. Prebiotics reduce body fat and alter intestinal microbiota in children who are overweight or with obesity. Gastroenterology. 2017;153(3):711–22.

Nieuwenhuis D, Pujol-Gualdo N, Arnoldussen IA, Kiliaan AJ. Adipokines: A gear shift in puberty. Obes Rev. 2020;(January):1–10.

Nouws J, Fitch M, Mata M, Santoro N, Galuppo B, Kursawe R, et al. Altered in vivo lipid fluxes and cell dynamics in subcutaneous adipose tissues are associated with the unfavorable pattern of fat distribution in obese adolescent girls. Diabetes. 2019;68(6):1168–77.

O'Brien C, Young AJ, Sawka MN. Bioelectrical impedance to estimate changes in hydration status. Int J Sports Med. 2002;23(5):361–6.

Ohta M, Midorikawa T, Hikihara Y, Masuo Y, Sakamoto S, Torii S, et al. Validity of segmental bioelectrical impedance analysis for estimating fat-free mass in children including overweight individuals. Appl Physiol Nutr Metab. 2017;42(2):157–65.

Ohta M, Midorikawa T, Hikihara Y, Sakamoto S, Kawakami Y, Fukunaga T, et al. Body mass-to-waist ratio strongly correlates with skeletal muscle volume in children. PLoS One. 2017;12(5):1–13.

Okubo H, Crozier SR, Harvey NC, Godfrey KM, Inskip HM, Cooper C, et al. Diet quality across early childhood and adiposity at 6 years: The Southampton Women's Survey. Int J Obes. 2015;39(10):1456–62.

Ong C, Lee JH, Leow MKS, Puthucheary ZA. Skeletal muscle ultrasonography in nutrition and functional outcome assessment of critically ill children: Experience and insights from pediatric disease and adult critical care studies. J Parenter Enter Nutr. 2017;41(7):1091–9.

Ong K, Kratzsch J, Kiess W, Dunger D. Circulating IGF-I levels in childhood are related to both current body composition and early postnatal growth rate. J Clin Endocrinol Metab. 2002;87(3):1041–4.

Ong KK, Emmett P, Northstone K, Golding J, Rogers I, Ness AR, et al. Infancy weight gain predicts childhood body fat and age at menarche in girls. J Clin Endocrinol Metab. 2009;94(5):1527–32.

Oranchuk DJ, Stock MS, Nelson AR, Storey AG, Cronin JB. Variability of regional quadriceps echo intensity in active young men with and without subcutaneous fat correction. Appl Physiol Nutr Metab. 2020;1–24.

Orsso CE, Rubin DA, Silva MIB, Heymsfield SB, Gonzalez MC, Prado CM, et al. Assessment of body composition in pediatric overweight and obesity: A systematic review of the reliability and validity of common techniques. Obes Rev. 2020;1–18. In press.

Orsso CE, Tibaes JRB, Oliveira CLP, Rubin DA, Field CJ, Heymsfield SB, et al. Low muscle mass and strength in pediatrics patients: Why should we care? Clin Nutr. 2019;38(5):2002-15.

Orsso CE, Tibaes JRB, Rubin DA, Field CJ, Heymsfield SB, Prado CM, et al. Metabolic implications of low muscle mass in the pediatric population: A critical review. Metabolism. 2019;99:102–12.

Ortega FB, Ruiz JR, Castillo MJ, Sjöström M. Physical fitness in childhood and adolescence: A powerful marker of health. Int J Obes. 2008;32(1):1–11.

Paley C, Hull H, Ji Y, Toro-Ramos T, Thornton J, Bauer J, et al. Body fat differences by self-reported race/ethnicity in healthy term newborns. Pediatr Obes. 2016;11(5):361–8.

Palmer BF, Clegg DJ. The sexual dimorphism of obesity. Mol Cell Endocrinol. 2015;15:113–9.

Paris MT, Mourtzakis M, Day A, Leung R, Watharkar S, Kozar R, et al. Validation of bedside ultrasound of muscle layer thickness of the quadriceps in the critically ill patient (VALIDUM Study). J Parenter Enter Nutr. 2017;41(2):171–80.

Pate R, Oria M, Pillsbury L, editors. Fitness measures and health outcomes in youth. Washington: The National Academic Press; 2012.

Patni N, Li X, Adams-Huet B, Vasandani C, Gomez-Diaz RA, Garg A. Regional body fat changes and metabolic complications in children with dunnigan lipodystrophy-causing LMNA variants. J Clin Endocrinol Metab. 2019;104(4):1099–108.

Pausova Z, Mahboubi A, Abrahamowicz M, Leonard GT, Perron M, Richer L, et al. Sex differences in the contributions of visceral and total body fat to blood pressure in adolescence. Hypertension. 2012;59(3):572–9.

Pearl RL, Puhl RM. Weight bias internalization and health: A systematic review. Obes Rev. 2018;8(1):1141–63.

Pearson N, Timperio A, Salmon J, Crawford D, Biddle SJH. Family influences on children's physical activity and fruit and vegetable consumption. Int J Behav Nutr Phys Act. 2009;6:1–7.

Peña M-M, Dixon B, Taveras EM. Are you talking to ME? The importance of ethnicity and culture in childhood obesity prevention and management. Child Obes. 2012;8(1):23–7.

Pesta DH, Samuel VT. A high-protein diet for reducing body fat: Mechanisms and possible caveats. Nutr Metab. 2014;11(1):1–8.

Peterson CM, Su H, Thomas DM, Heo M, Golnabi AH, Pietrobelli A, et al. Tri-ponderal mass index vs body mass index in estimating body fat during adolescence. JAMA Pediatr. 2017;171(7):629–36.

Peterson MD, Zhang P, Saltarelli WA, Visich PS, Gordon PM. Low muscle strength thresholds for the detection of cardiometabolic risk in adolescents. Am J Prev Med. 2016;50(5):593–9.

Pfister KM, Gray HL, Miller NC, Demerath EW, Georgieff MK, Ramel SE. Exploratory study of the relationship of fat-free mass to speed of brain processing in preterm infants. Pediatr Res. 2013;74(5):576–83.

Phillips CM. Metabolically healthy obesity across the life course: Epidemiology, determinants, and implications. Ann N Y Acad Sci. 2017;1391(1):85–100.

Pietrobelli A, Forminca C, Wang Z, Heymsfield SB. Dual-energy X-ray absorptiometry body composition model: Review of physical concepts. Am J Physiol Metab. 1996;271(6):941–51.

Pigeyere M, Meyre D. Monogenic obesity. In: Freemark MS, editor. Pediatric Obesity: Etiology, pathogenesis and treatment. Second edition. New York: Springer International Publishing; 2018. p. 135–52.

Pigeyre M, Yazdi FT, Kaur Y, Meyre D. Recent progress in genetics, epigenetics and metagenomics unveils the pathophysiology of human obesity. Clin Sci. 2016;130:943–86.

Pillen S, Van Alfen N, Zwarts MJ. Muscle ultrasound: A grown-up technique for children with neuromuscular disorders. Muscle and Nerve. 2008;38(3):1213–4.

Pillen S, Verrips A, van Alfen N, Arts I, Sie L, Zwarts M. Quantitative skeletal muscle ultrasound: Diagnostic value in childhood neuromuscular disease. Neuromuscul Disord. 2007;17:509–16.

Pillen S. Skeletal muscle ultrasound. Eur J Transl Myol 2010; 2010;1(4):145–55.

Pineau JC, Lalys L, Bocquet M, Guihard-Costa AM, Polak M, Frelut ML, et al. Ultrasound measurement of total body fat in obese adolescents. Ann Nutr Metab. 2010;56(1):36–44.

Poissonnet CM, Burdi AR, Bookstein FL. Growth and development of human adipose tissue during early gestation. Early Hum Dev. 1983;8(1):1–11.

Pontzer H. Constrained total energy expenditure and the evolutionary biology of energy balance. Exerc Sport Sci Rev. 2015;43(3):110–6.

Prado CMM, Heymsfield SB. Lean tissue imaging: A new era for nutritional assessment and intervention. J Parenter Enter Nutr. 2014;38(8):940–53.

Prado CMM, Siervo M, Mire E, Heymsfield SB, Stephan BCM, Broyles S, et al. A population-based approach to define body-composition phenotypes. Am J Clin Nutr. 2014;99(6):1369–77.

Prado CMM, Wells JCK, Smith SR, Stephan BCM, Siervo M. Sarcopenic obesity: A critical appraisal of the current evidence. Clin Nutr. 2012;31(5):583–601.

Radley D, Cooke C, Fuller N, Oldroyd B, Truscott J, Coward W, et al. Validity of foot-to-foot bio-electrical impedance analysis body composition estimates in overweight and obese children. Int J Body Compos Res. 2009;7(1):15–20.

Radley D, Fields DA, Gately PJ. Validity of thoracic gas volume equations in children of varying body mass index classifications. Int J Pediatr Obes. 2007;2(3):180–7.

Raine LB, Khan NA, Drollette ES, Pontifex MB, Kramer AF, Hillman CH. Obesity, visceral adipose tissue, and cognitive function in childhood. J Pediatr. 2017;187(617):134-140.e3.

Ramel SE, Gray HL, Christiansen E, Boys C, Georgieff MK, Demerath EW. Greater early gains in fat-free mass, but not fat mass, are associated with improved neurodevelopment at 1 year corrected age for prematurity in very low birth weight preterm infants. J Pediatr. 2016;173:108–15.

Ramel SE, Gray HL, Ode KL, Younge N, Georgieff MK, Demerath EW. Body composition changes in preterm infants following hospital discharge: Comparison with term infants. J Pediatr Gastroenterol Nutr. 2011;53(3):333–8.

Ramires VV, Dumith SC, Wehrmeister FC, Hallal PC, Menezes AMB, Gonçalves H. Physical activity throughout adolescence and body composition at 18 years: 1993 Pelotas (Brazil) birth cohort study. Int J Behav Nutr Phys Act. 2016;13(1).

Ramírez-Vélez R, Peña-Ibagon JC, Martínez-Torres J, Tordecilla-Sanders A, Correa-Bautista JE, Lobelo F, et al. Handgrip strength cutoff for cardiometabolic risk index among Colombian children and adolescents: The FUPRECOL Study. Sci Rep. 2017;7(February):1–7.

Raschpichler MC, Sorge I, Hirsch W, Mende M, Sergeyev E, Kruber D, et al. Evaluating childhood obesity: Magnetic resonance-based quantification of abdominal adipose tissue and liver fat in children. Fortschr Röntgenstr. 2012;184(4):324–32.

Rasmussen AR, Wohlfahrt-Veje C, Tefre de Renzy-Martin K, Hagen CP, Tinggaard J, Mouritsen A, et al. Validity of self-assessment of pubertal maturation. Pediatrics. 2015;135(1):86–93.

Rauch F, Bailey DA, Baxter-Jones A, Mirwald R, Faulkner R. The "muscle-bone unit" during the pubertal growth spurt. Bone. 2004;34(5):771–5.

Rauch F, Schoenau E. The developing bone: Slave or master of its cells and molecules? Pediatr Res. 2001;50(3):309–14.

Rayar M, Webber CE, Nayiager T, Sala A, Barr RD. Sarcopenia in children with acute lymphoblastic leukemia. J Pediatr Hematol Oncol. 2013;35(2):98–102.

Rehman K, Akash MSH. Mechanisms of inflammatory responses and development of insulin resistance: How are they interlinked? J Biomed Sci. 2016;23(1):1–18.

Reilly SM, Saltiel AR. Adapting to obesity with adipose tissue inflammation. Nat Rev Endocrinol. 2017;13(11):633–43.

Resende C, Camelo Junior J, Vieira M, Perdona G, Ferriolli E, Pfrimer K, et al. Body composition in obese adolescents: Deuterium oxide dilution method, bioelectrical impedance and predictive equations. Curr Nutr Food Sci. 2013;9(10):73–81.

Reus L, Pillen S, Pelzer J, Hokken-koelega ACS, Otten BJ, Maria WG, et al. Growth hormone therapy , muscle thickness , and motor development in Prader-Willi syndrome : An RCT. 2014;134(6).

Riou MÈ, Jomphe-Tremblay S, Lamothe G, Finlayson GS, Blundell JE, Décarie-Spain L, et al. Energy compensation following a supervised exercise intervention in women living with overweight/obesity is accompanied by an early and sustained decrease in non-structured physical activity. Front Physiol. 2019;10(August):1–12.

Ripka WL, Orsso CE, Haqq AM, Luz TG, Prado CM, Ulbricht L. Lean mass reference curves in adolescents using dual-energy x-ray absorptiometry (DXA). PLoS One. 2020;15(2):e0228646.

Rizzoli R, Bianchi ML, Garabédian M, McKay HA, Moreno LA. Maximizing bone mineral mass gain during growth for the prevention of fractures in the adolescents and the elderly. Bone. 2010;46(2):294–305.

Rizzoli R, Bonjour J. Determinants of peak bone mass acquisition. In: Osteoporosis Contemporary Endocrinology. Humana, Cham; 2020. p. 115–37.

Roberts HC, Denison HJ, Martin HJ, Patel HP, Syddall H, Cooper C, et al. A review of the measurement of grip strength in clinical and epidemiological studies: Towards a standardised approach. Age Ageing. 2011;40(4):423–9.

Rodd C, Sharma AK. Prevalence of overweight and obesity in Canadian children, 2004 to 2013: Impact of socioeconomic determinants. Paediatr Child Health. 2017;22(3):153–8.

Rodd C, Sharma AK. Recent trends in the prevalence of overweight and obesity among Canadian children. CMAJ. 2016;188(13):E313–20.

Rodríguez-Cano AM, Mier-Cabrera J, Allegre-Dávalos AL, Muñoz-Manrique C, Perichart-Perera O. Higher fat mass and fat mass accretion during the first six months of life in exclusively breastfed infants. Pediatr Res. 2019;(April):1–7.

Roggero P, Giannì ML, Amato O, Orsi A, Piemontese P, Morlacchi L, et al. Is term newborn body composition being achieved postnatally in preterm infants? Early Hum Dev. 2009;85(6):349–52.

Rolland Y, Czerwinski S, Van Kan GA, Morley JE, Cesari M, Onder G, et al. Sarcopenia: Its assessment, etiology, pathogenesis, consequences and future perspectives. J Nutr Heal Aging. 2008;12(7):433–50.

Rolland-Cachera M, Deheeger M, Akrout M, Bellisle F. Influence of macronutrients on adiposity development: A follow up study of nutrition and growth from 10 months to 8 years of age. Int J Obes Relat Metab Disord. 1995;19(8):573–8.

Rolland-Cachera MF, Brambilla P, Manzoni P, Akrout M, Sironi S, Del Maschio A, et al. Body composition assessed on the basis of arm circumference and triceps skinfold thickness: A new index validated in children by magnetic resonance imaging. Am J Clin Nutr. 1997;65(6):1709–13.

Rolland-Cachera MF, Deheeger M, Maillot M, Bellisle F. Early adiposity rebound: Causes and consequences for obesity in children and adults. Int J Obes. 2006;30:S11–7.

Rollins NC, Bhandari N, Hajeebhoy N, Horton S, Lutter CK, Martines JC, et al. Why invest, and what it will take to improve breastfeeding practices? Lancet. 2016;387(10017):491–504.

Romero NB, Mezmezian M, Fidziańska A. Main steps of skeletal muscle development in the human. Morphological analysis and ultrastructural characteristics of developing human muscle. Handb Clin Neurol. 2013;113:1299–310.

Romitti PA, Zhu Y, Puzhankara S, James KA, Nabukera SK, Zamba GKD, et al. Prevalence of Duchenne and Becker muscular dystrophies in the United States. Pediatrics. 2015;135(3):513–21.

Rosner B, Cook N, Portman R, Daniels S, Falkner B. Determination of blood pressure percentiles in normal-weight children: Some methodological issues. Am J Epidemiol. 2008;167(6):653–66.

Ruan H, Dong LQ. Adiponectin signaling and function in insulin target tissues. J Mol Cell Biol. 2016;8(2):101–9.

Rudvik A, Månsson M. Evaluation of surrogate measures of insulin sensitivity - Correlation with gold standard is not enough. BMC Med Res Methodol. 2018;18(1):1–8.

Ruiz JR, Ortega FB, Tresaco B, Wärnberg J, Mesa JL, González-Gross M, et al. Serum lipids, body mass index and waist circumference during pubertal development in Spanish adolescents: The AVENA study. Horm Metab Res. 2006;38(12):832–7.

Saelens BE, Seeley RJ, van Schaick K, Donnelly LF, O'Brien KJ. Visceral abdominal fat is correlated with whole-body fat and physical activity among 8-y-old children at risk of obestiy. Am J Clin Nutr. 2007;85(1):46–53.

Saint-Maurice PF, Laurson K, Welk GJ, Eisenmann J, Gracia-Marco L, Artero EG, et al. Grip strength cutpoints for youth based on a clinically relevant bone health outcome. Arch Osteoporos. 2018;13(1).

Salehian B, Kejriwal K. Glucocorticoid-induced muscle atrophy: Mechanisms and therapeutic strategies. Endocr Pract. 1999;5(5):277–81.

Salvatore D, Simonides WS, Dentice M, Zavacki AM, Larsen PR. Thyroid hormones and skeletal muscle — new insights and potential implications. Nat Rev Endocrinol. 2014;10(4):206–14.

Samouda H, De Beaufort C, Stranges S, Van Nieuwenhuyse JP, Dooms G, Keunen O, et al. Subtraction of subcutaneous fat to improve the prediction of visceral adiposity: Exploring a new anthropometric track in overweight and obese youth. Pediatr Diabetes. 2017;18(5):399–404.

Sanchez-Escobedo S, Azcorra H, Bogin B, Hoogesteijn AL, Sámano R, Varela-Silva MI, et al. Birth weight, birth order, and age at first solid food introduction influence child growth and body composition in 6- to 8-year-old Maya children: The importance of the first 1000 days of life. Am J Hum Biol. 2020;(e23385):1–11.

Sass FA, Fuchs M, Pumberger M, Geissler S, Duda GN, Perka C, et al. Immunology guides skeletal muscle regeneration. Int J Mol Sci. 2018;19(3):1–19.

Sauder KA, Kaar JL, Starling AP, Ringham BM, Glueck DH, Dabelea D. Predictors of infant body composition at 5 months of age: the Healthy Start Study. J Pediatr. 2017;183:94–9.

Sayer AA, Cooper C. Fetal programming of body composition and musculoskeletal development. Early Hum Dev. 2005;81(9):735–44.

Sayer AA, Dennison EM, Syddall HE, Jameson K, Martin HJ, Cooper C. The developmental origins of sarcopenia: using peripheral quantitative computed tomography to assess muscle size in older people. J Gerontol A Biol Sci Med Sci. 2008;63(8):835-40 OD-2008/09/06.

Schaeffer DJ, Krafft CE, Schwarz NF, Chi L, Rodrigue AL, Pierce JE, et al. An 8-month exercise intervention alters frontotemporal white matter integrity in overweight children. Psychophysiology. 2014;51(8):728–33.

Scheurer JM, Zhang L, Plummer EA, Hultgren SA, Demerath EW, Ramel SE. Body composition changes from infancy to 4 Years and associations with early childhood cognition in preterm and full-term children. Neonatology. 2018;114(2):169–76.

Schoenau E. From mechanostat theory to development of the "Functional Muscle-Bone-Unit." J Musculoskelet Neuronal Interact. 2005;5(3):1–7.

Schoenfeld BJ. The mechanisms of muscle hypertrophy and their application to resistance training. J of Strength Cond Res. 2010;24(10):2857–72.

Scholten RR, Pillen S, Verrips A, Zwarts MJ. Quantitative ultrasonography of skeletal muscle in children: Normal values. Muscle Nerve. 2003;27(June):693–8

Schvey NA, Marwitz SE, Mi SJ, Galescu OA, Broadney MM, Young-Hyman D, et al. Weight-based teasing is associated with gain in BMI and fat mass among children and adolescents at-risk for obesity: A longitudinal study. Pediatr Obes. 2019;14(10):1–14.

Schvey NA, Shomaker LB, Kelly NR, Pickworth CK, Cassidy O, Galescu O, et al. Pressure to be thin and insulin sensitivity among adolescents. J Adolesc Heal. 2016;58(1):104–10.

Schwab RJ, Kim C, Bagchi S, Keenan BT, Comyn FL, Wang S, et al. Understanding the anatomic basis for obstructive sleep apnea syndrome in adolescents. Am J Respir Crit Care Med. 2015;191(11):1295–309.

Sebastiani G, García-Beltran C, Pie S, Guerra A, López-Bermejo A, de Toledo JS, et al. The sequence of prenatal growth restraint and postnatal catch-up growth: Normal heart but thicker intima-media and more pre-peritoneal fat in late infancy. Pediatr Obes. 2019;14(3):e12476.

Seo YG, Kim JH, Kim YM, Lim H, Ju YS, Kang MJ, et al. Validation of body composition using bioelectrical impedance analysis in children according to the degree of obesity. Scand J Med Sci Sport. 2018;28(10):2207–15.

Setayeshgar S, Maximova K, Ekwaru JP, Gray-Donald K, Henderson M, Paradis G, et al. Diet quality as measured by the Diet Quality Index-International is associated with prospective changes in body fat among Canadian children. Public Health Nutr. 2017;20(3):456–63.

Sethi JK, Vidal-Puig AJ. Thematic review series: Adipocyte biology. Adipose tissue function and plasticity orchestrate nutritional adaptation. J Lipid Res. 2007;48(6):1253–62.

Shafei AES, Nabih ES, Shehata KA, Abd Elfatah ESM, Sanad ABA, Marey MY, et al. Prenatal exposure to endocrine disruptors and reprogramming of adipogenesis: An early-life risk factor for childhood obesity. Child Obes. 2018;14(1):18–25.

Shaikh MG, Crabtree NJ, Shaw NJ, Kirk JMW. Body fat estimation using bioelectrical impedance. Horm Res. 2007;68(1):8–10.

Shen W, Chen J, Kwak S, Punyanitya M, Heymsfield SB. Between-slice intervals in quantification of adipose tissue and muscle in children. Int J Pediatr Obes. 2011;6(2):149–56.

Shen W, Punyanitya M, Silva AM, Chen J, Gallagher D, Sardinha LB, et al. Sexual dimorphism of adipose tissue distribution across the lifespan: A cross-sectional whole-body magnetic resonance imaging study. Nutr Metab (Lond). 2009;6(17):1–9.

Shen W, Punyanitya M, Wang Z, Gallagher D, St-Onge M-P, Albu J, et al. Total body skeletal muscle and adipose tissue volumes: Estimation from a single abdominal cross-sectional image. J Appl Physiol. 2004;97(6):2333–8.

Shen W, St-Onge M, Wang Z, Heymsfield S. Study of body composition: An overview. In: Heymsfield S, Lohman T, Wang Z, Going S, editors. Human Body Composition. 2nd ed. Champaign, IL: Human Kinetics; 2005. p. 3–14.

Shypailo RJ, Butte NF, Ellis KJ. DXA: Can it be used as a criterion reference for body fat measurements in children. Obesity. 2008;16(2):457–62.

Siervo M, Prado CM, Mire E, Broyles S, Wells JC, Heymsfield S, et al. Body composition indices of a load-capacity model: Gender-and BMI-specific reference curves. Public Health Nutr. 2014;18(7):1245–54.

Sinha R, Dufour S, Petersen KF, LeBon V, Enoksson S, Ma Y, et al. Assessment of skeletal muscle triglyceride content by ^{1}H nuclear magnetic resonance spectroscopy in lean and obese adolescents. Diabetes. 2002;51:1022–7.

Sioen I, Lust E, De Henauw S, Moreno LA, Jiménez-Pavón D. Associations between body composition and bone health in children and adolescents: A systematic reriew. Calcif Tissue Int. 2016;99(6):557–77.

Sirico F, Bianco A, D'Alicandro G, Castaldo C, Montagnani S, Spera R, et al. Effects of physical exercise on adiponectin, leptin, and inflammatory markers in childhood obesity: systematic review and meta-analysis. Child Obes. 2018;14(4):207–17.

Smith GI, Mittendorfer B, Klein S. Metabolically healthy obesity: Facts and fantasies. J Clin Invest. 2019;129(10):3978–89.

Smith JJ, Eather N, Morgan PJ, Plotnikoff RC, Faigenbaum AD, Lubans DR. The health benefits of muscular fitness for children and adolescents: A systematic review and meta-analysis. Sport Med. 2014;44(9):1209–23.

Socha P, Grote V, Gruszfeld D, Janas R, Demmelmair H, Closa-Monasterolo R, et al. Milk protein intake, the metabolic-endocrine response, and growth in infancy: Data from a randomized clinical trial. Am J Clin Nutr. 2011;94(SUPPL):1776S-1784S.

Spalding KL, Arner E, Westermark PO, Bernard S, Buchholz BA, Bergmann O, et al. Dynamics of fat cell turnover in humans. Nature. 2008;453(7196):783–7.

Springer F, Ehehalt S, Sommer J, Ballweg V, Machann J, Binder G, et al. Predicting volumes of metabolically important whole-body adipose tissue compartments in overweight and obese adolescents by different MRI approaches and anthropometry. Eur J Radiol. 2012;81(7):1488–94.

Statistics Canada. Physical activity and screen time among Canadian children and youth, 2016 and 2017. 82-625-X. 2019.

Stefan N, Schick F, Häring HU. Causes, characteristics, and consequences of metabolically unhealthy normal weight in humans. Cell Metab. 2017;26(2):292–300.

Steffl M, Chrudimsky J, Tufano JJ. Using relative handgrip strength to identify children at risk of sarcopenic obesity. PLoS One. 2017;12(5):1–9

Steinberg A, Manlhiot C, Li P, Metivier E, Pencharz PB, McCrindle BW, et al. Development and validation of bioelectrical impedance analysis equations in adolescents with severe obesity. J Nutr. 2019;149(7):1288–93.

Stevens J, Cai J, Truesdale K, Cuttler L, Robinson T, Roberts A. Percent body fat prediction equations for 8-to 17-year-old American children. Pediatr Obes. 2014;9(4):260–71.

Stoklossa CAJ, Sharma AM, Forhan M, Siervo M, Padwal RS, Prado CM. Prevalence of sarcopenic obesity in adults with class II/ III obesity using different diagnostic criteria. J Nutr Metab. 2017;2017.

Subar AF, Freedman LS, Tooze JA, Kirkpatrick SI, Boushey C, Neuhouser ML, et al. Addressing current criticism regarding the value of self-report dietary data. J Nutr. 2015;145(12):2639–45.

Subhan FB, Shulman L, Yuan Y, McCargar LJ, Kong L, Bell RC, et al. Association of pre-pregnancy BMI and gestational weight gain with fat mass distribution and accretion during pregnancy and early postpartum: A prospective study of Albertan women. BMJ Open. 2019;9(7).

Suissa K, Benedetti A, Henderson M, Gray-Donald K, Paradis G. Effects of dietary glycemic index and load on children's cardiovascular risk factors. Ann Epidemiol. 2019;40:1–7.

Sun K, Kusminski CM, Scherer PE. Adipose tissue remodeling and obesity. J Clin Invest. 2011;121(6):2094–101.

Suzuki D, Kobayashi R, Sano H, Hori D, Kobayashi K. Sarcopenia after induction therapy in childhood acute lymphoblastic leukemia: Its clinical significance. Int J Hematol. 2018;107(4):486–9.

Syme C, Abrahamowicz M, Leonard GT, Perron M, Richer L, Veillette S, et al. Sex differences in blood pressure and its relationship to body composition and metabolism in adolescence. Arch Pediatr Adolesc Med. 2009;163(9):818–25.

Symonds ME, Mostyn A, Pearce S, Budge H, Stephenson T. Endocrine and nutritional regulation of fetal adipose tissue development. J Endocrinol. 2003;179(3):293–9.

Szwimer E, Mougharbel F, Goldfield GS, Alberga AS. The association between weight-based teasing from peers and family in childhood and depressive symptoms in childhood and adulthood: A systematic review. Curr Obes Rep. 2020;

Tahir MJ, Haapala JL, Foster LP, Duncan KM, Teague AM, Kharbanda EO, et al. Higher maternal diet quality during pregnancy and lactation is associated with lower infant weight-for-length, body fat percent, and fat mass in early postnatal life. Nutrients. 2019;11(3):1–15.

Taksali SE, Caprio S, Dziura J, Dufour S, Calı AMG, Goodman TR, et al. High visceral and low abdominal subcutaneous fat stores in the obese adolescent: a determinant of an adverse metabolic phenotype. Diabetes. 2008;57(February):367–71.

Talma H, Chinapaw MJM, Bakker B, Hirasing RA, Terwee CB, Altenburg TM. Bioelectrical impedance analysis to estimate body composition in children and adolescents: A systematic review and evidence appraisal of validity, responsiveness, reliability and measurement error. Obes Rev. 2013;14(11):895–905.

Tauber M, Jouret B, Cartault A, Lounis N, Gayrard M, Marcouyeux C, et al. Adolescents with partial growth hormone (GH) deficiency develop alterations of body composition after GH discontinuation and require follow-up. J Clin Endocrinol Metab. 2003;88(11):5101–6.

Taylor RW, Grant AM, Williams SM, Goulding A. Sex differences in regional body fat distribution from pre- to postpuberty. Obesity. 2010;18(7):1410–6.

Teigen LM, Kuchnia AJ, Mourtzakis M, Earthman CP. The use of technology for estimating body composition: Strengths and weaknesses of common modalities in a clinical setting. Nutr Clin Pract. 2017;32(1):20–9.

Thangarajah D, Hyde MJ, Konteti VKS, Santhakumaran S, Frost G, Fell JME. Systematic review: Body composition in children with inflammatory bowel disease. Aliment Pharmacol Ther. 2015;42(2):142–57.

Theodore RF, Broadbent J, Nagin D, Ambler A, Hogan S, Ramrakha S, et al. Childhood to early mid-life systolic blood pressure trajectories: Early life predictors, effect modifiers, and adult cardiovascular outcomes. Hypertension. 2015;66(6):1108–15.

Thivel D, O'Malley G, Pereira B, Duché P, Aucouturier J. Comparison of total body and abdominal adiposity indexes to dual x-ray absorptiometry scan in obese adolescents. Am J Hum Biol. 2015;27(3):334–8.

Thivel D, Ring-Dimitriou S, Weghuber D, Frelut M-L, O'Malley G. Muscle strength and fitness in pediatric obesity: A systematic review from the European Childhood Obesity Group. Obes Facts. 2016;9(1):52–63.

Thivel D, Verney J, Miguet M, Masurier J, Cardenoux C, Lambert C, et al. The accuracy of bioelectrical impedance to track body composition changes depends on the degree of obesity in adolescents with obesity. Nutr Res [Internet]. 2018;54:60–8.

Thompson AA, Duckham RL, Desai MM, Choy CC, Sherar LB, Naseri T, et al. Sex differences in the associations of physical activity and macronutrient intake with child body composition: a cross-sectional study of 3- to 7-year-olds in Samoa. Pediatr Obes. 2020;e12603.

Timper K, Brü Ning JC. Hypothalamic circuits regulating appetite and energy homeostasis: Pathways to obesity. Disease models & mechanisms. 2017;10(6):679-89

Tomlinson DJ, Erskine RM, Morse CI, Winwood K, Onambélé-Pearson G. The impact of obesity on skeletal muscle strength and structure through adolescence to old age. Biogerontology. 2016;17(3):467–83.

Tong JF, Yan X, Zhu MJ, Ford SP, Nathanielsz PW, Du M. Maternal obesity downregulates myogenesis and β-catenin signaling in fetal skeletal muscle. AJP Endocrinol Metab. 2009;296(4):E917–24.

Toro-Ramos T, Paley C, Pi-Sunyer FX, Gallagher D. Body composition during fetal development and infancy through the age of 5 years. Eur J Clin Nutr. 2015;69(12):1279–89.

Tremblay MS, Chaput JP, Adamo KB, Aubert S, Barnes JD, Choquette L, et al. Canadian 24-Hour Movement Guidelines for the Early Years (0-4 years): An Integration of physical activity, sedentary behaviour, and sleep. BMC Public Health. 2016;41:S311–27.

Tsang TW, Briody J, Kohn M, Chin MC, Singh MF. Abdominal fat assessment in adolescents using dual-energy X-ray absorptiometry. J Pediatr Endocrinol Metab. 2009;22(9):781–94.

Tsuji S, Tsunoda N, Yata H, Katsukawa F, Onishi S, Yamazaki H. Relation between grip strength and radial bone mineral density in young athletes. Arch Phys Med Rehabil. 1995;76(3):234–8.

Tun HM, Bridgman SL, Chari R, Field CJ, Guttman DS, Becker AB, et al. Roles of birth mode and infant gut microbiota in intergenerational transmission of overweight and obesity from mother to offspring. JAMA Pediatr. 2018;172(4):368–77.

U.S. Department of Health and Human Services. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: Summary report. National Institutes of Health: Bethesda, MD. 2012; 12-7486.

Umano GR, Shabanova V, Pierpont B, Mata M, Nouws J, Tricò D, et al. A low visceral fat proportion, independent of total body fat mass, protects obese adolescent girls against fatty liver and glucose dysregulation: A longitudinal study. Int J Obes. 2019;43(4):673–82.

Valdimarsson Ö, Kristinsson JÖ, Stefansson SÖ, Valdimarsson S, Sigurdsson G. Lean mass and physical activity as predictors of bone mineral density in 16-20-year old women. J Intern Med. 1999;245(5):489–96.

Van Aller C, Lara J, Stephan BCM, Donini LM, Heymsfield S, Katzmarzyk PT, et al. Sarcopenic obesity and overall mortality: Results from the application of novel models of body composition phenotypes to the National Health and Nutrition Examination Survey 1999–2004. Clin Nutr. 2018; 38(1):264-70

van Hoek E, Koopman LP, Feskens EJM, Janse AJ. Assessment of epicardial adipose tissue in young obese children. Child Adolesc Obes. 2019;2(1):96–107.

Van Hulst A, Paradis G, Benedetti A, Barnett TA, Henderson M. Pathways linking birth weight and insulin sensitivity in early adolescence: A double mediation analysis. J Clin Endocrinol Metab. 2018;103(12):4524–32.

van Vliet S, Burd NA, van Loon LJ. The Skeletal Muscle Anabolic Response to Plant- versus Animal-Based Protein Consumption. J Nutr. 2015;145(9):1981–91.

Vanderwall C, Eickhoff J, Randall Clark R, Carrel AL. BMI z-score in obese children is a poor predictor of adiposity changes over time. BMC Pediatr. 2018;18(1):1–6.

Vásquez F, Salazar G, Díaz E, Lera L, Anziani A, Burrows R. Comparison of body fat calculations by sex and puberty status in obese schoolchildren using two and four compartment body composition models. Nutr Hosp. 2016;33(5):1116–22.

Veldhuis JD, Roemmich JN, Richmond EJ, Rogol AD, Lovejoy JC, Sheffield-Moore M, et al. Endocrine control of body composition in infancy, childhood, and puberty. Endocr Rev. 2005;26(1):114–46.

Verdijk LB, Snijders T, Drost M, Delhaas T, Kadi F, Van Loon LJC. Satellite cells in human skeletal muscle: From birth to old age. Age (Omaha). 2014;36(2):545–57.

Verney J, Metz L, Chaplais E, Cardenoux C, Pereira B, Thivel D. Bioelectrical impedance is an accurate method to assess body composition in obese but not severely obese adolescents. Nutr Res. 2016;36(7):663–70.

Victora CG, Bahl R, Barros AJD, França GVA, Horton S, Krasevec J, et al. Breastfeeding in the 21st century: Epidemiology, mechanisms, and lifelong effect. Lancet. 2016;387(10017):475–90.

Villela LD, Méio MDBB, Gomes Jr. SCS, de Abranches AD, Soares FVM, Moreira MEL. Body composition in preterm infants with intrauterine growth restriction: A cohort study. J Perinat Med. 2018;46(7):804–10.

Viswanathan V, Eugster EA. Etiology and treatment of hypogonadism in adolescents. Pediatr Clin North Am. 2011;58(5):1181–x.

Voortman T, Braun KVE, Kiefte-de Jong JC, Jaddoe VW V, Franco OH, van den Hooven EH. Protein intake in early childhood and body composition at the age of 6 years: The Generation R Study. Int J Obes. 2016;40(6):1018–25.

Wackerhage H, Rennie MJ. How nutrition and exercise maintain the human musculoskeletal mass. J Anat. 2006;208(4):451–8.

Wade M, Browne DT, Madigan S, Plamondon A, Jenkins JM. Normal birth weight variation and children's neuropsychological functioning: Links between language, executive functioning, and theory of mind. J Int Neuropsychol Soc. 2014;20(9):909–19.

Wagner KR. Genetic diseases of muscle. Neurol Clin. 2002;20(3):645–78.

Walker SP, Wachs TD, Grantham-Mcgregor S, Black MM, Nelson CA, Huffman SL, et al. Inequality in early childhood: Risk and protective factors for early child development. Lancet. 2011;378(9799):1325–38.

Wang H, Wilson GJ, Zhou D, Lezmi S, Chen X, Layman DK, et al. Induction of autophagy through the activating transcription factor 4 (ATF4)-dependent amino acid response pathway in maternal skeletal muscle may function as the molecular memory in response to gestational protein restriction to alert offspring to materna. Br J Nutr. 2015;4(2015):1–14.

Wang J, Pan L, Liu E, Liu H, Liu J, Wang S, et al. Gestational diabetes and offspring's growth from birth to 6 years old. Int J Obes. 2019;43(4):663–72.

Wang Z, St-Onge M-P, Lecumberri B, Pi-Sunyer FX, Heshka S, Wang J, et al. Body cell mass: Model development and validation at the cellular level of body composition. Am J Physiol Endocrinol Metab. 2004;286(1):E123–8.

Wannamethee SG, Atkins JL. Muscle loss and obesity: The health implications of sarcopenia and sarcopenic obesity. Proc Nutr Soc. 2015;74(4):405–12.

Wardle J, Carnell S, Haworth CM, Plomin R. Evidence for a strong genetic influence on childhood adiposity despite the force of the obesogenic environment. Am J Clin Nutr. 2008;87:398–404.

Watson K, Baar K. MTOR and the health benefits of exercise. Semin Cell Dev Biol. 2014;36:130–9.

Wattjes MP, Kley RA, Fischer D. Neuromuscular imaging in inherited muscle diseases. Eur Radiol. 2010;20(10):2447–60.

Watts K, Naylor L, Davis E, Jones T, Beeson B, Bettenay F, et al. Do skinfolds accurately assess changes in body fat in obese children and adolescents? Med Sci Sport Exerc. 2006;38(3):439–70.

Webber CE, Barr RD. Age and gender-dependent values of skeletal muscle mass in healthy children and adolescents. J Cachexia Sarcopenia Muscle. 2012;3(1):25–9.

Weber C, Noels H. Atherosclerosis: Current pathogenesis and therapeutic options. Nat Med. 2011;17(11):1410–22.

Weber DR, Leonard MB, Shults J, Zemel BS. A comparison of fat and lean body mass index to BMI for the identification of metabolic syndrome in children and adolescents. J Clin Endocrinol Metab. 2014;99(9):3208–16.

Weber M, Grote V, Closa-monasterolo R, Escribano J, Langhendries J, Dain E, et al. Lower protein content in infant formula reduces BMI and obesity risk at school age: Follow-up of a randomized trial. Am J Clin Nutr. 2014;1041–51.

Weiss R, Bremer AA, Lustig RH. What is metabolic syndrome, and why are children getting it? Ann N Y Acad Sci. 2013;1281(1):123–40.

Weiss R, Dufour S, Taksali SE, Tamborlane W V., Petersen KF, Bonadonna RC, et al. Prediabetes in obese youth: A syndrome of impaired glucose tolerance, severe insulin resistance, and altered myocellular and abdominal fat partitioning. Lancet. 2003;362(9388):951–7.

Weiss R, Taksali SE, Dufour S, Yeckel CW, Papademetris X, Cline G, et al. The "obese insulin-sensitive" adolescent: Importance of adiponectin and lipid partitioning. J Clin Endocrinol Metab. 2005;90(6):3731–7.

Wells JCK, Haroun D, Williams JE, Darch T, Eaton S, Viner R, et al. Evaluation of lean tissue density for use in air displacement plethysmography in obese children and adolescents. Eur J Clin Nutr. 2011;65(10):1094–101.

Wells JCK, Haroun D, Williams JE, Wilson C, Darch T, Viner RM, et al. Evaluation of DXA against the four-component model of body composition in obese children and adolescents aged 5-21 years. Int J Obes. 2010;34(4):649–55.

Wells JCK. Toward body composition reference data for infants, children, and adolescents. Adv Nutr. 2014;5(June):320S-329S.

Wells JCK. Using body composition assessment to evaluate the double burden of malnutrition. Ann Nutr Metab. 2019;75(2):103–8.

Wey HE, Binkley TL, Beare TM, Wey CL, Specker BL. Cross-sectional versus longitudinal associations of lean and fat mass with pQCT bone outcomes in children. J Clin Endocrinol Metab. 2011;96(1):106–14.

Whiting P, Rutjes A, Westwood M, Mallett S, Deeks J, Reitsma J, et al. QUADAS-2: A revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med. 2011;154(4):529–36.

Wibaek R, Vistisen D, Girma T, Admassu B, Abera M, Abdissa A, et al. Associations of fat mass and fat-free mass accretion in infancy with body composition and cardiometabolic risk markers at 5 years: The Ethiopian iABC birth cohort study. PLoS Med. 2019;16(8):1–22.

Willemsen LE, Koetsier MA, van Deventer SJ, van Tol EA. Short chain fatty acids stimulate epithelial mucin 2 expression through differential effects on prostaglandin E(1) and E(2) production by intestinal myofibroblasts. Gut. 2003;52(10):1442–7.

Williams JE, Wells JCK, Wilson CM, Haroun D, Lucas A, Fewtrell MS. Evaluation of Lunar Prodigy dual-energy X-ray absorptiometry for assessing body composition in healthy persons and patients by comparison with the criterion 4-component model. Am J Clin Nutr. 2006;83(5):1047–54.

Wittcopp C, Conroy R. Metabolic syndrome in children and adolescents. Pediatr Rev. 2016;37(5):193–202.

Wohlfahrt-Veje C, Tinggaard J, Winther K, Mouritsen A, Hagen CP, Mieritz MG, et al. Body fat throughout childhood in 2647 healthy Danish children: Agreement of BMI, waist circumference, skinfolds with dual X-ray absorptiometry. Eur J Clin Nutr. 2014;68(6):664–70.

Wolfe RR, Rutherfurd SM, Kim IY, Moughan PJ. Protein quality as determined by the Digestible Indispensable Amino Acid Score: Evaluation of factors underlying the calculation. Nutr Rev. 2016;74(9):584–99.

Wolfe RR. The underappreciated role of muscle in health and disease. Am J Clin Nutr. 2006;84(3):475–82.

Wong MC, Ng BK, Kennedy SF, Hwaung P, Liu EY, Kelly NN, et al. Children and adolescents' anthropometrics body composition from 3-D optical surface scans. Obesity. 2019;27(11):1738–49.

Wong WW, Nicolson M, Stuff JE, Butte NF, Ellis KJ, Hergenroeder AC, et al. Serum leptin concentrations in Caucasian and African-American girls. J Clin Endocrinol Metab. 1998;83(10):3574–7.

Woolcott OO, Bergman RN. Relative Fat Mass as an estimator of whole-body fat percentage among children and adolescents: A cross-sectional study using NHANES. Sci Rep. 2019;9(1):1–14.

World Health Organization (WHO). Report of the comission on ending childhood obesity: implementation plan: Executive summary. Vol. 1, Executive summary, Geneva: World Health OrganizationCC BYNC-SA 3.0 IGO. 2017.

Wosje KS, Khoury PR, Claytor RP, Copeland KA, Hornung RW, Daniels SR, et al. Dietary patterns associated with fat and bone mass in young children. Am J Clin Nutr. 2010;92(2):294–303.

Wosje KS, Knipstein BL, Kalkwarf HJ. Measurement error of DXA: Interpretation of fat and lean mass changes in obese and non-obese children. J Clin Densitom. 2006;9(3):335–40.

Wu H, Ballantyne CM. Skeletal muscle inflammation and insulin resistance in obesity. J Clin Invest. 2017;127(1):43–54.

Wu Y, Yu X, Li Y, Li G, Cheng H, Xiao X, et al. Adipose tissue mediates associations of birth weight with glucose metabolism disorders in children. Obesity. 2019;27(5):746–55.

Xi B, Zong X, Kelishadi R, Litwin M, Hong YM, Poh BK, et al. International waist circumference percentile cutoffs for central obesity in children and adolescents aged 6 to 18 years. J Clin Endocrinol Metab. 2020;105(4):1–15.

Xiao J, Cain A, Purcell SA, Ormsbee MJ, Contreras RJ, Kim JS, et al. Sarcopenic obesity and health outcomes in patients seeking weight loss treatment. Clin Nutr ESPEN. 2018;23:79–83.

Xiao J, Purcell SA, Prado CM, Gonzalez MC. Fat mass to fat-free mass ratio reference values from NHANES III using bioelectrical impedance analysis. Clin Nutr. 2018;37(6):2284–7.

Yan Y, Liu J, Zhao X, Cheng H, Huang G, Mi J. Abdominal visceral and subcutaneous adipose tissues in association with cardiometabolic risk in children and adolescents: The China Child and Adolescent Cardiovascular Health (CCACH) study. BMJ Open Diabetes Res Care. 2019;7(e000824):1–9.

Yau PL, Javier DC, Ryan CM, Tsui WH, Ardekani BA, Ten S, et al. Preliminary evidence for brain complications in obese adolescents with type 2 diabetes mellitus. Diabetologia. 2010;53(11):2298–306.

Young HJ, Jenkins NT, Zhao Q, Mccully KK. Measurement of intramuscular fat by muscle echo intensity. Muscle and Nerve. 2015;52(6):963–71.

Zemel BS. Quantitative computed tomography and computed tomography in children. Curr Osteoporos Rep. 2011;9:284–90.

Zhou J, Liu B, Liang C, Li Y, Song YH. Cytokine signaling in skeletal muscle wasting. Trends Endocrinol Metab. 2016;27(5):335–47.

Ziegler EE, O'Donnell AM, Nelson SE, Fomon SJ. Body composition of the reference fetus. Growth. 1976;40(4):329–41.

Appendices

Appendix A Supporting Information of Chapter 3

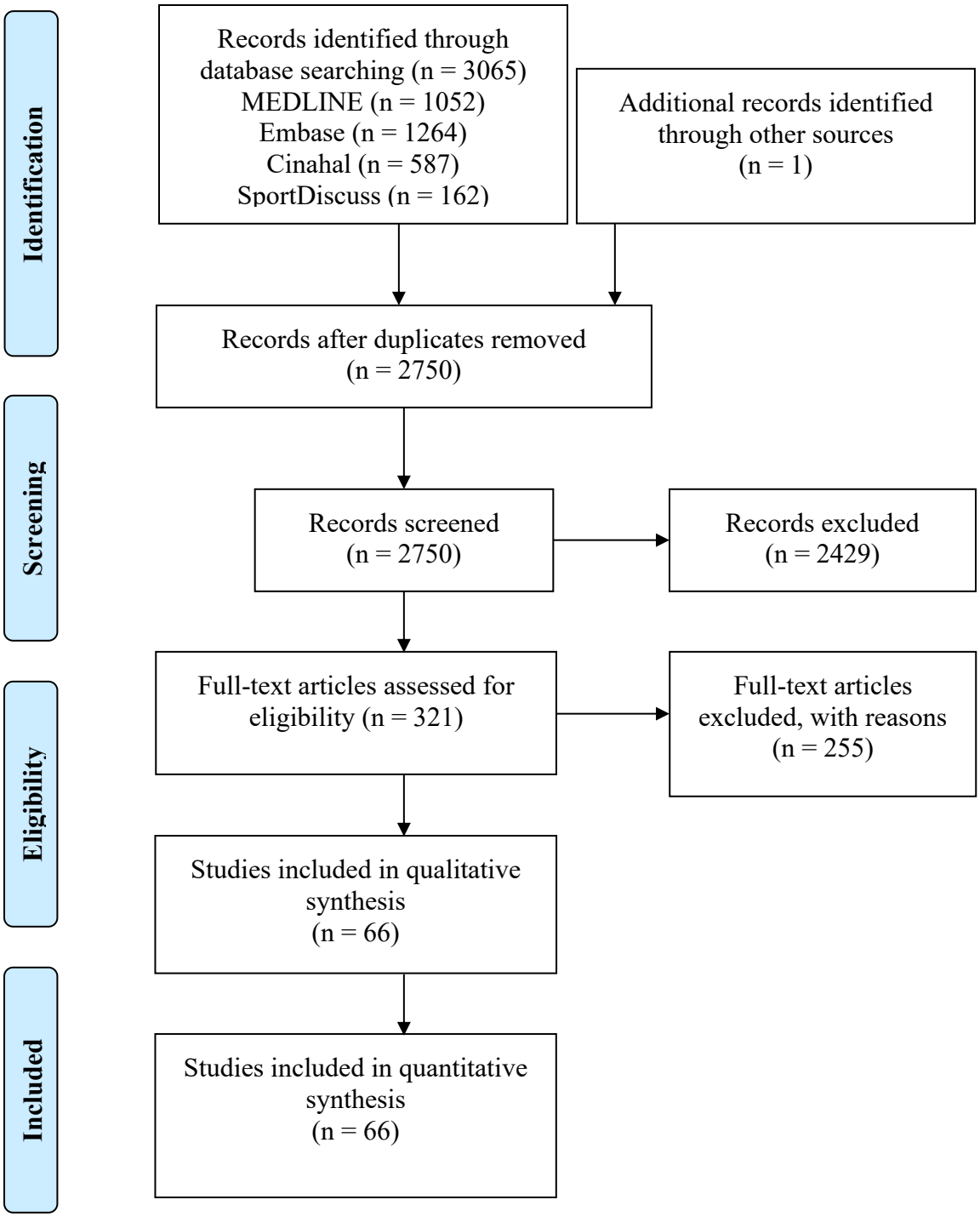


Figure A1 PRISMA flow diagram.

Table A1 Set of keywords entered in MEDLINE (Ovid).

Concept 1: body composition	Concept 2: pediatric population	Concept 3: overweight/obesity	Concept 4: validity/reliability
exp Body Composition/ or body composition.mp. or exp Muscle, Skeletal/ or skeletal or muscle*.mp. or exp Muscles/ or muscle*.mp. or fat-free mass.mp. or fat free mass.mp. or lean mass.mp. or (lean adj3 tissue).mp. or exp Adipose Tissue/ or adipose tissue.mp. or (adipose adj3 tissue).mp. or body fat.mp. or exp Adiposity/ or adiposity.mp. or fat.mp. or exp "Bone and Bones"/ or bone.mp. or exp Bone Density/ or bone density.mp. or (bone adj3 content).mp.	exp child/ or exp "congenital, hereditary, and neonatal diseases and abnormalities"/ or exp infant/ or adolescent/ or exp pediatrics/ or child, abandoned/ or exp child, exceptional/ or child, orphaned/ or child, unwanted/ or minors/ or (pediatric* or paediatric* or child* or newborn* or congenital* or infan* or baby or babies or neonat* or pre-term or preterm* or premature birth* or NICU or preschool* or pre-school* or kindergarten* or kindergarden* or elementary school* or nursery school* or (day care* not adult*) or schoolchild* or toddler* or boy or boys or girl* or middle school* or pubescen* or juvenile* or teen* or youth* or high school* or adolesc* or pre-pubesc* or prepubesc*).mp. or (child* or adolesc* or pediat* or paediat*).jn.	exp Overweight/ or overweight.mp. or exp Obesity/ obesity.mp. or exp Pediatric Obesity/ or pediatric obesity.mp. or pediatric overweight.mp. or childhood overweight.mp. or adolescent or obesity.mp. or adolescent overweight.mp. or infant obesity.mp. or infant overweight.mp.	exp Validation Studies/ or validation study*.mp. or validity.mp. or validation.mp. or exp "Reproducibility of Results"/ or reproducibility.mp. or reliability.mp. or precision.mp. or precise.mp. or exp Data Accuracy/ or accuracy.mp. or accurate.mp.

Table A2 Population characteristics of included studies.

Reference (1st author, year [ref.])	Group	Sample size (n)	Sex (M/F)	Age, mean ± SD (years)	BMI, mean ± SD	Sexual maturation	Ethnicity/race/ country
Aguirre, 2015 (1)	OW/OB	203	118/85	♂: 8.9 (8.4-9.1)[a,b] ♀: 7.9 (7.6-8.2)[a,b]	*BMI SD* ♂: 1.01 (0.13-2.10)[a,b] ♀: 0.82 (0.22-1.84)[a,b]	Prepubertal (TS 1)	Chilean
Asayama, 2002 (2)	OB	75	75/0	♂: 6-14[c]	*BMI (kg/m²)* No complication: 24.8 ± 0.7 Complication[d]: 28.0 ± 0.5	NR	Japanese
Atherton, 2013 (3)	OB	183	60/123	♂: 11.5 ± 2.39 ♀: 11.5 ± 2.59	*BMI SD* ♂: 3.1 ± 0.62 ♀: 3.1 ± 0.69	NR	UK
Ball, 2006 (4)*(cross-validation cohort)*	OW/OB	65	40/25	11.7 ± 1.6	NR	TS 1-2: n = 34 TS 3-5: n = 31	Latino
Bamman, 2013 (5)	OW/OB	28	35/43[a]	7.0 ± 1.6	*BMI (kg/m²)* 21.5 ± 3.7	NR	European (Belgium, UK, Sweden, Spain)
Battistini, 1992 (6)	OB	19	9/10	12.1 ± 1.8	*BMI (kg/m²)* 27.4 ± 3.1	NR	Italy
Bedogni, 1997 (7)	OB	30	16/14	10.5 ± 1.5	NR	NR	Italy
Bray, 2002 (8)	OB	114[a]	W: 30/25[a] AA: 31/28[a]	W-♂: 12.8 ± 0.1[a] W-♀: 12.5 ± 0.1[a] AA-♂: 12.9 ± 0.1[a] AA-♀: 12.7 ± 0.1[a]	*BMI (kg/m²)* W-♂: 23.9 ± 1.0[a] W-♀: 24.2 ± 1.1[a] AA-♂: 27.1 ± 1.1[a] AA-♀: 23.2 ± 0.8[a]	TS 1-2.5: n = 45[a] TS 3-5: n = 68[a]	USA W: n = 55[a] AA: n = 59[a]
Butcher, 2019 (9) *(baseline)*	OW & OB	OW: 25 OB: 16	33/33[a]	14.6 ± 1.6[a]	*BMI (kg/m²)* 21.4 ± 3.4[a]	Prepubertal: 4.5%[a] Early pubertal: 4.5%[a] Mid-pubertal: 27.3%[a] Late pubertal: 53%[a] Postpubertal: 10.6%[a]	USA W: 81.8%[a]
Chan, 2009 (10)	OB	138	101/37	11.9 ± 2.7	*BMI SD* ♂: 2.12 ± 0.43 ♀: 2.46 ± 0.47	NR	Chinese
Cleary, 2008 (11)	OW/OB	30	12/18	7.6 ± 1.3	*BMI (kg/m²)* ♂: 21.75 ± 4.20 ♀: 23.51 ± 2.79	Prepubertal	Australia

Reference (1st author, year [ref.])	Group	Sample size (n)	Sex (M/F)	Age, mean ± SD (years)	BMI, mean ± SD	Sexual maturation	Ethnicity/race/ country
Colantonio, 2015 (12)	OB	36	15/21	♂: 16.0 ± 0.9 ♀: 16.5 ± 1.5	*BMI (kg/m²)* ♂: 34.9 ± 4.4 ♀: 34.1 ± 3.7	TS 4-5	Brazil
Cortes-Castell, 2017 (13)*(cross-validation cohort)*	OW/OB	208	113/95	11.3 ± 2.8	*BMI (kg/m²)* 26.7 ± 4.3	NR	European, Caucasian
de Mello, 2005 (14)	OB	88	20/68	♂: 15.95 ± 1.54 ♀: 16.34 ± 1.41	*BMI (kg/m²)* ♂: 35.58 ± 4.34 ♀: 35.63 ± 4.40	Postpubertal	Brazil
Dias, 2019 (15)*(post intervention)*	OB	31	18/13	11.4 ± 1.9	*BMI (kg/m²)* 30.1 ± 4.3	TS 1-4	Australia
Eisenkolbl, 2001 (16)	OB	27	14/13	♂: 12.57 ± 3.27 ♀: 13.08 ± 2.40	*BMI (kg/m²)* ♂: 32.30 ± 7.04 ♀: 30.14 ± 5.13	NR	Austria
Elberg, 2004 (17)	OW/OB	40	15/25	♂: 10.6 ± 2.2a ♀: 11.3 ± 2.5a	*BMI SD* ♂: 2.6 ± 2.6a ♀: 2.4 ± 1.9a	*Breast* ♂: Median TS = 1 ♀: Median TS = 3 *Pubic hair* ♂: Median TS = 2a ♀: Median TS = 2a	USA ♂ W: n = 11 ♂ AA: n = 4 ♀ W: n = 11 ♀ AA: n = 14
Freedman, 2013 (18) *(Pediatric Rosetta cohort)*	OB	124	65/59	♂: 12.2 ± 4.0 ♀: 13.5 ± 5.0	*BMI SD*[e] ♂: 2.10 ± 0.5 ♀: 2.06 ± 0.6	NR	USA ♂ non-W: 80% ♀ non-W: 80%;
Garcia-Vicencio, 2016 (19)	OB	12	0/12	13.9 ± 0.9	*BMI (kg/m²)* 32.1 ± 4.2	*Breast* TS 2-3: n = 4 TS 4-5: n = 8 *Pubic hair* TS 2-3: n = 5 TS 4-5: n = 7	France
Gately, 2003 (20)	OW	30	18/12	♂: 13.99 ± 1.54a ♀: 14.27 ± 2.27a	*BMI (kg/m²)* ♂: 32.14 ± 6.43a ♀: 30.68 ± 3.77a	NR	UK
Gillis, 2000 (21)*(baseline)*	OB	67	38/29	11.5 ± 2.5	NR	NR	Canada, Caucasian
Goldfield, 2006 (22)	OW/OB	17	6/11	10.2 ± 1.2	*BMI (kg/m²)* 28.6 ± 5.2	NR	Canada

Reference (1st author, year [ref.])	Group	Sample size (n)	Sex (M/F)	Age, mean ± SD (years)	BMI, mean ± SD	Sexual maturation	Ethnicity/race/ country
Gonzalez-Ruiz, 2018 (23)	OW/OB	127	42/85	♂: 12.9 ± 1.2 ♀: 13.7 ± 1.7	*BMI (kg/m²)* ♂: 24.2 ± 2.5 ♀: 23.5 ± 4.1	♂ *genital* TS 1-2: 43.9% TS 3-5: 56.1% ♂ *pubic hair* TS 1-2: 48.7% TS 3-5: 51.3% ♀ *genital* TS 1-2: 3.5% TS 3-5: 96.5% ♀ *pubic hair* TS 1-2: 28.2% TS 3-5: 71.8%	Colombian
Haroun, 2005 (24)	OB	28	13/15	♂: 11.9 ± 2.0 ♀: 10.8 ± 2.2	*BMI SD* ♂: 2.48 ± 0.51 ♀: 2.63 ± 0.71	NR	UK
Haroun, 2009 (25) *(validation and cross-validation cohorts)*	OB	*Validation:* n = 78 *Cross-validation*: n = 17	*Validation:* 30/48 *Cross-validation:* 5/12	*Validation:* 12.0 ± 3.4 *Cross-validation*: 11.3 ± 3.5	*Validation* ♂: 27.4 ± 4.8 ♀: 26.8 ±4.2 *Cross-validation* ♂: 28.8 ± 4.4 ♀: 29.1 ± 5.4	*Validation* ♂ prepubertal: 23.3% ♂ pubertal: 76.7% ♀ prepubertal: 17.0% ♀ pubertal: 83	UK, W
Hofsteenge, 2015 (26)	OB	103	42/61	♂: 14.1 ± 1.7 ♀: 14.7 ± 1.7	*BMI SD* ♂: 3.05 ± 0.32 ♀: 2.94 ± 0.35	Prepubertal: n = 32 Pubertal: n = 65	Netherlands
Hui, 2018 (27)	OB	12	6/6	16.1 ± 0.6	*BMI (kg/m²)* 31.3 ± 2.3	NR	China, Asian
Kabiri, 2015 (28)	OW & OB	OW: 11 OB: 22	26/29a	8.47 ± 1.65a	*BMI SD* 0.07 ± 1.18a	Prepubertal, pubertal	USA W: n = 15 Black: n = 36 Hispanic: n = 33 Other race: n = 16
Kasvis, 2015 (29)	OW/OB	89	41/48	♂: 10.0 ± 1.7 ♀: 9.7 ± 1.7	*BMI SD* 2.86 ± 0.74	♂ TS ≤3: n = 37 ♂ TS >4: n = 4 ♀ TS ≤3: n = 44 ♀ TS >4: n = 4	Canada W: n = 69 Mixed: n = 9 Black, Asian, or Hispanic: n = 11
Koot, 2014 (30)	OB	92	35/57	13.9 ± 2.2	*BMI SD* 3.29 ± 0.33	NR	The Netherlands European: n = 61 Middle East: n = 13; Other: n = 18

Reference (1st author, year [ref.])	Group	Sample size (n)	Sex (M/F)	Age, mean ± SD (years)	BMI, mean ± SD	Sexual maturation	Ethnicity/race/ country
Lazzer, 2003 (31)	OW/OB	53	20/33	♂: 14.1 ± 1.4 ♀: 15.2 ± 1.4	*BMI (kg/m²)* ♂: 27.2 ± 4.9 ♀: 28.4 ± 3.5	NR	France
Lazzer, 2008 (32)	OB	58	27/31	♂: 13.7 ± 1.4 ♀: 14.3 ± 1.4	*BMI SD* ♂: 2.5 ± 0.4 ♀: 3.0 ± 0.6	♂ TS: 3.4 ± 1.2 ♀ TS: 4.5 ± 0.8	Italy, Caucasian
Lu, 2003 (33)	OB	64	44/20	♂: 12.2 ± 1.4 ♀: 13.4 ± 2.2	*BMI (kg/m²)* ♂: 30.1 ± 5.3 ♀: 29.6 ± 4.3	NR	China, Asian
Luque, 2014 (34, 35)	NW/OW/OB	171a	84/87a	7-yeara	*BMI (kg/m²)* ♂: 16.44 (15.00-18.09)a·b ♀: 16.59 (15.50-18.36)a·b	NR	Spain
Lyra, 2015 (36) ***(baseline)***	OB	111	NR	12.0 ± 1.9	*BMI SD* 2.3 ± 0.5	NR	Brazil
Meredith-Jones, 2015 (37) ***(baseline)***	OW/OB	95	39/56	♂: 6.3 ± 1.4a ♀: 6.5 ± 1.5a	*BMI SD* ♂: 0.9 ± 0.9a ♀: 0.8 ± 1.0a	NR	New Zealanda, European ♂: 79.0% European ♀: 79.2% Maori ♂: 13.6% Maori ♀: 14.2% Pacific ♂: 1.2% Pacific ♀: 1.9% Other ♂: 4.9% Other ♀: 4.7%
Mooney, 2011 (38)	OW/OB	331a	117/154a	12-17a·c	*BMI (kg/m²)* ♂: 20.3 ± 3.5a ♀: 21.3 ± 3.4a	NR	USA
NewtonJr, 2005 (39)*(Study 1)*	OW/OB	54	0/54	13.1 ± 1.4	*BMI (kg/m²)* 36.0 ± 7.4	NR	USA, AA
Ohta, 2017 (40)	OW/OB	40	23/17	♂: 9.5 ± 1.8 ♀: 9.3 ± 1.5	*BMI (kg/m²)* ♂: 21.6 ± 2.7 ♀: 20.7 ± 1.4	NR	Japan, Japanese
Pineau, 2010 (41)	OB	94	37/57	12-19c	*BMI (kg/m²)* ♂: 36.3 ± 5.2 ♀: 38.0 ± 5.1	NR	France
Radley, 2007 (42)	OW & OB	OW: 44 OB: 120	OW: 15/29 OB: 52/68	♂ OW: 12.1 ± 2.5 ♀ OW: 13.6 ± 2.9 ♂ OB: 13.5 ± 2.1 ♀ OB: 14.9 ± 1.8	♂ OW: 1.97 ± 0.28 ♀ OW: 1.84 ± 0.32 ♂ OB: 3.17 ± 0.46 ♀ OB: 3.13 ± 0.53	NR	UK and USA
Radley, 2009 (43)	OW/OB	52	38/14	♂: 13.6 ± 1.3 ♀: 14.7 ± 2.2	*BMI SD* ♂: 2.70 ± 0.76 ♀: 2.78 ± 0.74	NR	UK

Reference (1st author, year [ref.])	Group	Sample size (n)	Sex (M/F)	Age, mean ± SD (years)	BMI, mean ± SD	Sexual maturation	Ethnicity/race/ country
Raschpichler, 2012 (44)	OB	10	7/3	13.3 ± 3.5	*BMI (kg/m²)* 33.3 ± 8.6	NR	Germany
Resende, 2013 (45)	OB	55	29/26	♂: 10.47 ± 1.35 ♀: 10.45 ± 1.24	*BMI (kg/m²)* ♂: 31.45 ± 3.42 ♀: 31.04 ± 5.02	TS 1: 36.36% TS 2: 34.54% TS 3: 14.54% TS 4: 5.45% TS 5: 1.82%	Brazil
Rolland-Cachera, 1997 (46)	OB	11	6/5	12.8 ± 1.9	*BMI (kg/m²)* 29.7 ± 4.0	NR	Italy
Samouda, 2017 (47)	OW/OB	181	85/96	♂: 11.9 ± 2.3 ♀: 12.4 ± 2.4	*BMI SD* ♂: 1.8 ± 0.5 ♀: 1.8 ± 0.5	NR	Luxembourg
Seo, 2018 (48)	OB	316	187/129	11.5 ± 2.1	NR	♂ TS 2: 55.7% ♀ TS 2: 80.8%	Korea
Shaikh, 2007 (49)	OB	46	24/22	11.0 ± 2.1[f]	*BMI SD* 3.0 ± 0.14	NR	NR
Shypailo, 2008 (50)	NW/OW/OB	1384[a]	609/775	1.7-17.2[a,c]	*BMI SD* ♂: 0.6 ± 1.2[a] ♀: 0.3 ± 1.3[a]	NR	USA
Springer, 2012 (51)	OB	40	22/18	♂: 13.9 ± 1.5 ♀: 14.1 ± 1.1	*BMI SD* ♂: 2.61 ± 0.47 ♀: 2.56 ± 0.58	NR	Germany
Steinberg, 2019 (52) ***(validation cohort)***	OB	65	20/45	15.8 ± 2.0	*BMI (kg/m²)* 45.6 ± 7.5	NR	Canada
Stevens, 2014 (53) ***(cross-validation cohort)***	OW & OB	OW: 914 OB: 880	OW: 557/357 OB: 574/306	♂: 12.4 ± 0.1[a,f] ♀: 12.4 ± 0.1[a,f]	*BMI SD* ♂: 0.49 ± 0.03[a,f] ♀: 0.49 ± 0.04[a,f]	NR	USA Non-Hispanic W ♂: 61.1%[a] Non-Hispanic W ♀: 63.3%[a] Non-Hispanic Black ♂: 14.8%[a] Non-Hispanic Black ♀: 14.0%[a] Mexican American ♂: 11.6%[a] Mexican American ♀: 10.4%[a] Other ♂: 12.5%[a] Other ♀: 14.4%[a]
Thivel, 2015 (54)	OB	119	61/58	12.2 ± 2.8	*BMI (kg/m²)* 29.7 ± 6.8	TS 3-4	France
Thivel, 2018 (55)	OB	113	31/82	14 ± 0.9	NR	TS 3-5	France

Reference (1st author, year [ref.])	Group	Sample size (n)	Sex (M/F)	Age, mean ± SD (years)	BMI, mean ± SD	Sexual maturation	Ethnicity/race/ country
Tsang, 2009 (56)	OW/OB	16	6/10	14.1 ± 1.9	*BMI (kg/m²)* 33.8 ± 7.0	NR	Australia
Vasquez, 2016 (57)	OB	61	33/28	♂ TS 1-2: 11.5 ± 1.1 ♂ TS 3-5: 13.6 ± 1.0 ♀ TS 1-2: 8.4 ± 0.8 ♀TS 3-5: 11.5 ± 1.7	NR	♂ TS 1-2: n = 19 ♂ TS 3-5: n = 14 ♀ TS 1-2: n = 5 TS 3-5: n = 23	Chile
Verney, 2016 (58)	OB	138	28/110	14 ± 1.5	*BMI (kg/m²)* 33.0 ± 4.8	TS 3-5	France
Wabitsch, 1996 (59)	OW/OB	146	69/77	12.7 ± 3.0	*BMI (kg/m²)* 28.8 ± 4.9	NR	Germany
Watts, 2006 (60)*(baseline)*	OB	38	21/17	12.7 ± 2.1	*BMI (kg/m²)* 32.6 ± 0.9	TS 3-5	Australia
Wells, 2010 (61)	OB	*Cross-sectional:* 153 *Longitudinal:* 51	*Cross-sectional:* 57/96 *Longitudinal:* 18/33	*Cross-sectional:* ♂: 12.0 ± 3.2 ♀: 11.3 ± 3.3 *Longitudinal:* 10.7 ± 2.2	*BMI SD* *Cross-sectional:* ♂: 2.7 ± 0.7 ♀: 2.7 ± 0.7 *Longitudinal:* *3.0* ± 0.6	*Cross-sectional:* TS 1-2: n = 81 TS 3-5: n = 69	UK *Cross-sectional:* W European ♂: n = 38 W European ♀: n = 67 Asian ♂: n = 6 Asian ♀: n = 8 Other ♂: n = 7 Other ♀: n = 8 *Longitudinal:* W European: n = 31 Asian: n = 7 Black: n = 7 Other: n = 6
Wells, 2011 (62)	OB	106	39/66	♂: 12.6 ± 3.5 ♀: 11.7 ± 3.6	*BMI SD* ♂: 2.6 ± 0.7 ♀: 2.6 ± 0.8	NR	UK W European: n = 76 Asian: n = 7 Black African or Afro-Caribbean: n = 12 Other: n = 10
Williams, 2006 (63)	OB	37	11/26	12.6 ± 2.66	*BMI SD* ♂: 2.77 ± 0.68 ♀: 2.77 ± 0.73	NR	UK
Wohlfahrt-Veje, 2014 (64)	OW & OB	OW: 74 OB: 6	♂ OW: 30 ♀ OW: 44 ♂ OB: 3 ♀ OB: 3	♂: 10.8 (7.7-14.2)a ♀: 11.2 (7.9-14.7)a	*BMI SD* ♂: 0.12 (-2.67-3.17)a,g ♀: 0.15 (-2.64-3.28)a,g	TS 1-2 ♂: 91.6%a ♀: 56.8%a TS 3-5: ♂:8.4%a ♀: 43.2%a	Denmark, Caucasian – Danish

Reference (1st author, year [ref.])	Group	Sample size (n)	Sex (M/F)	Age, mean ± SD (years)	BMI, mean ± SD	Sexual maturation	Ethnicity/race/ country
Woolcott, 2019 (65)	OW & OB	8-14 years OW: 896 OB: 996 15-19 years OW: 783 OB: 832	8-14 years ♂ OW: 500 ♀ OW: 396 ♂ OB: 555 ♀ OB: 441 15-19 years ♂ OW: 447 ♀ OW: 336 ♂ OB: 515 ♀ OB: 317	8-14 years ♂: 11.0 ± 0.1a ♀: 11.1 ± 0.1a 15-19 years ♂: 16.9 ± 0.1a ♀: 17.1 ± 0.1a	*BMI (kg/m²)* 8-14 years ♂: 20.1 ± 0.1a ♀: 20.7 ± 0.2a 15-19 years ♂: 24.2 ± 0.2a ♀: 24.2 ± 0.2a	NR	American – NHANES 1999-2006
Wosje, 2006 (66)	OB	32	17/15	12.6 ± 2.9	*BMI (kg/m²)* 32.6 (23.7 - 55.8)	NR	USA

[a] Data was not stratified by weight categories, meaning that data from individuals with normal weight are combined with data from individuals with overweight/obesity.
[b] Median (interquartile range)
[c] Range (minimum-maximum)
[d] Children with serum TG, ALT or insulin level above the reference values for the population
[e] Median ± interquartile range
[f] Mean ± standard error
[g] Mean (range)
Abbreviations: AA, African-American; BMI, body mass index; F, female; M, male; n, number of participants); NR, not reported; NW/OW/OB, normal weight, overweight and obesity groups combined; OB, obesity group; OW, overweight group; OW/OB, overweight and obesity groups combined; OW & OB, results from overweight and obesity groups reported separately; SD, standard deviation; TS, Tanner stage; UK, United Kingdom; W, White.
Symbols: ♂, male; ♀, female

Table A3 Quality assessment of included studies according index test.

	Index Test	**Anthropometrics**						
	Study reference	(7)	(13)	(46)	(47)	(54)	(8)	(65)
Domains	*A. Risk of Bias*							
Patient selection	• Was an adequate description of patient characteristics provided? (e.g. missing information on ethnicity, puberty status, recruitment)	N	Y	Y	Y	Y	Y	Y
	• Was a consecutive or random sample of patients enrolled?	Y	Y	Y	Y	Y	Y	Y
	• Did the study avoid inappropriate exclusions?	U	N	U	Y	U	U	Y
	Could the selection of patients have introduced bias?	**U**	**L**	**L**	**L**	**L**	**L**	**L**
Index test	• Were the index test results interpreted without knowledge of the results of the reference standard?	Y	Y	Y	Y	Y	Y	Y
	• Was an adequate description of the index test and protocol provided?	U	Y	Y	Y	Y	Y	Y
	• Were there important flaws in the pre-test procedures or in the conduction of the test?	U	N	N	N	N	N	N
	• Was an appropriate approach used to analyse and report the data?	Y	Y	Y	Y	Y	Y	Y
	• Was the index test performed by trained personnel?	U	U	U	Y	Y	U	U
	Could the conduct or interpretation of the index test have introduced bias?	**U**	**L**	**L**	**L**	**L**	**L**	**L**
Reference standard	• Is the reference standard likely to correctly classify the target condition?	Y	Y	Y	Y	Y	Y	Y
	• Were the reference standard results interpreted without knowledge of the results of the index test?	Y	Y	Y	Y	Y	Y	Y
	• Was an adequate description of the reference standard and protocol provided?	Y	U	Y	Y	Y	Y	Y
	• Were there important flaws in the pre-test procedures or conduction of the test?	N	U	N	N	N	N	N
	• Was an appropriate approach used to analyse and report the data?	Y	Y	Y	Y	Y	Y	Y
	• Was the reference standard performed by trained personnel?	U	U	Y	U	Y	U	U
	Could the reference standard, its conduct or its interpretation have introduced bias?	**L**	**U**	**L**	**L**	**L**	**L**	**L**
Flow and timing	• Was there an appropriate interval between index test(s) and reference standard?	U	U	Y	U	U	U	U
	• Did all patients receive a reference standard?	Y	Y	Y	Y	Y	Y	Y
	• Did patients receive the same reference standard?	Y	Y	Y	Y	Y	Y	Y
	• Were the test conditions similar for the measurements?	U	U	Y	U	U	U	Y
	• Were all patients included in the analysis?	Y	Y	Y	Y	N	Y	Y
	Could the patient flow have introduced bias?	**U**	**U**	**L**	**U**	**U**	**U**	**L**
	B. Concerns regarding applicability							
Patient selection	**Is there concern that the included patients do not match the review question?**	**L**	**L**	**L**	**L**	**L**	**L**	**L**
Index test	• If using predictive equations, were they developed and validated in a population similar to the one under study?	N	Y	N	N	N	Y	Y

		Index Test: Anthropometrics						
	Study reference	(7)	(13)	(46)	(47)	(54)	(8)	(65)
Reference standard	**Is there concern that the index test, its conduct, or interpretation differ from the review question?**	**H**	**L**	**H**	**H**	**H**	**L**	**L**
	• If using predictive equations, were they developed and validated in a population similar to the one under study?	U	N/a	N/a	N/a	N/a	Y	N/a
	Is there concern that the target condition as defined by the reference standard does not match the review question?	**L**	**N/a**	**N/a**	**N/a**	**N/a**	**L**	**N/a**

		Index Test: Skinfolds													
	Study reference	(41)	(60)	(4)	(1)	(5)	(10)	(17)	(18)	(23)	(38)	(53)	(2)	(8)	(64)
Domains	*A. Risk of Bias*														
Patient selection	• Was an adequate description of patient characteristics provided? (e.g. missing information on ethnicity, puberty status, recruitment)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	• Was a consecutive or random sample of patients enrolled?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	• Did the study avoid inappropriate exclusions?	Y	Y	Y	Y	U	U	U	U	Y	Y	Y	Y	U	Y
	Could the selection of patients have introduced bias?	**L**	**L**	**L**	**L**	**L**	**L**	**L**	**L**	**L**	**L**	**L**	**L**	**L**	**L**
Index test	• Were the index test results interpreted without knowledge of the results of the reference standard?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	• Was an adequate description of the index test and protocol provided?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	• Were there important flaws in the pre-test procedures or in the conduction of the test?	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	• Was an appropriate approach used to analyse and report the data?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	• Was the index test performed by trained personnel?	U	Y	Y	Y	U	U	Y	U	Y	Y	Y	Y	U	Y
	Could the conduct or interpretation of the index test have introduced bias?	**L**	**L**	**L**	**L**	**L**	**L**	**L**	**L**	**L**	**L**	**L**	**L**	**L**	**L**
Reference standard	• Is the reference standard likely to correctly classify the target condition?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	• Were the reference standard results interpreted without knowledge of the results of the index test?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	• Was an adequate description of the reference standard and protocol provided?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	• Were there important flaws in the pre-test procedures or conduction of the test?	N	N	N	N	N	N	N	Y	N	N	N	N	N	N
	• Was an appropriate approach used to analyse and report the data?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	• Was the reference standard performed by trained personnel?	U	U	Y	U	U	U	U	U	Y	Y	Y	U	U	U
	Could the reference standard, its conduct or its interpretation have introduced bias?	**L**	**L**	**L**	**L**	**L**	**L**	**L**	**H**	**L**	**L**	**L**	**L**	**L**	**L**
Flow and timing	• Was there an appropriate interval between index test(s) and reference standard?	U	U	Y	U	Y	U	U	U	Y	Y	Y	Y	U	Y
	• Did all patients receive a reference standard?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y
	• Did patients receive the same reference standard?	Y	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y
	• Were the test conditions similar for the measurements?	U	U	N	U	U	U	Y	U	Y	Y	Y	Y	U	Y
	• Were all patients included in the analysis?	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y

		Index Test	Skinfolds													
	Study reference		(41)	(60)	(4)	(1)	(5)	(10)	(17)	(18)	(23)	(38)	(53)	(2)	(8)	(64)
	Could the patient flow have introduced bias?		**H**	**U**	**H**	**U**	**L**	**U**	**H**	**H**	**L**	**L**	**L**	**L**	**U**	**L**
	B. Concerns regarding applicability															
Patient selection	**Is there concern that the included patients do not match the review question?**		**L**	**L**	**L**	**L**	**L**	**L**	**L**	**L**	**L**	**L**	**L**	**L**	**L**	**L**
Index test	• If using predictive equations, were they developed and validated in a population similar to the one under study?		N	N	Y	N	Yes	No	Yes	No	N	N	Y	N	Y	N
	Is there concern that the index test, its conduct, or interpretation differ from the review question?		**H**	**H**	**L**	**H**	**L**	**H**	**L**	**H**	**H**	**H**	**L**	**H**	**L**	**H**
Reference standard	• If using predictive equations, were they developed and validated in a population similar to the one under study?		N/a	N/a	N/a	U	U	N/a	N/a	N/a	N/a	N/a	N/a	N/a	Y	N/a
	Is there concern that the target condition as defined by the reference standard does not match the review question?		**N/a**	**N/a**	**N/a**	**U**	**U**	**N/a**	**N/a**	**N/a**	**N/a**	**N/a**	**N/a**	**N/a**	**L**	**N/a**

		Index Test	BIA															
	Study reference		(6)	(21)	(25)	(43)	(45)	(57)	(11)	(22)	(26)	(31)	(8)	(34)	(35)	(9)	(28)	(59)	(16)
Domains		*A. Risk of Bias*																	
Patient selection	• Was an adequate description of patient characteristics provided? (e.g. missing information on ethnicity, puberty status, recruitment)		N	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	N	N	Y	Y	N	Y
	• Was a consecutive or random sample of patients enrolled?		Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	• Did the study avoid inappropriate exclusions?		U	Y	Y	Y	U	Y	Y	Y	Y	Y	U	U	U	Y	N	U	Y
	Could the selection of patients have introduced bias?		**U**	**L**	**L**	**L**	**U**	**L**	**L**	**L**	**L**	**L**	**L**	**U**	**U**	**L**	**L**	**U**	**L**
Index test	• Were the index test results interpreted without knowledge of the results of the reference standard?		Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	• Was an adequate description of the index test and protocol provided?		N	N	N	Y	N	Y	Y	Y	Y	Y	N	N	N	Y	Y	Y	N
	• Were there important flaws in the pre-test procedures or in the conduction of the test?		U	U	U	U	U	N	U	U	U	U	U	U	U	N	N	Y	U
	• Was an appropriate approach used to analyse and report data?		Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	• Was the index test performed by trained personnel?		U	Y	U	U	U	U	Y	Y	U	U	U	Y	Y	Y	Y	U	U
	Could the conduct or interpretation of the index test have introduced bias?		**L**	**U**	**U**	**U**	**U**	**L**	**U**	**U**	**U**	**U**	**U**	**U**	**U**	**L**	**L**	**H**	**U**
Reference standard	• Is the reference standard likely to correctly classify the target condition?		Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	• Were the reference standard results interpreted without knowledge of the results of the index test?		Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y

	Index Test	BIA																
	Study reference	(6)	(21)	(25)	(43)	(45)	(57)	(11)	(22)	(26)	(31)	(8)	(34)	(35)	(9)	(28)	(59)	(16)
Flow and timing	• Was an adequate description of the reference standard and protocol provided?	Y	N	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	• Were there important flaws in the pre-test procedures or conduction of the test?	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	• Was an appropriate approach used to analyse and report the data?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	• Was the reference standard performed by trained personnel?	U	Y	U	U	U	U	Y	U	U	U	U	Y	Y	Y	Y	Y	U
	Could the reference standard, its conduct or its interpretation have introduced bias?	**L**	**H**	**L**	**L**	**U**	**L**	**L**	**L**	**L**	**L**	**L**	**L**	**L**	**L**	**L**	**L**	**L**
	• Was there an appropriate interval between index test(s) and reference standard?	Y	U	U	Y	Y	U	Y	Y	Y	Y	U	U	U	Y	Y	Y	U
	• Did all patients receive a reference standard?	Y	N	Y	Y	Y	Y	Y	Y	N	Y	Y	N	N	N	N	Y	Y
	• Did patients receive the same reference standard?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	• Were the test conditions similar for the measurements?	Y	U	U	Y	Y	U	Y	Y	Y	Y	U	U	U	Y	Y	Y	U
	• Were all patients included in the analysis?	Y	N	Y	Y	N	Y	N	Y	N	Y	Y	N	N	N	N	Y	Y
	Could the patient flow have introduced bias?	**L**	**H**	**U**	**L**	**L**	**U**	**L**	**L**	**H**	**L**	**U**	**H**	**H**	**L**	**H**	**L**	**U**
	B. Concerns regarding applicability																	
Patient selection	**Is there concern that the included patients do not match the review question?**	**L**	**L**	**L**	**L**	**L**	**L**	**L**	**L**	**L**	**L**	**L**	**L**	**L**	**L**	**L**	**L**	**L**
Index test	• If using predictive equations, were they developed and validated in a population similar to the one under study?	N	N	Y	U	N	U	N	U	N	U	N	Y	Y	N	N	Y	U
	Is there concern that the index test, its conduct, or interpretation differ from the review question?	**H**	**H**	**H**	**U**	**H**	**U**	**H**	**U**	**H**	**U**	**H**	**L**	**L**	**H**	**H**	**L**	**U**
Reference standard	• If using predictive equations, were they developed and validated in a population similar to the one under study?	N	U	N	N	U	N	N/a	N/a	N/a	N/a	Y	N/a	N/a	N/a	N/a	N	N/a
	Is there concern that the target condition as defined by the reference standard does not match the review question?	**H**	**U**	**H**	**H**	**U**	**H**	**N/a**	**N/a**	**N/a**	**N/a**	**L**	**N/a**	**N/a**	**N/a**	**N/a**	**H**	**N/a**

	Index Test	BIA															
	Study reference	[21]	[22]	[23]	[24]	[11]	[16]	[17]	[25]	[26]	[27]	[28]	[29]	[30]	[31]	[32]	[33]
Domains	*A. Risk of Bias*																
Patient selection	• Was an adequate description of patient characteristics provided? (e.g. missing information on ethnicity, puberty status, recruitment)	Y	Y	Y	Y	Y	Y	Y	N	Y	N	Y	Y	Y	N	Y	N
	• Was a consecutive or random sample of patients enrolled?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	• Did the study avoid inappropriate exclusions?	Y	N	Y	Y	Y	Y	Y	U	Y	U	Y	Y	Y	U	Y	Y
	Could the selection of patients have introduced bias?	**L**	**L**	**L**	**L**	**L**	**L**	**L**	**U**	**L**	**U**	**L**	**L**	**L**	**U**	**L**	**U**
Index test	• Were the index test results interpreted without knowledge of the results of the reference standard?	Y	Y	N/a	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	• Was an adequate description of the index test and protocol provided?	Y	Y	N/a	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	N
	• Were there important flaws in the pre-test procedures or in the conduction of the test?	Y	U	N/a	U	N	U	Y	N	U	Y	Y	N	N	U	U	U
	• Was an appropriate approach used to analyse and report the data?	Y	Y	N/a	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y
	• Was the index test performed by trained personnel?	Y	U	N/a	U	U	U	U	U	Y	U	Y	U	U	U	U	U
	Could the conduct or interpretation of the index test have introduced bias?	**H**	**U**	**L**	**U**	**L**	**U**	**H**	**L**	**U**	**H**	**H**	**L**	**L**	**U**	**U**	**U**
Reference standard	• Is the reference standard likely to correctly classify the target condition?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	• Were the reference standard results interpreted without knowledge of the results of the index test?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	• Was an adequate description of the reference standard and protocol provided?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
	• Were there important flaws in the pre-test procedures or conduction of the test?	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	• Was an appropriate approach used to analyse and report the data?	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y
	• Was the reference standard performed by trained personnel?	U	U	Y	U	U	Y	Y	U	U	y	Y	U	Y	U	U	U
	Could the reference standard, its conduct or its interpretation have introduced bias?	**L**	**L**	**L**	**L**	**L**	**L**	**L**	**L**	**H**	**L**	**L**	**L**	**L**	**L**	**L**	**U**
Flow and timing	• Was there an appropriate interval between index test(s) and reference standard?	Y	U	Y	Y	U	U	Y	Y	Y	Y	Y	U	Y	U	Y	U
	• Did all patients receive a reference standard?	Y	Y	Y	N	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	U	Y
	• Did patients receive the same reference standard?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	• Were the test conditions similar for the measurements?	Y	U	Y	Y	U	U	Y	Y	Y	U	Y	U	Y	U	Y	U
	• Were all patients included in the analysis?	N	Y	Y	N	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y
	Could the patient flow have introduced bias?	**L**	**U**	**L**	**L**	**U**	**U**	**L**	**L**	**L**	**H**	**L**	**U**	**L**	**U**	**U**	**U**
	B. Concerns regarding applicability																
Patient selection	**Is there concern that the included patients do not match the review question?**	**L**	**L**	**L**	**L**	**L**	**L**	**L**	**L**	**L**	**L**	**L**	**L**	**L**	**L**	**L**	**L**
Index test	• If using predictive equations, were they developed and validated in a population similar to the one under study?	U	Y	N/a	U	N	U	U	U	U	U	Y	N	Y	U	U	N
	Is there concern that the index test, its conduct, or interpretation differ from the review question?	**U**	**L**	**N/a**	**U**	**H**	**U**	**U**	**U**	**U**	**U**	**L**	**H**	**L**	**U**	**U**	**H**
Reference standard	• If using predictive equations, were they developed and validated in a population similar to the one under study?	N/a	N/a	N/a	N/a	N	N/a	N/a	N/a	N/a	N/a	N/a	N/a	N/a	N/a	N/a	N/a
	Is there concern that the target condition as defined by the reference standard does not match the review question?	N/a	N/a	N/a	N/a	H	N/a	N/a	N/a	N/a	N/a	N/a	N/a	N/a	N/a	N/a	N/a

	Index Test	ADP							DXA										
	Study reference	(62)	(20)	(32)	(57)	(12)	(42)	(14)	(29)	(56)	(66)	(63)	(20)	(57)	(3)	(61)	(8)	(50)	(15)
Domains	*A. Risk of Bias*																		
Patient selection	• Was an adequate description of patient characteristics provided? (e.g. missing information on ethnicity, puberty status, recruitment)	N	Y	Y	Y	Y	Y	N	Y	Y	Y	N	Y	Y	N	Y	Y	Y	Y
	• Was a consecutive or random sample of patients enrolled?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	• Did the study avoid inappropriate exclusions?	U	Y	N	Y	Y	N	U	Y	Y	Y	U	Y	Y	Y	U	U	U	U
	Could the selection of patients have introduced bias?	**U**	**L**	**L**	**L**	**L**	**L**	**U**	**L**	**L**	**L**	**U**	**L**	**L**	**U**	**L**	**L**	**L**	**L**
Index test	• Were the index test results interpreted without knowledge of the results of the reference standard?	Y	Y	Y	Y	Y	Y	Y	N/a	N/a	N/a	Y	Y	Y	Y	Y	Y	Y	Y
	• Was an adequate description of the index test and protocol provided?	N	Y	Y	N	Y	Y	Y	N/a	N/a	N/a	Y	Y	Y	Y	Y	Y	Y	Y
	• Were there important flaws in the pre-test procedures or in the conduction of the test?	U	N	N	Y	N	N	N	N/a	N/a	N/a	N	N	N	N	N	N	Y	N
	• Was an appropriate approach used to analyse and reportdata?	Y	U	Y	Y	Y	Y	N	N/a	N/a	N/a	Y	Y	Y	Y	Y	Y	Y	Y
	• Was the index test performed by trained personnel?	U	U	U	U	U	U	U	N/a	N/a	N/a	U	U	U	U	U	U	U	Y
	Could the conduct or interpretation of the index test have introduced bias?	**H**	**L**	**L**	**H**	**L**	**L**	**H**	**N/a**	**N/a**	**N/a**	**L**	**L**	**L**	**L**	**L**	**L**	**H**	**L**
Reference standard	• Is the reference standard likely to correctly classify the target condition?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	• Were the reference standard results interpreted without knowledge of the results of the index test?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	• Was an adequate description of the reference standard and protocol provided?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	• Were there important flaws in the pre-test procedures or conduction of the test?	N	N	N	N	Y	N	N	N	N	N	N	N	N	N	N	N	N	N
	• Was an appropriate approach used to analyse and reportthe data?	Y	U	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	• Was the reference standard performed by trained personnel?	U	U	U	U	Y	U	U	Y	U	Y	U	U	U	U	U	U	U	U
	Could the reference standard, its conduct or its interpretation have introduced bias?	**L**	**L**	**L**	**L**	**L**	**L**	**H**	**L**	**L**	**L**	**L**	**L**	**L**	**L**	**L**	**L**	**L**	**L**
Flow and timing	• Was there an appropriate interval between index test(s) and reference standard?	U	Y	U	U	Y	U	Y	Y	Y	Y	Y	Y	U	U	Y	U	Y	Y
	• Did all patients receive a reference standard?	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	N	Y	Y	Y

	Index Test	ADP							DXA										
	Study reference	(62)	(20)	(32)	(57)	(12)	(42)	(14)	(29)	(56)	(66)	(63)	(20)	(57)	(3)	(61)	(8)	(50)	(15)
	• Did patients receive the same reference standard?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	• Were the test conditions similar for the measurements?	U	Y	U	U	Y	U	U	Y	Y	Y	Y	Y	U	U	Y	U	Y	Y
	• Were all patients included in the analysis?	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	Y	N	Y	Y	N
	Could the patient flow have introduced bias?	**U**	**L**	**U**	**U**	**L**	**U**	**L**	**L**	**L**	**L**	**L**	**L**	**U**	**U**	**H**	**U**	**L**	**L**
Patient selection	**Is there concern that the included patients do not match the review question?**	**L**	**L**	**L**	**L**	**L**	**L**	**L**	**L**	**L**	**L**	**L**	**L**	**L**	**L**	**L**	**L**	**L**	**L**
Index test	• If using predictive equations, were they developed and validated in a population similar to the one under study?	N	N	N	U	N	N	N	N/a	N/a	N/a	N/a	N/a	N/a	N/a	N/a	N/a	N/a	N/a
	Is there concern that the index test, its conduct, or interpretation differ from the review question?	**H**	**H**	**H**	**U**	**H**	**H**	**H**	**N/a**	**N/a**	**N/a**	**N/a**	**N/a**	**N/a**	**N/a**	**N/a**	**N/a**	**N/a**	**N/a**
Reference standard	• If using predictive equations, were they developed and validated in a population similar to the one under study?	N	N	N/a	N	N/a	N	N/a	N/a	N/a	N/a	N	N	N	N	N	Y	N/a	N/a
	Is there concern that the target condition as defined by the reference standard does not match the review question?	**H**	**H**	**N/a**	**H**	**N/a**	**H**	**N/a**	**N/a**	**N/a**	**N/a**	**H**	**H**	**H**	**H**	**H**	**L**	**N/a**	**L**

	Index Test	Isotope dilution			Ultrasound			MRI					3-C model
	Study reference	(20)	(57)	(8)	(41)	(30)	(19)	(30)	(4)	(27)	(44)	(51)	(24)
Domains	*A. Risk of Bias*												
Patient selection	• Was an adequate description of patient characteristics provided? (e.g. missing information on ethnicity, puberty status, recruitment)	Y	Y	Y	Y	N	Y	N	Y	Y	N	Y	Y
	• Was a consecutive or random sample of patients enrolled?	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y
	• Did the study avoid inappropriate exclusions?	Y	Y	U	Y	U	U	U	Y	Y	Y	U	Y
	Could the selection of patients have introduced bias?	**L**	**L**	**L**	**L**	**U**	**H**	**U**	**L**	**L**	**U**	**L**	**L**
Index test	• Were the index test results interpreted without knowledge of the results of the reference standard?	Y	Y	Y	Y	Y	N/a	N/a	N/a	Y	Y	Y	Y
	• Was an adequate description of the index test and protocol provided?	Y	N	Y	Y	Y	N/a	N/a	N/a	Y	Y	Y	Y
	• Were there important flaws in the pre-test procedures or in the conduction of the test?	N	N	N	N	N	N/a	N/a	N/a	N	N	N	N
	• Was an appropriate approach used to analyse and report the data?	Y	Y	Y	Y	Y	N/a	N/a	N/a	Y	Y	Y	Y
	• Was the index test performed by trained personnel?	U	U	U	U	Y	N/a	N/a	N/a	U	Y	U	U

	Index Test	Isotope dilution			Ultrasound			MRI					3-C model
	Study reference	(20)	(57)	(8)	(41)	(30)	(19)	(30)	(4)	(27)	(44)	(51)	(24)
Reference standard	**Could the conduct or interpretation of the index test have introduced bias?**	**L**	**H**	**L**	**L**	**L**	**N/a**	**N/a**	**N/a**	**L**	**L**	**L**	**L**
	• Is the reference standard likely to correctly classify the target condition?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	• Were the reference standard results interpreted without knowledge of the results of the index test?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	• Was an adequate description of the reference standard and protocol provided?	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y
	• Were there important flaws in the pre-test procedures or conduction of the test?	N	N	N	N	N	N	N	N	N	N	N	N
	• Was an appropriate approach used to analyse and report the data?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	• Was the reference standard performed by trained personnel?	U	U	U	U	Y	U	Y	Y	U	Y	U	U
Flow and timing	**Could the reference standard, its conduct or its interpretation have introduced bias?**	**L**	**H**	**L**	**L**	**L**	**L**	**L**	**L**	**L**	**H**	**L**	**L**
	• Was there an appropriate interval between index test(s) and reference standard?	Y	U	U	U	Y	Y	Y	Y	Y	Y	Y	Y
	• Did all patients receive a reference standard?	Y	Y	Y	Y	Y	Y	N	N	Y	Y	Y	N
	• Did patients receive the same reference standard?	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y
	• Were the test conditions similar for the measurements?	Y	U	U	U	U	Y	Y	Y	Y	Y	Y	Y
	• Were all patients included in the analysis?	Y	Y	Y	N	Y	Y	N	N	Y	Y	Y	N
	Could the patient flow have introduced bias?	**L**	**U**	**U**	**H**	**H**	**L**	**L**	**L**	**L**	**L**	**L**	**H**
	B. Concerns regarding applicability												
Patient selection	**Is there concern that the included patients do not match the review question?**	**L**	**L**	**L**	**L**	**L**	**L**	**L**	**L**	**L**	**L**	**L**	**L**
Index test	• If using predictive equations, were they developed and validated in a population similar to the one under study?	N	U	Y	N/a	N/a	N/a	N/a	N/a	N/a	N/a	Y	N
	Is there concern that the index test, its conduct, or interpretation differ from the review question?	**H**	**U**	**L**	**N/a**	**N/a**	**N/a**	**N/a**	**N/a**	**N/a**	**N/a**	**L**	**H**
Reference standard	• If using predictive equations, were they developed and validated in a population similar to the one under study?	N	N	Y	N/a	N/a	N/a	N/a	N/a	N/a	N/a	Y	N
	Is there concern that the target condition as defined by the reference standard does not match the review question?	**H**	**H**	**L**	**N/a**	**N/a**	**N/a**	**N/a**	**N/a**	**N/a**	**N/a**	**L**	**H**

Abbreviations: 3-C, three-compartment model; ADP, air-displacement plethysmography; BIA, bioelectrical impedance analysis; DXA, dual-energy X-ray absorptiometry; H, high risk; L, low risk; MRI, magnetic resonance imaging; N, no; N/a, not applicable; U, unclear; Y, yes

Table A4 Findings for agreement between predictive equations using anthropometric measures and reference standard.

Reference (1st author, year [ref.])	**Anthropometric measures and equation**	**Reference standard**	**Bland-Altman Analysis**	**Systematic effect**	**Associations**
Bedogni, 1997 (7)	Proposed prediction equation to estimate TBW using body weight TBW, ECW	Deuterium oxide for TBW measures; spectrophotometry Bromide dilution for ECW measures; high-performance liquid chromatography	TBW (L): All bias = 3.1; LoA = -1.0 to 7.2 ECW (L): All bias = 0.9; LoA = -1.6 to 3.4	*Mean difference ± SD; ANOVA test* TBW (L): n.s. p-value; ECW (L): n.s. p-value	NR
Cortes-Castell, 2017 (13)	Proposed prediction equation %BF: Males: %BF = 62.627 – 11245.580 x BMI^{-2} – 259.114 x BMI^{-1} + 2.310 x Age – 0/151 x Age^2 Females: %BF = 62.627 – 11245.580 x BMI^{-2} FMI: Males: FMI = 18.655 + 0.007 x BMI^2- 293.601 x BMI^{-1} + 0.112 x Age - 0.018 x Age^2 Females: FMI = 18.655 + 0.007 x BMI^2- 293.601 x BMI^{-1} %BF, FMI	DXA; GE Lunar/DPX-N (GE Healthcare, Little Chalfont, UK)	%BF: All bias = 0.06; LoA = -9.8 to 9.9 FMI (kg/m^2): All bias = -0.04; LoA = -2.7 to 2.6	Bias ± SD %BF: p = 0.857 FMI: p = 0.670	NR
Rolland-Cachera, 1997 (46)	**UFA (cm^2):** UFA = UMA – TUA UMA = (mid-upper arm circumference – (triceps skinfolds x π))^2/(4π) TUA = mid-upper arm $circumference^2$/(4π) **UFE (cm^2):** UFE = mid-upper arm circumference x (triceps skinfolds/2)	MRI; 0.5 T (MRT-50 A, Toshiba, Tokyo, Japan); T1-weighted scans were taken at midhumerus (right side) AT segmentation: manual trackball technique	UFA (cm^2): All bias = -10.3; LoA = -23.4 to 2.8 UFE (cm^2): All bias = -2.1; LoA = -16.0 to 11.8	NR	FM area (cm^2): UFA: r = 0.84; p <0.001 UFE: r = 0.82; p <0.001
Samouda, 2017 (47)	Developmental group; Proposed prediction equation; Males: VAT = 0.747 × WC − 72.53 (r = 0.747; R^2 = 0.558) Females: VAT = 1.11 × WC– (−0.675 × Proximal thigh circumference) + 0.26 × Age– (−46.761) (r = 0.746; R^2 = 0.557) VAT	MRI; 1.5T GE Signa HDXT System (General Electric Medical Systems, Milwaukee, Wisconsin); T1-weighted images acquired at L4-L5 level AT segmentation: semiquantitative method using ImageJ, and visual inspection	VAT (cm^2) ♂: Bias = -50.7; LoA = -80.07 to -20.59 ♀: Bias = 4.8; LoA = -24.44 to 34.43	NR	VAT (cm^2) ♂: r = -0.827; p <0.0001 ♀: r = -0.799; p <0.0001

Reference (1st author, year [ref.])	**Anthropometric measures and equation**	**Reference standard**	**Bland-Altman Analysis**	**Systematic effect**	**Associations**
Thivel, 2015 (54)	Body adiposity index (BAI) BAI = [(HC)/((height)$^{1.5}$) - 18)] BAI-Waist circumference (BAIw) BAIw = [(WC)/((height)$^{1.5}$) - 18)] BAI-Pediatric (BAIp) BAIp = [(HC)/((height)$^{0.8}$) - 38)] Visceral adiposity index (VAI) Boys: VAI = {WC/[39.68 (1.88 x BMI)]} x (TG/1.03) x (1.31/HDL-C) Girls: VAI = {WC/[36.58 + (1.89 x BMI)]} x (TG/0.81) x (1.52/HDL-C)	DXA; QDR-4500 A (Hologic, Waltham, USA)	%BF BAI: Bias = -3.48; LoA = -12.67 to 5.66[a] BAIw: Bias = -7.17; LoA = -17.29 to 2.97a BAIp: Bias = -4.62; LoA = -19.02 to 9.71a	%BF BAI: p <0.001 BAIw: p <0.001 BAIp: p <0.001	*Pearson or Spearman correlation; Lin's CCC; ICC* BAI %BF All: r = 0.67; p <0.001; Lin's CCC = 0.56; ICC = 0.16 ♂: r = 0.66; p <0.001; Lin's CCC = 0.50; ICC = 0.24 ♀: r = 0.65; p <0.001; Lin's CCC = 0.57; ICC = 0.07 BAIw%BF All: r = 0.57; p <0.001; Lin's CCC = 0.31; ICC = 0.45 ♂: r = 0.61; p <0.001; Lin's CCC = 0.38; ICC = 0.37 ♀: r = 0.54; p <0.001; Lin's CCC = 0.25; ICC = 0.52 BAIp%BF All: r = 0.64; p <0.001; Lin's CCC = 0.46; ICC = 0.15 ♂: r = 0.63; p <0.001; Lin's CCC = 0.47; ICC = 0.20 ♀: r = 0.65; p <0.001; Lin's CCC = 0.45; ICC = 0.10 Abdominal %BF All: r = 0.27; p <0.01; Lin's CCC = 0.002; ICC = 0.96 ♂: r = 0.17; p =0.0022; Lin's CCC = 0.002; ICC = 0.97 ♀: r = 0.41; p =0.2388; Lin's CCC = 0.001; ICC = 0.96

[a]Bias, and lower and upper limits of agreement were extracted from Bland-Altman plots using Plot Digitizer, an open source software (v.2.6.8; http://plotdigitizer.sourceforge.net).

Abbreviations:%BF, percent body fat; BMI, body mass index; BAI, body adiposity index; BAIw, body adiposity index – waist circumference; BAIp, body adiposity index – pediatric; CCC, concordance correlation coefficient; DXA, dual-energy X-ray absorptiometry; ECW; extracellular water;FM, fat mass; FMI, fat mass index; HC, hip circumference; HDL, high-density lipoprotein; ICC, intraclass correlation coefficient; LoA, limits of agreement (lower to upper); L4, fourth lumbar vertebrae; L5, fifth lumbar vertebrae; MRI, magnetic resonance imaging; ns., not significant; NR, not reported; r = correlation coefficient; SD, standard deviations; TBW, total body water; TG, triglycerides; TUA, total upper arm area; UMA, upper arm muscle area; UFA, upper arm fat area; UFE, upper arm fat area estimate; VAI, visceral adiposity index; VAT, visceral adipose tissue; WC, waist circumference. *Symbols:* ♂, males; ♀, females.

Table A5 Description of skinfold equations used by the included articles.

Equation	Predictive equation	Reference of included studies
Slaughter 1 (67)	♂: %BF= (0.735 ×sum of the triceps and calf skinfold) + 1.0 ♀:%BF= (0.610 × sum of the triceps and calf skinfold) + 5.1	(1, 18, 23, 38, 41, 60)
Slaughter 2 (67)	♂: %BF= 0.783× (sum of triceps and subscapular skinfold) + 1.6[a] ♀:%BF= 0.546 × (sum of triceps and subscapular skinfold) + 9.7	(10)
Huang (68)	FM (kg) = 0.649 × weight -0.311 × height + 0.132 × abdominal skinfold - 1.837 × gender - 0.962 × Tanner stage + 27.754	(1)
Ramirez (69)	FM (kg) = -1.067 × sex+0.458 × triceps skinfold +0.263 ×weight -5.407	(1)
Durnin&Rahaman (70)	%BF = [4.95/(1.1369-0.0598 × log(sum of biceps and subscapular skinfold-thickness (mm))) - 4.5] × 100	(10)
Lohman (71)	%BF = [5.28/body density - 4.86] × 100, where body density is: ♂: [g/ml] = 1.1690-0.0788 × (log(sum of four skinfolds: biceps, triceps, subscapular and suprailiac)) ♀:[g/ml] = 1.2063-0.0999 × (log(sum of four skinfolds: biceps, triceps, subscapular and suprailiac))	(10)
Dezenberg (72)	%BF = [(0.332 × weight) + (0.230 × triceps) + (0.641 × sex) + (0.857 × ethnicity) - 8.004], where sex is: 1 for male and 2 for female; and ethnicity is: 1 for white and 2 for African American.	(17)
ACSM 3-sites (73)	*Three-Site Formula (abdomen, iliac crest, triceps)* ♂:%BF = 0.39287 ×(sum3 skinfolds) - 0.00105 ×(sum3 skinfolds)^2 + 0.15772 ×(age) - 5.18845 ♀:%BF = 0.41563 ×(sum3 skinfolds) - 0.00112× (sum3 skinfolds)^2 + 0.03661 ×(age) + 4.03653	(60)
ACSM 4-sites (73)	*Four-Site Formula (abdomen, iliac crest, triceps, thigh)* ♂:%BF = 0.29288 ×(sum4 skinfolds) - 0.0005 ×(sum4 skinfolds)^2 + 0.15845 ×(age) -5.76377 ♀:%BF = 0.29669×(sum4 skinfolds) - 0.00043× (sum4 skinfolds)^2 + 0.02963 ×(age) +1.4072	(60)
Brozek (74)	%BF =4.570/Body Density – 4.142 where density was calculated according to the formula (Nogamine's equation for Japanese children) ♂:Body density= 1.0879 - 0.00154 × sum of triceps and subscapular skinfold thickness ♀:Body density= 1.0794- 0.00142 ×sum of triceps and subscapular skinfold thickness.	(60)

Equation	Predictive equation	Reference of included studies
Ball (4)	*Proposed prediction equation* VAT = (1.27 × waist circumference) -(3.47 × Tanner stage) - (0.36 × calf skinfolds) -52.37 SAT = (8.48 × waist circumference) + (3.73 × triceps skinfolds) + (43.23 × Gender) - 501.93	(4)
Bamman (5)	*Proposed prediction equation* FM (kg)= (0.26912 ×hip circumference (cm)) + (0.16961× triceps skinfolds (mm))+0.34585 FMres - 15.226. Where: FMres is fat mass resistance, was calculated as total body mass (kg) minus resistance index (cm^2Ohm), and resistance index was calculated as squared height (cm^2) divided by resistance (Ohm). Note: resistance index was obtained by foot-to-foot bioelectrical resistance, using TANITA BC 420 SMA digital scale (TANITA Corp.)	(5)
Stevens (53)	*Proposed prediction equation* ♂: %BF = 28.009373 - 0.038460 × (age - 161) - 0.425327 × (Race1) + 0.350376 × (Race2) - 0.238080 × (Race3) - 0.106154 × (Race4) - 0.113560 × (weight - 56) - 10.010607 × (height – 1.58) + 0.353623 × (waist - 76) + 0.690984 × (triceps - 15) - 0.016657 × (triceps - 15)2 - 0.000852 ×(age - 161) × (weight - 56) ♀: %BF = 31.836841 - 0.609018 × (menses) + 0.003317 × (age - 161) - 0.975391 × (Race1) + 0.499227 × (Race2) + 0.602171 × (Race3) + 0.173877 × (Race4) + 0.053756 ×(weight - 56) - 18.641446 × (height – 1.58) + 0.218830 × (waist - 76) + 0.744310 × (triceps - 15) - 0.018648 × (triceps -15)2 – 0.194114 × (menses) × (triceps-15) + 0.005748 × (menses) ×$(triceps)^2$ where, Menses = menarche status (girls) is 0 if have not started period and 1 if started periods; Race1 = 1 if non-Hispanic Black and 0 if not non-Hispanic Black; Race2 = 1 if Mexican American and 0 if not Mexican American; Race3 = 1 if Other Hispanic and 0 if not Other Hispanic; Race4 =1 if Other non-Hispanic race group including non-Hispanic multiracial and 0 if not other non-Hispanic race group; weight = weight in kilograms; height = height in meters; waist = waist circumference in centimeters; triceps = triceps skinfolds in millimeters.	(53)

[a]Chan et al., 2009 used the following equation instead BF (%)= 0.783 (triceps + subscapular skinfolds) - 1.7

Abbreviations: %BF, percent body fat; FM, fat mass expressed in kg; FMres, fat mass resistance; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue.

Symbols: ♂, males; ♀, females.

Table A6 Findings for agreement between predictive equations using skinfold measures and reference standard.

Reference (1st author, year [ref.])	**Skinfold technique; compartment of interest**	**Reference standard**	**Bland-Altman Analysis**	**Systematic effect**	**Associations**
Aguirre, 2015 (1)	Slaughter, Huang, and Ramirez %BF	3-C model	Slaughter %BF ♂: Bias = -8.97; LoA = -15.72 to -2.21 ♀: Bias = -12.69; LoA = -18.95 to -6.42 Huang %BF ♂: Bias = -2.89; LoA = -10.58 to 4.78 ♀: Bias = -0.04; LoA = -9.48 to 9.39 Ramirez %BF ♂: Bias = -2.51; LoA = -9.70 to 4.64 ♀: Bias = -4.67; LoA = -14.34 to 5.02	Slaughter %BF ♂: p <0.001 ♀: p <0.001 Huang %BF ♂: p <0.001 ♀: n.s. p-value Ramirez %BF ♂: n.s. p-value ♀: p <0.001	Slaughter %BF ♂: R^2 = 0.70; SEE = 0.06 ♀: R^2 = 0.68; SEE = 0.06 Huang %BF ♂: R^2 = 0.65; SEE = 0.05 ♀: R^2 = 0.34; SEE = 0.09 Ramirez %BF ♂: R^2 = 0.66; SEE = 0.07 ♀: R^2 = 0.54; SEE = 0.08
Bamman, 2013 (5)	Proposed prediction equation	3-C model	FM (kg): Bias = -0.10 LoA = -3.04 to 2.84	NR	NR
Asayama, 2002 (2)	Brozek (body density was calculated using the Nogamine's equation for Japanese children)	CT scan; GE-9800 scanner (General Electric Medical Systems, Waukesha, USA); single CT scan at the umbilicus level AT segmentation: Density Mask software; -40 to -140 HU	NR	NR	*Pearson correlation %BF vs:* TAT (cm^2): r = 0.708; p <0.001 VAT (cm^2): r = 0.524; p <0.001 SAT (cm^2): r = 0.710; p <0.001 VAT/SAT (cm^2): r = 0.088; n.s. p-value
Ball, 2006 (4)	Proposed prediction equation	MRI; GE 1.5T (Signa LX Echospeed, Waukesha, USA); T1-weighted images; single slice at the umbilicus level AT segmentation: manual delineation of areas for VAT and SAT	NR	VAT: Mean difference ± SD = -3.0 ± 16.5; p = 0.2 SAT: Mean difference ± SD = -1.0 ± 48.4; p = 0.8	*Regression of residual on predicted* VAT: Beta = -0.14; SE = 0.12; p = 0.3 SAT: Beta = 0.006; SE = 0.05; p = 0.9
Elberg, 2004 (17)	Dezenberg	DXA; Hologic QDR-2000 (software v.5.64);	African American Δ %BF ♂ bias = -1.1; LoA = -6.4 to 4.2	African American Δ %BF ♂: n.s. p-value	NR

Reference (1st author, year [ref.])	**Skinfold technique; compartment of interest**	**Reference standard**	**Bland-Altman Analysis**	**Systematic effect**	**Associations**
		Hologic 4500 A (software v.11.2).	♀ bias = -0.3; LoA = -7.9 to 7.3 White Δ %BF ♂ bias = 1.4; LoA = -5.3 to 8.1 ♀ bias = 0.1; LoA = -11.5 to 11.7	♀: n.s. p-value White Δ %BF ♂: n.s. p-value ♀: n.s. p-value	
Chan, 2009 (10)	Durin&Rahaman, Slaughter, Lohmann, and proposed prediction equation Holtain caliper; single trained observer; measurements in triplicate	DXA; Hologic QDR-4500A (Hologic, Waltham, USA)	Durin&Rahaman%BF All bias: 0.54; LoA = -9.8 to 10.9 ♂ bias: 1.01; LoA = -10.1 to 12.1 ♀ bias: -0.76; LoA = -8.5 to 6.9 Slaughter %BF All bias = 7.35; LoA = -8.1 to 22.8 ♂ bias = 8.09; LoA = -8.7 to 24.8 ♀ bias = 5.23; LoA = -5.1 to 15.6 Lohmann %BF All bias = 1.38; LoA = -9.1 to 11.9 ♂ bias = 0.94; LoA = -10.1 to 12.0 ♀ bias = 2.58; LoA = -6.2 to 11.4 Proposed equation %BF All bias = 0.001; LoA = -10.2 to 10.3 ♂ bias = -0.007; LoA = -11.1 to 11.1 ♀ bias = 0.023; LoA = -7.5 to 7.6	*Paired t-test* Durin&Rahaman%BF All: n.s. p-value ♂: n.s. p-value ♀: n.s. p-value Slaughter %BF All: p<0.0001 ♂: p<0.0001 ♀: p<0.0001 Lohmann %BF All: p<0.005 ♂: n.s. p-value ♀: p<0.005 Proposed equation %BF All: n.s. p-value ♂: n.s. p-value ♀: n.s. p-value	NR
Freedman, 2013 (18)	Slaughter equation Lange caliper; right side %BF	DXA; GE Lunar DPX (Pediatric software v.3.8G); GE Lunar DPX-L (Pediatric software 1.5G)	NR	%BF ♂ SF ≥50 mm: Mean difference ± IQR = 12.0 ± 10.0 ♂ SF >80 mm (n = 12): n = 9 overestimated 20-40% points n = 3 overestimated >40% points ♀ SF ≥60 mm: Mean difference ± IQR = 5.8 ± 9.0	NR
Gonzalez-Ruiz, 2018 (23)	Slaughter equation Holtain caliper; level 2 expert	DXA; Hologic Horizon (Hologic Horizon DXA System®, Quirugil,	%BF ♂: Bias = -9.0; LoA = -21.3 to 3.2 ♀: Bias = -11.1; LoA = -18.3 to 3.9	*Paired t-test* %BF ♂: p <0.0001	%BF

Reference (1st author, year [ref.])	**Skinfold technique; compartment of interest**	**Reference standard**	**Bland-Altman Analysis**	**Systematic effect**	**Associations**
	certified by the ISAK %BF	Columbia); Discovery software (v.12.3)		♀: p <0.0001	♂: r = 0.532; p <0.0001; Lin's CCC = 0.227 (95% CI 0.092 to 0.353) ♀: r = 0.711; p <0.0001; Lin's CCC = 0.179 (95% CI 0.119 to 0.238)
Mooney, 2011 (38)	Slaughter equation Harpenden caliper; trained investigator (120h experience); right side; average of three measurements %BF	DXA; Hologic QDR-4500 (Hologic Inc., Bedford, Massachusetts, USA); software v.11.2; pediatric software	BF 30% ♂: Bias = 3.32; 95% CI = 2.26-4.38 ♀: Bias = 0.49; 95% CI = -0.18-1.17 BF 40% ♂: Bias = 4.53; 95% CI = 2.81-6.25 ♀: Bias = 1.30; 95% CI = 0.15-2.75	BF 30% ♂: p <0.05 ♀: n.s. p-value BF 40% ♂: p <0.05 ♀: p <0.05	NR
Pineau, 2010 (41)	Slaughter equation Harpenden caliper; single trained investigator %BF	DXA; Hologic QDR-4500 (Hologic, Bedford, USA); software v.11.2.5	%BF All: Bias = -4.1; LoA = -25.1 to 18.0	%BF All: p<0.001	FM (kg) All: R^2 = 0.47; n.s. p-value
Stevens, 2014 (53)	Proposed prediction equation Holtain caliper; two trained investigators %BF	DXA; Hologic QDR-4500 A (Hologic,Bedford, USA)	NR	*Mean difference (95%CI)* Base model %BF ♂ OW: -1.025 (-1.676 to -0.378); p = 0.003[a] ♀ OW: -0.567 (-1.159 to 0.032); p = 0.061[a] ♂ OB: -0.020 (-0.715 to 0.675) a♀ OB: -0.211 (-1.099 to 0.683)[a] Base model + selected terms: ♂ OW: -0.352 (-0.960 to 0.257)[a] ♀ OW: -0.339 (-0.815 to 0.533)[a]	NR

Reference (1st author, year [ref.])	**Skinfold technique; compartment of interest**	**Reference standard**	**Bland-Altman Analysis**	**Systematic effect**	**Associations**
				♂ OB: -0.204 (-0.752 to 0.280)[a] ♀ OB:-0.154 (-0.696 to 0.384)a	
Watts, 2006 (60)	Slaughter, ACSM 3-sites equation, and 4-sites equation Harpenden caliper; right side; measurements in triplicate; single trained investigator. %BF	DXA; Norland XR36 pencil-beam	NR	NR	%BF – Baseline *DXA vs:* Slaughter: r = 0.51; p <0.01 3-sites: r = 0.53; p <0.01 4-sites: r = 0.61; p <0.01 Δ %BF – Changes from baseline to post-exercise training (8 wks) *DXA vs:* Slaughter: r = 0.21; n.s. p-value 3-sites: r = -0.05; n.s. p-value 4-sites: r = -0.02; n.s. p-value Δ Abdominal %BF – Changes from baseline to post-exercise training (8 wks) r = 0.37; p <0.05 3-sites: r = 0.36; p <0.05

[a]Bias, and lower and upper limits of agreement were extracted from Bland-Altman plots using Plot Digitizer, an open source software (v.2.6.8; http://plotdigitizer.sourceforge.net).

Abbreviations: ACSM, American College of Sports Medicine; AT, adipose tissue; %BF, percent body fat; 3-C, three-compartment; CI, confidence interval; CCC, concordance correlation coefficient; CT, computed tomography; DXA, dual-energy x-ray absorptiometry; FM, fat mass; ISAK, International Society for the Advancement of Kinanthropometry; IQR, interquartile range; LoA, limits of agreement; MRI, magnetic resonance imaging; OB, obese; OW, overweight; ns., not significant; NR, not reported; r = correlation coefficient; SAT, subcutaneous adipose tissue; SE, standard error; SEE, standard error of estimates; SF, skinfold thickness; TS, Tanner stage; VAT, visceral adipose tissue;

Symbols: ♂, males; ♀, females; Δ, difference.

Table A7 Findings for agreement between bioelectrical impedance analysis and reference standard.

Reference (1st author, year [ref.])	BIA device/equation; compartment of interest	Reference standard	Bland-Altman Analysis	Systematic effect	Associations
Kasvis, 2015 (29)	Foot-to-foot; single-frequency; Tanita TBF-310 (Tanita Corp., Tokyo, Japan) Manufacturer's software equation: %BF, FM, FFM	DXA; Hologic Discovery A (Hologic Inc, Bedford, USA); PEX software v.13.3:3	%BF: Bias = -0.398; LoA = -8.685 to 7.889 FM (kg): Bias = -0.070; LoA = -4.973 to 4.833 FFM (kg): Bias = -0.439; LoA = -5.327 to 4.448	NR	*Pearson correlation* %BF: r = 0.772; p <0.0001 FM (kg): r = 0.951; p <0.0001 FFM (kg): r = 0.909; p <0.0001
Radley, 2009 (43)	Foot-to-foot; single-frequency; Tanita TBF-310 (Tanita Corp., Tokyo, Japan) Manufacture's software equation %BF, FM, FFM	4-C model[a]	%BF[b] All: Bias = -1.3; LoA = -11.2 to 8.6 ♂: Bias = -1.6;LoA = -10.9 to 7.7 ♀: Bias = -0.4; LoA = -6.9 to 6.1 FM (kg) All: Bias = -0.7; LoA = -9.1 to 7.7 ♂: Bias = -0.8; LoA = -10.1 to 8.5 ♀: Bias = -0.5; LoA = -5.6 to 5.5 FFM (kg) All: Bias = 0.7; LoA = -7.7 to 9.1 ♂: Bias = 0.8; LoA = -8.5 to 10.1 ♀: Bias = 0.5; LoA = -5.0 to 6.0	NR	NR
Thivel, 2018 (55)	Hand-to-foot; multifrequency; Tanita MC-780 (Tanita Corp., Tokyo, Japan) Manufacturer's software equation %BF, FM, FFM	DXA; Hologic QDR-4500A (Hologic, Waltham, USA)	%BF: Bias = 0.98; LoA = -18.85 to 20.80[c] FM (kg): Bias = 0.98; LoA = -23.02 to 24.68[c] FMM (kg): Bias = 0.21; LoA = -19.43 to 18.91[c]	NR	*Spearman correlation* %BF: r = 0.82; p <0.001 FM (kg): r = 0.94; p <0.001 FFM (kg): r = 0.85; p <0.001
Verney, 2016 (58)	Hand-to-foot; multifrequency; Tanita MC-780 (Tanita Corp., Tokyo, Japan) Manufacturer's software equation %BF, FM, FFM	DXA; Hologic QDR-4500A (Hologic, Waltham, USA)	%BF: Bias = 1.90; LoA = -7.93 to 11.79[c] FFM (kg): Bias = -3.49; LoA = -12.32 to 5.41[c]	*Paired t-test* %BF: p <0.001 FM (kg): p <0.001 FFM (kg): p <0.001	*Pearson or Spearman correlation; Lin's CCC; ICC* %BF: r = 0.779; p <0.001; Lin's CCC = 0.67; ICC = 0.66

Reference (1st author, year [ref.])	BIA device/equation; compartment of interest	Reference standard	Bland-Altman Analysis	Systematic effect	Associations
					FM (kg): r = 0.933; p <0.001; Lin's CCC = 0.89; ICC = 0.88 FFM (kg): r = 0.847; Lin's CCC = 0.77; ICC = 0.76
Meredith-Jones, 2015 (37)	Hand-to-foot; multifrequency; Tanita BC-418 (Tanita Corp., Tokyo, Japan) Manufacturer's software equation %BF, FM, FFM (changes from baseline to follow-up)	DXA; GE Lunar Prodigy (GE Medical Systems, Madison, USA); software v.13.6; pediatric mode	NR	*Mean difference*[d] %BF ♂: 0.38 (-0.36 to 1.12) ♀: -0.18 (-0.82 to 0.46) FM (kg) ♂: 0.07 (-0.14 to 0.27) ♀: 0.04 (-0.19 to 0.28) FFM (kg) ♂: -0.08 (-0.35 to 0.20) ♀: 0.14 (-0.10 to 0.38)	NR
Shaikh, 2007 (49)	Hand-to-foot; multifrequency; Tanita BC-418 (Tanita Corp., Tokyo, Japan) Manufacturer's software equation %BF, FM	DXA; GE Lunar Prodigy (GE Medical Systems, Madison, USA); software v.8.1	%BF: Bias = -5.3; LoA = -15.4 to 3.8 FM (kg): Bias = -2.4; LoA = - 8.3 to 3.6	NR	*Pearson correlation* %BF: r = 0.832; p <0.001 FM (kg): r = 0.971; p <0.001
Aguirre, 2015 (1)	Hand-to-foot; multifrequency; Tanita BC-418 (Tanita Corp., Tokyo, Japan) Manufacturer's software equation; raw data were entered on the equation of Ramirez %BF	3-C model[e]	Tanita %BF ♂: Bias = -4.70; LoA = -10.35 to 0.95 ♀: Bias = -7.09; LoA = -12.30 to -1.88 Ramirez %BF ♂: Bias = 3.58; LoA = -3.08 to 10.24 ♀: Bias = 0.86; LoA = -4.83 to 6.54	*Kruskall-Wallis test with post hoc adjustments* Tanita %BF ♂: p <0.001 ♀: p <0.001 Ramirez %BF ♂: p <0.001 ♀: ns. p-value	*Regression analysis; SEE* Tanita %BF ♂: R^2=0.80; p < 0.05; SEE = 0.05 ♀: R^2=0.78; p < 0.05; SEE = 0.07 Ramirez %BF ♂: R^2=0.72;p < 0.05; SEE = 0.07 ♀: R^2=0.73; p < 0.05; SEE = 0.08
Haroun, 2009 (25)	Hand-to-foot; multifrequency; Tanita BC-418 (Tanita Corp., Tokyo, Japan)	3-C model[e]	FM (kg) All: Bias = -3.5; LoA = -7.7 to 0.7[c] FFM (kg)	*Paired t-test* FM (kg) ♂: p <0.001 ♀: p <0.001	*HT^2/Z (from BIA) & FFM (from 3C model)* *Linear regression analysis* r = 0.98; p <0.001

Reference (1st author, year [ref.])	BIA device/equation; compartment of interest	Reference standard	Bland-Altman Analysis	Systematic effect	Associations
	Manufacture's software equation FM, FFM		All: Bias = 2.3; LoA = -1.9 to 6.4[c]	FFM (kg) ♂: p <0.001 ♀: p <0.001	
Vasquez, 2016 (57)	Hand-to-foot; multifrequency; Tanita BC-418 (Tanita Corp., Tokyo, Japan) Manufacturer's software equation %BF	4-C model[a]	%BF ♂ TS 1-2: Bias = -6.449; LoA = -15.31 to 2.41 ♂ TS 3-5: Bias = -0.596; LoA = -9.75 to 8.56 ♀ TS 1-2: Bias = -2.059; LoA = -10.42 to 6.30 ♀ TS 3-5: Bias = 1.041; LoA = -6.270 to 8.351		*Lin's CCC; Regression analysis; SEE* %BF ♂ TS 1-2: *Lin's CCC* = 0.352; R^2 = 0.43; SEE = 0.12 ♂ TS 3-5: *Lin's CCC* = 0.721; R^2 = 0.78; SEE = 0.08 ♀ TS 1-2: *Lin's CCC* = 0.516; R^2 = 0.34; SEE = 0.34 ♀ TS 3-5: *Lin's CCC* = 0.754; R^2 = 0.63; SEE = 0.09
Atherton, 2013 (3)	Hand-to-foot; multifrequency; Tanita BC-418 (Tanita Corp., Tokyo, Japan) FFM was estimated as whole-body impedance index (height^2/Z) Standard deviation scores (SDS) were calculated using authors' dataset.	4-C model[a]	FFM SDS: Bias = -0.25; LoA = -1.4 to 0.9[f]	NR	*Bland-Altman correlation* FFM SDS Unadjusted correlation coefficient: r = -0.059; p = 0.14 Correlation coefficient adjusted for age: r = -0.036; p = 0.37
Goldfield, 2006 (22)	Foot-to-foot; single-frequency; Tanita TBF 300-A (Tanita Corp., Tokyo, Japan); standard mode Manufacturer's software %BF, FM, FFM	DXA; GE Lunar Prodigy (GE Medical Systems, Madison, USA)	%BF: Bias = -5.45; LoA = -12.8 to 2.0 FM (kg): Bias = -3.09; LoA = -8.7 to 2.5 FFM (kg): Bias = 3.43; LoA = -1.0 to 7.8	*Paired t-test* %BF: p <0.05 FM (kg): p <0.05 FMM (kg): p <0.05	*Pearson correlation* %BF: r = 0.85; p <0.001 FM (kg): r = 0.97; p <0.001 FMM (kg): r = 0.94; p <0.001
Mooney, 2011 (38)	Hand-to-hand; OMRON HBF-306 (Omron Healthcare, Kyoto, Japan); normal mode	DXA; Hologic QDR-4500 Elite "Acclaim Series" (Hologic Inc.,	%BF ♂ with %BF (by DXA) >30% OMRON: Bias = 0.85; LoA = -0.32 to 2.03	*Line-of-best-fit analysis* ♂ with %BF (by DXA) >30%: OMRON: ns. p-value	NR

Reference (1st author, year [ref.])	BIA device/equation; compartment of interest	Reference standard	Bland-Altman Analysis	Systematic effect	Associations
	Manufacturer's software equation Foot-to-foot; single-frequency; Tanita 300-A (Tanita Corp., Tokyo, Japan); standard mode Manufacturer's software equation Foot-to-foot; single-frequency; Tanita-521 (Tanita Corp., Tokyo, Japan); child mode Manufacturer's software equation %BF	Bedford, USA); software v.11.2; pediatric option was selected	Tanita 300A: Bias = -4.26; LoA = -5.86-2.67 Tanita 521: Bias = 0.22; LoA = -1.09-1.54 ♂ with %BF (by DXA) >40% OMRON: Bias = 0.99; LoA= -0.91-2.89 Tanita 300A: Bias = -4.42; LoA = -6.90-1.96 Tanita 521: Bias = 0.84; LoA = -1.27-2.94 ♀ with %BF (by DXA) >30% OMRON: Bias = -2.36; LoA= -3.12-1.59 Tanita 300A: Bias = -0.96; LoA = -1.83-0.09 Tanita 521: Bias = 2.41; LoA = 1.70-3.12 ♀ with %BF (by DXA) >40% OMRON: Bias = -3.80; LoA= -5.48-2.13 Tanita 300A: Bias = 1.42; LoA = -0.34-3.18 Tanita 521: Bias = 3.29; LoA = 1.77-4.81	Tanita 300A: p <0.05 Tanita 521: ns. p-value ♂ with %BF (by DXA) >40%: OMRON: ns. p-value Tanita 300A: p <0.05 Tanita 521: ns. p-value ♀ with %BF (by DXA) >30%: OMRON: p <0.05 Tanita 300A: p <0.05 Tanita 521: p <0.05 ♀ with %BF (by DXA) >40%: OMRON: p <0.05 Tanita 300A: ns. P-value Tanita 521: p <0.05	
Gonzalez-Ruiz, 2018 (23)	Hand-to-foot; multifrequency; SecamBCA 514 (secagmbh& co. kg, Hamburg, Germany) Foot-to-foot; single-frequency; Tanita BC 420-MA (Tanita Corp., Tokyo, Japan) Manufacturer's software equation %BF	DXA; Hologic Horizon with Discovery software (Bellingham, USA)	Seca BIA %BF ♂: Bias = -14.6; LoA = -22.9 to -6.3 ♀: Bias = -8.5; LoA = -14.8 to -2.3 Tanita BIA %BF ♂: Bias = -14.0; LoA = -25.8 to -2.2 ♀: Bias = -11.3; LoA = -20.1 to -2.4	*Paired t-test* Seca BIA %BF ♂: p <0.001 ♀: p <0.001 Tanita BIA %BF ♂: p <0.001 ♀: p <0.001	*Correlation coefficient; Lin's CCC* Seca BIA %BF ♂: r = 0.726 ; p <0.001; *Lin's CCC* = 0.149 ♀: r = 0.846; p <0.001; *Lin's CCC* =0.323 Tanita BIA %BF ♂: r = 0.430 ; p = 0.005; *Lin's CCC* = 0.096 ♀: r = 0.652; p = 0.005; *Lin's CCC* = 0.175
Lazzer, 2003 (31)	Hand-to-foot; multifrequency; BIA 101 RJL (RJL Systems Inc., Detroit, USA) Manufacturer's software equation	DXA; Hologic QDR-4500 (Hologic Inc., Bedford, USA); software v. 9.10	%BF BIA 101: Bias = -2.9; LoA = -8.4 to 2.5 Tanita: Bias = -2.5; LoA = -10.6 to 5.7 Téfal: Bias = -1.8; LoA = -16.7 to 13.1 FM (kg) BIA 101: Bias = -2.3; LoA = -6.7 to 2.1	*Paired t-test* %BF BIA 101: p = 0.001 Tanita: p = 0.001 Téfal: p = 0.096 FM (kg)	NR

Reference (1st author, year [ref.])	BIA device/equation; compartment of interest	Reference standard	Bland-Altman Analysis	Systematic effect	Associations
	Foot-to-foot; single-frequency; Tanita BF-625 (Tanita Corp. of America Inc., Arlington Heights, USA) Manufacturer's software equation Foot-to-foot; TéfalBodymaster Vision (Téfal, Rumilly, France) Manufacturer's software equation %BF, FM		Tanita: Bias = -1.7; LoA = -7.7 to 4.3 Téfal: Bias = -0.7; LoA = -11.9 to 10.6	BIA 101: p = 0.001 Tanita: p = 0.001 Téfal: p = 0.399	
Lu, 2003 (33)	Foot-to-foot; single-frequency; Tanita TBF-410 (Tanita Corp., Tokyo, Japan) Manufacturer's software equation %BF, FM, FFM	DXA; Hologic QDR-4500 (Waltham, USA)	%BF[c] All: Bias = -0.36; LoA = -11.22 to 10.59 ♂: Bias = -0.67; LoA = -11.71 to 10.42 ♀: Bias = 0.09; LoA = -10.46 to 10.64 FM (kg)[g] All: Bias = -0.49; LoA = -8.50 to 7.71 ♂: Bias = -0.79; LoA = -8.80 to 7.28 ♀: Bias = -0.06; LoA = -7.83 to 7.53 FFM (kg)[c] All: Bias = -0.82; LoA = -8.67 to 7.00 ♂: Bias = -0.66; LoA = -8.64 to 7.35 ♀: Bias = -1.15; LoA = -8.71 to 6.37	*Paired t-test* FM (kg) All: p >0.05 ♂: p >0.05 ♀: p >0.05	*Linear regression* %BF: All: r = 0.85; p <0.001 ♂: r = 0.87; p <0.001 ♀: r = 0.94; p <0.001 FM (kg): All: r = 0.93; p <0.001 ♂: r = 0.94; p <0.001 ♀: r = 0.93; p <0.001 FFM (kg): All: r = 0.95; p <0.001 ♂: r = 0.96; p <0.001 ♀: r = 0.87; p <0.001
Lyra, 2015 (36)	Hand-to-foot; RJL BIA Quantum (RJL Systems Inc., Detroit, USA) Manufacturer's software equation %BF, FM, FFM	DXA; GE Lunar DPX-IQ (Lunar Radiation Corporation, Madison, USA); sofware v. 4.7e	NR	*Mann-Whitney test* %BF – Baseline: mean difference = -8.5; p <0.001 *Student t-test* FFM (kg) – Baseline: Mean difference = 7.5; p <0.001	NR
Gillis, 2000 (21)	Hand-to-foot; BIA-101A (RJL Systems Inc., Detroit, USA) Houtkooper equation	UW; measured residual lung volume; Lohman equation to	FFM (kg) Bias = 0.93; LoA = -5.2 to 6.6[c]	NR	*Linear regression* FFM (kg): r = 0.96; SEE = 3.20 kg; p <0.0001

Reference (1st author, year [ref.])	BIA device/equation; compartment of interest	Reference standard	Bland-Altman Analysis	Systematic effect	Associations
	FFM	calculate body density			
NewtonJr, 2005 (39)	Hand-to-foot; RJL BIA 101Q (RJL Systems Inc., Detroit, USA) Raw data were entered on the equations of Bray, Deurenberg, Kushner, Lewy, Schaefer, Sun, Supraspongsin %BF	DXA; Hologic QDR-2000 (Hologic Inc., Waltham, MA, USA); software v.5.60	%BF Bray: Bias = -0.4; LoA = -7.4 to 6.6[c] Deurenberg: Bias = -7.3; LoA = -15.8 to 1.3[c] Kushner: Bias = 0.5; LoA = -6.9 to 7.9[c] Lewy: Bias = -0.01; LoA = -8.0 to 8.0[c] Schaefer: Bias = 6.7; LoA = 0.3 to 12.9[c] Sun: Bias = -3.2; LoA = -9.8 to 3.4[c] Supraspongsin: Bias = -16.9; LoA = -24.9 to -8.7[c]	*Paired t-test* %BF Bray: p = 0.410 Deurenberg: p <0.001 Kushner: p = 0.319 Lewy: p = 0.904 Schaefer: p <0.001 Sun: p <0.001 Supraspongsin: p <0.001	*Bland-Altman regression analysis* %BF Bray: β= -0.28; p <0.001 Deurenberg: β = -0.60; p <0.001 Kushner: β= -0.02; p = 0.765 Lewy: β= -0.34; p <0.001 Schaefer: β = *0.03;* p = 0.607 Sun: β= -0.10; p = 0.105 Supraspongsin: β= -0.46 p <0.001
Wabitsch, 1996 (59)	Hand-to-foot; AKERN BIA 101/S (RJL Systems Inc., Detroit, USA) Predictive TBW equation (developed using baseline data): TBW = 0.35 x RI + 0.27 x age + 0.14 x weight – 0.12 (RI = height^2/resistance)	Deuterium oxide	NR	NR	*Correlation between the changes of measured and predicted TBW (after weight loss):* TBW r = 0.21; p <0.05
Battistine, 1992 (6)	Hand-to-foot; Human IM (Dietosystem Medica, Milan, Italy) Manufacture's software equation; raw data were entered in the equation of Davies; TBW	Deuterium oxide	NR	TBW Manufacture's equation: Mean difference = -2.7; p <0.0001 Davies equation: Mean difference = -5.7; p <0.0001	*Unadjusted correlation coefficient:* Manufacture's equation r = 0.94; n.s p-value[h] Davies r = 0.93; n.s p-value[h]

Reference (1st author, year [ref.])	BIA device/equation; compartment of interest	Reference standard	Bland-Altman Analysis	Systematic effect	Associations
Lazzer, 2008 (32)	Hand-to-foot; multifrequency; Human IM Plus II (Dietosystem Medica, Milan, Italy) Manufacturer's software equation; authors also developed a population-specific equation[i] %BF, FFM	DXA; Lunar Prodigy (GE Lunar Medical Systems, Milwaukee, USA; Pediatric software v.1.5	%BF BIA: Bias = -5.84; LoA = -14.9 to 3.22 FFM Predictive equation: Bias = -1.5; LoA = -7.2 to 4.1	*Bland-Altman analysis* FFM Predictive equation: p <0.0001	*Pitman's test* %BF BIA: R = 0.103; p = 0.441
Cleary, 2008 (11)	Hand-to-foot; single-frequency; Bodystat 1500 (BodyStat Ltd., Douglas, Isle of Man, British Isles). Manufacturer's software (default equation is Houtkooper); raw data were also entered on the equations of Deurenberg 1, Deurenberg 2, Schaffer %BF, FM, FFM	DXA; Hologic QDR 4500 (Hologic Inc, Bedford); Pediatric Whole body 2004 software (v. 12.3)	%BF Houtkooper: Bias = -2.62; LoA = -8.75 to 3.51 Deurenberg 1: Bias = 2.70; LoA = -5.74 to 11.15 Deurenberg 2: Bias = -12.10; LoA = -19.27 to -4.93 Schaefer: Bias = 1.18; LoA = -6.93 to 9.30	*Paired t-test* %BF Houtkooper: p <0.000 Deurenberg 1: p = 0.001 Deurenberg 2: p <0.000 Schaefer: p = 0.121 FM (kg) Houtkooper: p = 0.001 Deurenberg 1: p <0.000 Deurenberg 2: p <0.000 Schaefer: p = 0.010 FFM (kg) Houtkooper: p <0.000 Deurenberg 1: p = 0.010 Deurenberg 2: p <0.000 Schaefer: p = 0.102	*Pearson or Spearman correlations* %BF Houtkooper: r = 0.856 Deurenberg 1: r = 0.834 Deurenberg 2: r = 0.836 Schaefer: r = 0.835 FM (kg) Houtkooper: r = 0.966 Deurenberg 1: r = 0.965 Deurenberg 2: r = 0.939 Schaefer: r = 0.938 FFM (kg) Houtkooper: r = 0.972 Deurenberg 1: r = 0.961 Deurenberg 2: r = 0.971 Schaefer: r = 0.966
Resende, 2013 (45)	Hand-to-foot; single-frequency; Bodystat 1500 (Douglas, Isle of Man, British Isles) FFM was calculated using the Houtkooper equation TBW was estimated using the equation proposed by Kushner FM, FFM, TBW	Deuterium oxide	FM (kg): Bias = -5.816; LoA = -14.024 to 2.392 FFM (kg): Bias = 5.88; LoA = -2.424 to 14.202 TBW (L): Bias = 5.55; LoA = -1.116 to 12.156	*Paired t-test* FM (kg): p <0.05 FFM (kg): p <0.05 TBW (L): p <0.05	*Pearson correlation* FM (kg): r = 0.89; p <0.001 FFM (kg): r = 0.91; p <0.001 TBW (L): r = 0.89; p <0.001
Eisenkolbl, 2001 (16)	Hand-to-foot; multifrequency; BIA 2000-M (Data Input	DXA; Hologic QDR-4500	%BF All: Bias = -4.48; LoA = -10.22 to 1.27[j] ♂: Bias = -6.27; LoA = -11.44 to -1.10	*Paired t-test* All: p <0.001 ♂: p <0.001	*Generalized linear regression* %BF

Reference (1st author, year [ref.])	BIA device/equation; compartment of interest	Reference standard	Bland-Altman Analysis	Systematic effect	Associations
	GmbH, Hofheim, Germany); measurements at 50 kHz Manufacturer's equation %BF	(Hologic Inc., Bedford, USA)	♀: Bias = -1.94; LoA = -7.21 to 3.33	♀: p <0.001	♂: r = 0.919 ♀: r = 0.923
Ohta, 2017 (40)	Hand-to-foot; single frequency; Muscle-α (Art Haven 9 Co, Kyoto, Japan); whole-body and segmental BIA Authors developed population-specific equations[k] FFM (whole-body and regional [arm, trunk, leg])	DXA; Hologic Delphi A-QDR (Hologic Inc., Bedford, USA); Whole-body and segmental	FFM (kg) Arm: Bias = 0.26; LoA = -0.26 to 0.78 Trunk: Bias = -0.30; LoA = -2.37 to 1.76 Leg: Bias = 0.23; LoA = -1.56 to 2.02 Whole-body: Bias = -0.15; LoA = -3.52 to 3.21	*Paired t-test* FFM (kg) Arm: p <0.05 Trunk: ns. p-value Leg: ns. p-value Whole-body: ns. p-value	FFM (kg) Arm: R^2 = 0.893; SEE = 0.25 kg Trunk: R^2 = 0.898; SEE = 1.05 kg Leg: R^2 = 0.886; SEE = 0.91 kg Whole-body: R^2 = 0.939; SEE = 1.71 kg
Seo, 2018 (48)	Hand-to-foot; multifrequency; InBody 720 Body Composition Analyzer (BioSpace Co., Ltd., Seoul, Korea); segmental measurements (upper and lower body [left and right], and trunk) Manufacturer's software equations %BF, FM, FFM	DXA; GE Lunar Prodigy Advance (GE Medical Systems Lunar, Madison, USA); pediatric software v. encore 14.0	%BF All: Bias = -1.79; LoA = -6.57 to 2.99 OB: Bias = -2.48; LoA = -6.85 to 1.89 MO: Bias = -0.30; LoA = -4.63 to 4.03 FM (kg) All: Bias = -0.84; LoA = -4.14 to 2.51 OB: Bias = -1.31; LoA = -4.07 to 1.45 MO: Bias = 0.15; LoA = -3.48 to 3.78 FFM (kg) All: Bias = 1.37; LoA = -1.84 to 4.58 OB: Bias = 1.77; LoA = -0.99 to 4.53 MO: Bias = 0.52; LoA = -2.97 to 4.01	*Paired t-test* %BF All: <0.05 OB: <0.05 MO: ns.p-value FM (kg) All: <0.05 OB: <0.05 MO: ns.p-value FFM (kg) All: <0.05 OB: <0.05 MO: <0.05	*Lin's concordance correlation* %BF All: r = 0.774 OB: r = 0.693 MO: r = 0.825 FM (kg) All: r = 0.970; s. p-value OB: r = 0.941 MO: r = 0.967; s. p-value FFM (kg) All: r = 0.977; s. p-value OB: r = 0.971; s. p-value MO: r = 0.982; s. p-value

[a]FM (kg) = [(2.747 x body volume) – (0.710 x total body water)] + [(1.460 x bone mineral content) – (2.050 x body weight)]

[b] Lower and upper limits of agreement were calculated from the 95th limits of agreement.

[c] Bias, and lower and upper limits of agreement were extracted from Bland-Altman plots using Plot Digitizer, an open source software (v.2.6.8; http://plotdigitizer.sourceforge.net).

[d] Mean difference and 95% confidence interval between index test and reference standard for changes in body composition from baseline to follow-up.

[e]FM (kg) = [(2.220 x body volume) - (0.764 x total body water)] - (1.465 x body weight)

[f] Lower and upper limits of agreement were calculated using the following equation: lower limit of agreement = bias – LoA; upper limit of agreement = bias + LoA.
[g] FM (kg) = [(2.220 x body volume) - (0.764 x total body water)] - (1.465 x body weight)
[h] Values do not lie on the line of unit, indicating the presence of bias.
[i] Fat-free mass was calculated using the following equation: FFM (kg) = 0.87 x ZI + 3.1 (adjusted coefficient of determination = 0.91; RMSE=2.7 kg, P<0.001
[j] Lower and upper limits of agreement were calculated using the following equations: lower limit of agreement = bias - (1.96 x standard deviation); upper limit of agreement = bias + (1.96 x standard deviation).
[k] Arm FFM (kg) = (0.359 x BI index) +0.197; Trunk FFM (kg) = (0.208 x BI index) - 0.876; Leg FFM (kg) = (0.449 x BI index) – 0.087; Whole body FFM (kg) = (0.306 x BI index) – 0.358
Abbreviations: 4-C, four-compartment; BIA, bioelectrical impedance analysis; %BF, percent body fat; CI, confidence interval; CCC, concordance correlation coefficient; DXA, dual-energy x-ray absorptiometry; FFM, fat-free mass expressed in kg; FM, fat mass expressed in kg; HT^2/Z, height squared divided by impedance; ICC, intraclass correlation coefficient; LoA, limits of agreement; MO, morbid obesity group; OB, obesity group; OW, overweight group; ns., not significant; NR, not reported; r = correlation coefficient; R^2, coefficient of determination; SD, standard deviation; SEE, standard error of estimates; TBW, total body water; TS, Tanner Stage.
Symbols: ♂, males; ♀, females.

Table A8 Findings for agreement between ultrasound and reference standard.

Reference (1st author, year [ref.])	Index test	Reference standard	Bland-Altman Analysis	Systematic effect	Associations
Koot, 2014 (30)	B-mode ultrasound; Philips ATL HDI 5000 (Philips Healthcare, Eindhoven, the Netherlands); 3.5 MHz transducer Measurement site: midline just above the umbilicus (minimal pressure); thickness was measured in millimetres (mm) VAT	MRI 3.0 Tesla MR system (Intera, Philips Healthcare) for participants weighting ≤150 kg or WC ≤150 cm 1.0 Tesla MR scanner (Panorama, Philips Healthcare) for participants weighting >150 kg or WC >150 cm Five transverse slices were selected just above the umbilicus, at the third lumbar vertebrae level Automated segmentation using Matlab software (MathWorks, Inc, Natick, USA) and manually corrected by two blinded and trained operators	NR	NR	VAT All: r = 0.60; p = 0.47 ♂: r = 0.62; p = 0.97 ♀: r = 0.50; p = 0.1
Pineau, 2010 (41)	A-mode ultrasound; GEM device (EA Company, Vandoeuvre-les-Nancy, France); 2.25 MHz transducer Measurement site: posterior abdominal wall at the umbilical level (right and left sides); midthigh (inner aspect of the thigh, 20 cm proximal to the knee); thickness was measured in mm. %BF was estimated using multiple regression models for males and females including the ultrasound and anthropometric variables.	DXA; Hologic QDR/4500 W (Hologic, Bedford, USA); software v. 11.2.5.	%BF ♂: Bias = -0.42; LoA = -4.6 to 4.5[a] ♀: Bias = 0.11; LoA = -5.8 to 5.8a	NR	*Coefficient of determination; SEE* %BF All: R^2=0.47; p-value NR ♂: R^2=0.94; SEE = 2.3 ♀: R^2=0.61; SEE = 2.7

[a]Bias, and lower and upper limits of agreement were extracted from Bland-Altman plots using Plot Digitizer, an open source software (v.2.6.8; http://plotdigitizer.sourceforge.net).

Abbreviations: %BF, percent body fat; LoA, limits of agreement; ns., not significant; MRI, magnetic resonance imaging; NR, not reported; r = correlation coefficient; R^2, coefficient of determination; SEE, standard error of estimates; VAT, visceral adipose tissue; WC, waist circumference.

Symbols: ♂, males; ♀, females.

Table A9 Findings for agreement between air displacement plethysmography and reference standard.

Reference (1st author, year [ref.])	ADP technique; compartments of interest	Reference standard	Bland-Altman Analysis	Systematic effect	Associations
Colantonio, 2015 (12)	BOD POD®; measured TGV (L); Lohman equation to predict %BF; laboratory CV= 3.2% %BF	DXA; GE Lunar MD plus; Encore v. 8.5 software; slow mode UW	Reported, but unclear results.	*Paired t-test* *ADP vs. DXA* %BF: p = 0.001 *ADP vs. UW* %BF: p = 0.001	*Interclass correlation coefficient* *ADP vs. DXA* ICC = 0.37 (10.046 to 0.626) *ADP vs. UW* ICC = 0.190 (0.000; 0.490)
de Mello, 2005 (14)	BOD POD®; measured TGV; Siri equation to predict FM %BF, FM, FFM	DXA; GE Lunar DPX-IQ	*NR*	NR	*Linear regression and Person correlation* %BF: r = 0.75; p <0.05 FM (kg): r = 0.92; p <0.05 FFM (kg): r = 0.88; p <0.05
Lazzer, 2008 (32)	BOD POD®; software v. 1.69; measured TGV; Siri and Lohman equations to predict %BF %BF	DXA; GE Lunar Prodigy; pediatric software v.1.5	Siri %BF: Bias = -2.11; LoA = -8.82 to 4.61 Lohman %BF: Bias = -3.80; LoA =-10.27 to 2.67	NR	*Pitman's test* Siri %BF: r = 0.401; p = 0.002 Lohman %BF: r = 0.315; p = 0.001
Gately, 2003 (20)	BOD POD®; software v. 1.69; Crapo equation to estimate TGV (L);Siri and Lohman equations to predict %BF %BF	4-C model[a]	Siri %BF All: Bias = 1.8; LoA = -1.7 to 5.3[b] ♂: Bias = 1.8; LoA = -1.3 to 4.9[b] ♀: Bias = 1.8; LoA = -2.4 to 6.0[b] Lohman %BF All: Bias = -0.04; LoA = -3.6 to 3.6[b] ♂: Bias = 0.2; LoA = -3.0 to 3.4[b] ♀: Bias = -0.4; LoA = -4.6 to 3.8[b]	Siri %BF All: TE = 2.50 ♂: TE = 2.33 ♀: TE = 2.74 Lohman %BF All: TE = 1.82 ♂: TE = 1.59 ♀: TE = 2.11	*Correlation coefficient* Siri %BF All: r = 0.96; p <0.001; SEE = 1.74 ♂: r = 0.97; p <0.001; SEE = 1.61 ♀: r = 0.93; p <0.05; SEE = 1.86 Lohman %BF All: r = 0.95; ns. p-value; SEE = 1.81 ♂: r = 0.97; ns. p-value; SEE = 1.67

Reference (1st author, year [ref.])	ADP technique; compartments of interest	Reference standard	Bland-Altman Analysis	Systematic effect	Associations
					♀: r = 0.94; ns. p-value; SEE = 1.68
Vasquez, 2016 (57)	BOD POD® (mod 2000) %BF	4-C model[c]	%BF All: Bias = 2.437; LoA =-2.09 to 7.03[b] ♂ TS 1-2: Bias = 3.172; LoA = -1.58 to 7.92[b] ♂ TS 3-5: Bias = 2.359; LoA = -1.614 to 6.333[b] ♀ TS 1-2: Bias = 1.952; LoA = -2.444 to 6.347[b] ♀ TS 3-5: Bias = 2.151; LoA = -2.758 to 7.086[b]	NR	*Correlation coefficient* ♂ TS 1-2: 0.819 ♂ TS 3-5: 0.932 ♀ TS 1-2: 0.838 ♀ TS 3-5: 0.893 *Regression analysis* ♂ TS 1-2: r^2 = 0.87; SEE = 0.07 ♂ TS 3-5: r^2 = 0.96; SEE = 0.03 ♀ TS 1-2: r^2 = 0.92; SEE = 0.23 ♀ TS 3-5: r^2 = 0.93; SEE = 0.03
Radley, 2007 (42)	BOD POD®; software v. 1.69; Crapo and Fields equations to predict TGV (L); Lohman equation to predict %BF TGV and %BF	BOD POD; Software v. 1.69; Measured TGV; Lohman equation to predict %BF	TGV_{Crapo}(L)b ♂ OW: Bias = 0.32; LoA = -0.52 to 1.16 ♀ OW: Bias = 0.50; LoA = -0.51 to 1.51 ♂ OB: Bias = 0.75; LoA = -0.17 to 1.67 ♀ OB: Bias = 0.57; LoA = -0.27 to 1.41 TGV_{Fields} (L)b ♂ OW: Bias = 0.12; LoA = -0.64 to 0.88 ♀ OW: Bias = 0.11; LoA = -0.91 to 1.13 ♂ OB: Bias = 0.53; LoA = -0.42 to 1.48 ♀ OB: Bias = 0.19; LoA = -0.67 to 1.05 $\%BF_{Crapo}$ (%)b ♂ OW: Bias = 1.1; LoA = -1.9 to 4.1	TGV_{Crapo}(L) ♂ OW: p <0.05; ♀ OW: p <0.001 ♂ OB: p <0.001 ♀ OB: p <0.001 TGV_{Fields} (L) ♂ OB: p <0.001 ♀ OB: p <0.01 FM_{Crapo} (%) ♂ OW: p <0.05 ♀ OW: p <0.001 ♂ OB: p <0.001 ♀ OB: p <0.001 FM_{Fields} (%) ♂ OB: p <0.001 ♀ OB: p <0.05	NR

Reference (1st author, year [ref.])	ADP technique; compartments of interest	Reference standard	Bland-Altman Analysis	Systematic effect	Associations
			♀ OW: Bias = 1.8; LoA = -2.1 to 5.7 ♂ OB: Bias = 1.7; LoA = -0.5 to 3.9 ♀ OB: Bias = 1.3; LoA = -0.8 to 3.4 $\%BF_{Fields}$ (%)b ♂ OW: Bias = 0.5; LoA = -3.3 to 4.3 ♀ OW: Bias = 0.4; LoA = -3.3 to 4.1 ♂ OB: Bias = 1.1; LoA = -1.1 to 3.3 ♀ OB: Bias = 0.4; LoA = -1.7 to 2.5		
Wells, 2011 (62)	BOD POD®; predicted TGV (L); Lohman equation for density of LT, FM	4-C model[c]	*Cross-sectional cohort* Density LT (kg/l) All: Bias = -0.0025; LoA = -0.0197 to 0.0147[d] ♂: Bias = 0.0029; LoA = -0.0120 to 0.0178[d] ♀: Bias = -0.0057; LoA = -0.0209 to 0.0095 [d] FM (kg) All: Bias = -0.68; LoA = -4.79 to 3.43 [d] ♂: Bias = -0.43; LoA = -3.26 to 2.40 [d] ♀: Bias = -1.33; LoA = -5.53 to 2.87 [d]	*Cross-sectional cohort* Density LT (kg/l) All: p = 0.003 ♂: p = 0.019 ♀: p <0.001 FM (kg) All: p = 0.001 ♂: p = 0.066 ♀: p <0.0001	*Bias FM (kg)* ♂: r = 0.44; p = 0.005
Wells, 2011 (62) (continued)	BOD POD®; predicted TGV (L); Lohman equation for density of LT, FM	4-C model[c]	*Longitudinal cohort – Baseline* Density LT (kg/l) All: Bias = 0.0023; LoA = -0.0004 to 0.005[d] ♂: Bias = -0.0008; LoA = -0.0158 to 0.0142[d]	*Longitudinal cohort – Baseline* Density LT (kg/l) All: p = 0.057 ♂: p = 0.6 ♀: p = 0.041 FM (kg)	

Reference (1st author, year [ref.])	ADP technique; compartments of interest	Reference standard	Bland-Altman Analysis	Systematic effect	Associations
			♀: Bias = 0.0040; LoA = -0.0184 to 0.0264[d] FM (kg) All: Bias = 0.32; LoA = -2.45 to 3.09[d] ♂: Bias = 0.11; LoA = -2.65 to 2.87[d] ♀: Bias = 0.45; LoA = -2.35 to 3.25[d]	All: p = 0.088 ♂: p = 0.70 ♀: p = 0.067	

[a]%BF = [(2.7474/body density) – (0.714 x total body water relative to body mass) + (1.1474 x bone mineral mass relative to body mass) – 2.0503] x 100
[b]Bias, and lower and upper limits of agreement were extracted from Bland-Altman plots using Plot Digitizer, an open source software (v.2.6.8; http://plotdigitizer.sourceforge.net).
[c]FM (kg) = [(2.747 x body volume) – (0.710 x total body water)] + [(1.460 x bone mineral content) – (2.050 x body weight)]
[d]Lower and upper limits of agreement were calculated using the following equation: lower limit of agreement = bias – LoA; upper limit of agreement = bias + LoA
Abbreviations: 4-C, four-compartment; ADP, air displacement plethysmography; %BF, percent body fat; CV, coefficient of variation; DXA, dual energy x-ray absorptiometry; UW, underwater weighing; FM, fat mass; ns., not significant; LoA, limits of agreement; LT, lean tissue; NR, not reported; SDS, standard deviations; OB, obese; OW, overweight; SEE, standard error of estimates; TE, total error; TGV, thoracic gas volume; TS, Tanner stage.
Symbols: ♂, males; ♀, females

Table A10 Findings for agreement between dual energy X-ray absorptiometry and reference standard.

Reference (1st author, year [ref.])	DXA devices and compartments of interest	Reference standard	Bland-Altman Analysis	Systematic effect	Associations
Atherton, 2013 (3)	GE Lunar Prodigy (GE Medical Systems,Madison, USA); Encore 2002 software FM, FFM; SD was calculated using authors' reference dataset.	4-C model[a]	FM SD: Bias = insignificant; LoA = ±0.4 FFM SD: Bias = 0.07; LoA = -0.85 to 0.99[b]	NR	*Bland-Altman correlations* FM SD: Unadjusted: r = -0.11; p = 0.001 Adjusted for age: r = -0.15; p <0.001 FFM SD: Unadjusted: r = 0.14; p < 0.001 Adjusted for age: r = 0.18; p <0.001
Vasquez, 2016 (57)	GE Lunar Prodigy/DPX-NT 9 (Lunar Radiology, WI, USA) %BF	4-C model[a]	%BF All: Bias = 1.053; LoA = -5.064 to 7.198[c] ♂ TS 1-2: Bias = 0.241; LoA = -5.62 to 6.10[d] ♂ TS 3-5: Bias = 2.124; LoA = -3.56 to 7.81[d] ♀ TS 1-2: Bias = 1.052; LoA = -4.03 to 6.13[d] ♀ TS 3-5: Bias = 1.116; LoA = -5.63 to 7.86[d]	NR	*Correlation coefficient* %BF ♂ TS 1-2: 0.866 ♂ TS 3-5: 0.886 ♀ TS 1-2: 0.722 ♀ TS 3-5: 0.785 *Regression analysis* ♂ TS 1-2: r^2 = 0.75; SEE = 0.06 ♂ TS 3-5: r^2 = 0.87; SEE = 0.07 ♀ TS 1-2: r^2 = 0.66; SEE = 0.23 ♀ TS 3-5: r^2 = 0.69; SEE = 0.07
Wells, 2010 (61)	GE Lunar Prodigy (GE Medical Systems,Madison, USA); Encore 2002 software; standard or thick scan mode FM, FFM	4-C model[a]	*Cross-sectional sample* FM (kg): Bias = 0.88; LoA = -3.30 to 5.05 *Longitudinal sample* FM (kg) All: Bias = 0.86; LoA= -3.33 to 5.05[b] ♂: Bias = 0.69; LoA = -2.38 to 3.76[b] ♀: Bias = 0.96; LoA = -3.78 to 5.70[b] FMM (kg) All: Bias = -1.0; LoA = -5.20 to 3.20[b] ♂: Bias = -0.67; LoA = -3.63 to 2.29[b] ♀: Bias = -1.20; LoA = -5.95 to 3.55[b]	*Longitudinal sample – Paired t-test* FM (kg) All: p <0.0001 ♂: p = 0.001 ♀: p <0.0001 FMM (kg) All: p <0.0001 ♂: p = 0.001 ♀: p <0.0001	*Correlation between the bias and the magnitude of the variable* FM (kg) All: r = 0.17; p = 0.037 ♂: r = -0.19;p = 0.16 ♀: r = 0.30; p = 0.003 FMM (kg) All: r = -0.32; p <0.0001 ♂: r = -0.24; p = 0.07 ♀: r = -0.43; p <0.0001
Gately, 2003 (20)	GE Lunar Prodigy (GE Medical Systems,Madison, USA); software v. 5.0; standard or thick scan mode %BF	4-C model[e]	%BF All: Bias = 1.9; LoA = -2.1 to 5.9[c] ♂: Bias = 1.7; LoA= -2.1 to 5.5[c] ♀: Bias = 2.2; LoA= -2.2 to 6.6[c]	%BF All: TE = 2.74 ♂: TE = 2.52 ♀: TE = 3.05	%BF *Correlation coefficient* ♂: r ≥0.98; p <0.001 ♀: r ≥0.95; p <0.001 *Regression analysis*

Reference (1st author, year [ref.])	DXA devices and compartments of interest	Reference standard	Bland-Altman Analysis	Systematic effect	Associations
					All: r^2 = 0.94; p <0.001; SEE = 2.02 ♂: r^2 = 0.96; p <0.01; SEE = 1.97 ♀: r^2 = 0.90; p <0.01; SEE = 2.14
Williams, 2006 (63)	GE Lunar Prodigy (GE Medical Systems,Madison, USA); Encore 2002 software; standard or thick scan mode %BF, FM, FFM	4-C model[a]	%BF ♂: Bias = 1.41; LoA = -1.18 to 4.00[d] ♀: Bias = 1.03; LoA = -2.47 to 4.53[d] FM (kg) ♂: Bias = 0.93; LoA = -0.93 to 2.79[d] ♀: Bias = 0.46; LoA= -1.96 to 2.88[d] FMM (kg) ♂: Bias = -1.02; LoA= -3.01 to 0.97[d] ♀: Bias = -0.80; LoA = -3.29 to 1.69[d]	*Paired t-test* %BF ♂: p <0.01 ♀: p <0.01 FM (kg) ♂: p <0.01 ♀: ns. p-value FMM (kg) ♂: p <0.01 ♀: p <0.01	*Pearson correlation between the bias and the mean values* %BF ♂: r = -0.54; ns. p-value ♀: r = -0.52; p <0.01 FM (kg) ♂: r = -0.08; ns. p-value ♀: r = -0.24; ns. p-value FMM (kg) ♂: r = -0.03; ns. p-value ♀: r = -0.05; ns. p-value

[a]FM (kg) = [(2.747 x body volume) – (0.710 x total body water)] + [(1.460 x bone mineral content) – (2.050 x body weight)]
[b]Lower and upper limits of agreement were calculated using the following equation: lower limit of agreement = bias – LoA; upper limit of agreement = bias + LoA.
[c]Bias, and lower and upper limits of agreement were extracted from Bland-Altman plots using Plot Digitizer, an open source software (v.2.6.8; http://plotdigitizer.sourceforge.net).
[d]Lower and upper limits of agreement were calculated from the 95th limits of agreement.
[e]%BF = [(2.7474/body density) – (0.714 x total body water relative to body mass) + (1.1474 x bone mineral mass relative to body mass) – 2.0503] x 100
Abbreviations: 4-C, four-compartment; %BF, percent body fat; DXA, dual-energy x-ray absorptiometry; FFM, fat-free mass; FM, fat mass; LoA, limits of agreement; ns., not significant; NR, not reported; SD, standard deviation; SEE, standard error of estimates; TE, total error; TS, Tanner stage
Symbols: ♂, males; ♀, females.

Table A11 Findings for agreement between isotope dilution and reference standard.

Reference (1st author, year [ref.])	Index test	Reference standard	Bland-Altman Analysis	Systematic effect	Associations
Gately, 2003 (20)	Deuterium dilution; 0.35 mol ^2H_2O; mass spectrometry; FFM was then estimated by assuming that water accounts for 73% of FFM (TBW73) and utilizing the age- and gender-specific water contents given by Lohman (TBWLoh) %BF	4-C model[a]	%BF TBW73 All: Bias = -2.0; LoA = -6.1 to 2.1 ♂: Bias = -1.6; LoA = -5.6 to 2.4 ♀: Bias = -2.7; LoA = -6.6 to 1.2 TBWLoh All: Bias = -0.3; LoA = -4.1 to 3.5 ♂: Bias = -0.1; LoA = -3.8 to 3.6 ♀: Bias = -0.6; LoA = -4.5 to 3.3	%BF TBW73 All: TE = 2.86 ♂: TE = 2.55 ♀: TE = 3.27 TBWLoh All: TE = 1.90 ♂: TE = 1.84 ♀: TE = 2.00	*Correlation coefficient* %BF TBW73 All: r = 0.93; p <0.001; SEE = 2.12 ♂: r = 0.95; p <0.01; SEE = 2.06 ♀: r = 0.91; p <0.001; SEE = 2.03 TBWLoh All: r = 0.95; ns. p-value; SEE = 1.95 ♂: r = 0.96; ns. p-value; SEE = 1.89 ♀: r= 0.92; ns. p-value; SEE = 1.93
Vasquez, 2016 (57)	Deuterium dilution; 4 g deuterium oxide 99.8%; mass spectrometry %BF	4-C model[b]	%BF All: Bias = 0.178; LoA = -5.595 to 6.056 ♂ TS 1-2: Bias = -0.941; LoA = -6.92 to 5.04 ♂ TS 3-5: Bias = -0.155; LoA = -4.24 to 3.93 ♀ TS 1-2: Bias = 2.684; LoA = -1.052 to 6.420 ♀ TS 3-5: Bias = 0.861; LoA = -5.359 to 7.081	NR	*Lin's CCC; Regression analysis; SEE* %BF ♂ TS 1-2: *Lin's CCC* = 0.851; R^2 = 0.75; SEE = 0.07 ♂ TS 3-5:*Lin's CCC* = 0.959; R^2 = 0.94; SEE = 0.02 ♀ TS 1-2: *Lin's CCC* = 0.689; R^2 = 0.81; SEE = 0.22 ♀ TS 3-5: *Lin's CCC* = 0.809; R^2 = 0.77; SEE = 0.06

[a] FM (kg) = [(2.7474/Db) – (0.7145 x w)+ (1.1474 x m) -2.0503] x 100

[b] FM (kg) = [(2.747 x BV) – (0.710 x TBW)] + [(1.460 x BMC) –(2.050 x W)]

Abbreviations: 4-C, four-compartment; %BF, percent body fat; CCC, concordance correlation coefficient; FFM, fat-free mass; FM, fat mass; LoA, limits of agreement; ns., not significant; NR, not reported; r = correlation coefficient; R^2, coefficient of determination; SEE, standard error of estimates; TBW, total body water; TE, total error; TS, Tanner Stage.

Symbols: ♂, males; ♀, females.

Table A12 Findings for agreement between magnetic resonance imaging and reference standard.

Reference (1st author, year [ref.])	Index test	Reference standard	Bland-Altman Analysis	Systematic effect	Associations
Raschpichler, 2012 (44)	MRI; 1.5 T GyroscanIntera (Philips Medical Systems, Best, The Netherlands); scans were taken from the upper edge of T9 to the symphysis Semi-automatic segmentation of adipose tissue using the "Abdominal adipose tissue assessment plug-in" protocol in the ImageJ software (Rasband, 2004; version 1.42) SAT, VAT, TAT	MRI; 1.5 T GyroscanIntera (Philips Medical Systems, Best, The Netherlands); scans were taken from the upper edge of T9 to the symphysis Semi-automatic segmentation of adipose tissue using the SliceOmatic software (Rasband, 2004; version 1.42)	NR	*Paired Wilcoxon test* Calculated differences (mean) TAT (ml): mean difference = 189.7; p ≤0.05 VAT (ml): mean difference = 87.0; p ≤0.05 SAT (ml): 102.6; p ≤0.05	NR
Hui, 2018 (27)	MRI; 3.0 T whole-body scanner; Philips Achieva X-series (Philips Medical System, Best, The Netherlands) Segmentation method proposed by authors consisted of: - Fat image: a) inhomogeneity correction, de-noising, smoothing, Otsu's method; b) spoke template, cut connecting tissues, get largest connecting region; c) subtract SAT from TAT; d) VAT (with MAT); e) final VAT - Co-registered T2* image: a) inhomogeneity correction, de-noising, smoothing, intensity filter; b) multiply T2* mask to VAT (with MAT); c) Final VAT SAT, VAT, TAT	MRI; 3.0 T whole-body scanner; Philips Achieva X-series (Philips Medical System, Best, The Netherlands) Semi-automatic segmentation using Matlab (R2011a, Mathworks, Natick, USA) Fat signals were derived from the seven-peak spectral model of fat and monoexponential T2* were used for fitting.	SAT (cm^3): Bias = 173.58; LoA = -630.28 to 977.44 VAT (cm^3): Bias = -143.58; LoA = -1001.96 to 714.80 TAT (cm^3): Bias = 64.19; LoA = -287.30 to 415.68	NR	*Pearson correlation; ICC* SAT (cm^3) Section 1: r = 0.984; p <0.05; ICC = 0.971 Section 2: r = 0.978; p <0.05; ICC = 0.979 Section 3: r = 0.872; p <0.05; ICC = 0.818 VAT (cm^3) Section 1: r = 0.866; p <0.05; ICC = 0.862 Section 2: r = 0.873; p <0.05; ICC = 0.865 Section 3: r = 0.636; p <0.05; ICC = 0.509 TAT (cm^3) Section 1: r = 0.989; p <0.05; ICC = 0.989 Section 2: r = 0.996; p <0.05; ICC = 0.994 Section 3: r = 0.985; p <0.05; ICC = 0.980
Springer, 2012 (51) (continued	MRI; 1.5 T Magnetom Sonata (Siemens Healthcare, Erlangen, Germany); 2D	Whole-body MRI; 1.5 T Magnetom Sonata (Siemens Healthcare,	NR	NR	*Spearman correlation* *Single slice TAT vs. whole-body TAT*

Reference (1st author, year [ref.])	Index test	Reference standard	Bland-Altman Analysis	Systematic effect	Associations
on next page)	axial T1-weighted fast spin-echo sequence Semi-automatic segmentation using MatLab (v.6.5, MathWorks, Matick, MA)	Erlangen, Germany); 2D axial T1-weighted fast spin-echo sequence			Femoral head: ♂: r = 0.93; p <0.0001 / ♀: r = 0.95; p <0.0001 Head of humerus: ♂: r = 0.76; p <0.0001 / ♀: r = 0.83; p <0.0001 *Single slice SAT vs. whole-body TAT* Umbilicus: ♂: r = 0.91; p <0.0001 / ♀: r = 0.88; p <0.0001
Springer, 2012 (51)	Single axially oriented slices and stacks of five parallel oriented adjacent slices were evaluated at the femoral head, head of humerus, and at the umbilicus level. Adipose tissue of the trunk, and lower and upper extremities were also evaluated. SAT, VAT, and TAT	Semi-automatic segmentation using MatLab (v.6.5, MathWorks, Matick, MA) Whole-body volume of SAT, VAT, and TAT were evaluated.			*Single slice SAT vs. whole-body SAT* Umbilicus: ♂: r = 0.91; p <0.0001 / ♀: r = 0.92; p <0.0001 *5-slice SAT vs. whole-body TAT* Femoral head: ♂: r = 0.92; p <0.0001 / ♀: r = 0.92; p <0.0001 Head of humerus: ♂: r = 0.81; p <0.0001 / ♀: r = 0.88; p <0.0001 Umbilicus: ♂: r = 0.91; p <0.0001 / ♀: r = 0.91; p <0.0001 *5-slice SAT vs. whole-body SAT* Femoral head: ♂: r = 0.94; p <0.0001 / ♀: r = 0.94; p <0.0001 Head of humerus: ♂: r = 0.81; p <0.0001 / ♀: r = 0.80; p <0.0001 Umbilicus: ♂: r = 0.89; p <0.0001 /♀: r = 0.93; p <0.0001

Reference (1st author, year [ref.])	Index test	Reference standard	Bland-Altman Analysis	Systematic effect	Associations
					Single slice VAT vs. whole-body TAT ♂: r = 0.38; p = 0.0821 / ♀: r = 0.53; p = 0.0226 *Single slice VAT vs. whole-body VAT* ♂: r = 0.71; p <0.0001 / ♀: r = 0.94; p <0.0001 *5-slice VAT vs. whole-body TAT* Femoral head: ♂: r = 0.44; p = 0.0411 / ♀: r = 0.66; p = 0.0028 Umbilicus: ♂: r = 0.36; p = 0.0956 / ♀: r = 0.52; p = 0.0287 *5-slice VAT vs. whole-body VAT* ♂: r = 0.68; p = 0.0005 / ♀: r = 0.58; p = 0.0122 Umbilicus: ♂: r = 0.68; p = 0.0005 / ♀: r = 0.93; p <0.0001

Abbreviations: %BF, percent body fat; FM, fat mass; LoA, limits of agreement; ns., not significant; MRI, magnetic resonance imaging; NR, not reported; r = correlation coefficient; R^2, coefficient of determination; SEE, standard error of estimates; TAT, total adipose tissue; VAT, visceral adipose tissue.
Symbols: ♂, males; ♀, females.

Table A13 Description of predictive equations for body composition used in bioelectrical impedance analysis.

Equation	N (sex)	Age range, years	Weight status	Predictive equation	BIA device
Bedogni (7)	55 (29 M)	11.2 (1.8)	OB	TBW = 0.726 (H^2/Imp) - 1.524 FFM = TBW/0.732	Human IM Scan
Bray/Pennington (75)	129 (65 M)	10.79 (0.05)	NW/OW	%BF = {1 - [0.4(H^2/Resistance) + 0.148W + 3.32]/ 0.76W} 100	Xitron
Davies (76)	26 (12 M)	5.24-17.85	NW/OW/ OB	TBW = 0.6(H^2/Imp) - 0.5	
Deurenberg 90 (77)	246 (130 M)	10-15		FFM = 0.438 [10^4(H^2/R) + 0.308W+ 1.6SEX + 7.04H – 8.5	RJL
Deurenberg 91 (78)	827 (361 M)	7-15		≤15y: 0.406 [10^4(H^2/Imp) + 0.360W + 5.58H + 0.56SEX - 6.48 ≥16y: 0.340 [10^4(H^2/Imp) + 15.34H + 0.273W - 0.127AGE + 1.56SEX – 12.44	RJL
Gray (79)	87 (25 M)	19-74	NW/OB	♂: FFM = 0.00139H^2 - 0.0801R + 0.187W + 39.830 ♀: FFM = 0.00151H^2 - 0.0344R + 0.140W - 0.158AGE + 20.387	RJL
Goran (80)	61 (32 M)	4-6	Not reported	FFM = [0.59(H^2/Resistance)) + 0.065W + 0.04] / 0.769 – 0.0025AGE – 0.019SEX	RJL 101A
Hamilton (52)	27 (13 M)	15.7 (1.9)	OB	FM = 47.52 + 0.859W - 0.0703Imp - 0.9722(H^2/R)	IMP SFB7 Impedimed
Haroun (25)	78 (30 M)	5-22	OB	FFM = -2.211 + 1.115(H^2/Imp)	Tanita BC-418 MA
Hofsteenge (26)	103 (43 M)	14.5 (1.7)	OB	FFM = 0.527(H^2/Imp) + 0.306W - 1.862	Hydra ECF/ICF (Xiltron Technologies)
Horie (81)	119 (36 M)	18-62	OB	FFM = W - (23.25 + 0.13AGE + 1W + 0.09R - 0.80H)	Quadscan 4000
Houtkooper (82)	95 (53 M)	10-14	NW	FFM = 0.61(H^2/R) + 0.25W + 1.31	RJL 101
Kushner (83)	116	0.02-66	Not reported	%BF = {W - [0.59(H^2/R) + 0.065W + 0.04 / 0.754W} 100	RJL 101
Kyle (84)	343 (202 M)	22-94	NW/OW/ OB	FFM = -4.104 + 0.518(H^2/R) + 0.231W + 0.130Reac + 4.229SEX	Xitron4000b

Equation	N (sex)	Age range, years	Weight status	Predictive equation	BIA device
Lazzer1 (85)	143 (60 M)	12-17	OB	♂: FM = 0.755 W - 0.720(H^2/R) - 0.221Reac + 17.84 ♀: FM = 0.705W - 0.522(H^2/R) - 0.133Reac + 8.83	RJL System, Analycor and Analycor XF models
Lazzer 2 (32)	58 (27 M)	10-17	OB	FFM = 0.87(H^2/Imp) + 3.1	Human IM plus II
Lewy (86)	40 (19 M)	11.7 (1.4)	NW/OB	%BF = [W - 0.62 (H2/R) + 0.2W -1.94]/100W	RJL System
Lukaski (87)	114 (47 M)	18-50	NW/OB	FFM = 0.756(H2/R) + 0.110W + 0.107Reac - 5.463	RJL System
Ramirez (69)	167 (87 M)	9.6 (2.4)	NW/OB	FFM = 0.661(H^2/R) + 0.200W - 0.320	Imp DF50 Impedimed
Schaffer (88)	112 (59 M)	3.9-19.3	NW	FFM = 0.65(H^2/Imp) + 0.68AGE + 0.15	Holtain
Sun (89)	1304 (526 M)	12-94	NW/OW/ OB	♂: FFM = -10.68 + 0.65(H^2/R) + 0.26W + 0.02R ♀: FFM = -9.53 + 0.69(H^2/R) + 0.17W + 0.02R	RJL Systems model 101
Suprasongsin (90)	56 (28 M)	8-26	NW/OW/ OB	FFM = 0.524(H^2/R) + 0.415W - 0.32	RJL
Wabitsch (59)	146 (69 M)	5.5-17.8	OB	TBW = 0.35(H^2/R) + 0.27AGE + 0.14W - 0.12 FFM = TBW/0.732 (28)	RJL System 101S

Abbreviations: %BF, percent body fat; FM, fat mass; FFM, fat-free mass; H, height; Imp, impedance; Reac, reactance; NW, normal weight; OB, obesity; OW, overweight; TBW, total body water; W, weight

References

1. Aguirre CA, Salazar GDC, Lopez De Romaña D V., Kain JA, Corvalán CL, Uauy RE. Evaluation of simple body composition methods: Assessment of validity in prepubertal Chilean children. Eur J Clin Nutr. 2015;69(2):269-273.

2. Asayama K, Dobashi K, Hayashibe H, et al. Threshold values of visceral fat measures and their anthropometric alternatives for metabolic derangement in Japanese obese boys. Int J Obes. 2002;26(2):208-213.

3. Atherton RR, Williams JE, Wells JCK, Fewtrell MS. Use of fat mass and fat free mass standard deviation scores obtained using simple measurement methods in healthy children and patients: Comparison with the reference 4-component model. PLoS One. 2013;8(5):1-10.

4. Ball GDC, Huang TTK, Cruz ML, Shaibi GQ, Weigensberg MJ, Goran MI. Predicting abdominal adipose tissue in overweight Latino youth. Int J PediatrObes. 2006;1(4):210-216.

5. Bammann K, Huybrechts I, Vicente-Rodriguez G, et al. Validation of anthropometry and foot-to-foot bioelectrical resistance against a three-component model to assess total body fat in children: The IDEFICS study. Int J Obes. 2013;37(4):520-526

6. Battistini N, Brambilla P, Virgili F, et al. The prediction of total body water from body impedance in young obese subjects. Int J Obes. 1992;16(3):207-212.

7. Bedogni G, Bollea MR, Severi S, Trunfio O, Manzieri AM, Battistini N. The prediction of total body water and extracellular water from bioelectric impedance in obese children. Eur J Clin Nutr. 1997;51(3):129-133.

8. Bray GA, DeLany JP, Volaufova J, Harsha DW, Champagne C. Prediction of body fat in 12-y-old African American and white children: Evaluation of methods. Am J Clin Nutr. 2002;76(5):980-990.

9. Butcher A, Kabiri LS, Brewer W, Ortiz A. Criterion validity and sensitivity to change of a pediatric bioelectrical impedance analysis scale in adolescents. Child Obes. 2019;15(2):142-148.

10. Chan DFY, Li AM, So HK, Yin J, Nelson EAS. New skinfold-thickness equation for predicting percentage body fat in Chinese obese children. Hong Kong J Paediatr. 2009;14(2):96-102.

11. Cleary J, Daniells S, Okely AD, Batterham M, Nicholls J. Predictive validity of four bioelectrical impedance equations in determining percent fat mass in overweight and obese children. J Am Diet Assoc. 2008;108(1):136-139.
12. Colantonio E, Dâmaso AR, Caranti DA, Pinheiro MM, Tufik S, De Mello MT. Clinical performance of 3-body fat measurements in obese adolescents 15 to 18 years-old. Rev Bras Med. 2015;72(3):77-82.
13. Cortés-Castell E, Juste M, Palazón-Bru A, Monge L, Sánchez-Ferrer F, Rizo-Baeza MM. A simple equation to estimate body fat percentage in children with overweightness or obesity: A retrospective study. PeerJ. 2017;2017(4):1-14.
14. de Mello MT, Damaso AR, Antunes HKM, et al. Body composition evaluation in obese adolescents: The use of two different methods. Rev Bras Med do Esporte. 2005;11(5):251-254.
15. Dias KA, Ramos JS, Wallen MP, et al. Accuracy of longitudinal assessment of visceral adipose tissue by dual-energy X-ray absorptiometry in children with obesity. J Obes. 2019;2019:1-12.
16. Eisenkölbl J, Kartasurya M, Widhalm K. Underestimation of percentage fat mass measured by bioelectrical impedance analysis compared to dual energy X-ray absorptiometry method in obese children. Eur J Clin Nutr. 2001;55(6):423-429. doi:10.1038/sj.ejcn.1601184
17. Elberg J, McDuffie J, Sebring N, et al. Comparison of methods to assess change in children's body composition. Am J Clin Nutr. 2004;80(1):64-69. doi:10.1038/jid.2014.371
18. Freedman DS, Horlick M, Berenson GS. A comparison of the Slaughter skinfold-thickness equations and BMI in predicting body fatness and cardiovascular disease risk factor levels in children. Am J Clin Nutr. 2013;98(6):1417-1424.
19. Garcia-Vicencio S, Coudeyre E, Kluka V, et al. The bigger, the stronger? Insights from muscle architecture and nervous characteristics in obese adolescent girls. Int J Obes. 2016;40(2):245-251.
20. Gately PJ, Radley D, Cooke CB, et al. Comparison of body composition methods in overweight and obese children. J Appl Physiol. 2003;95(5):2039-2046.
21. Gillis L, Bar-Or O, Calvert R. Validating a practical approach to determine weight control in obese children and adolescents. Int J Obes. 2000;24(12):1648-1652.

22. Goldfield GS, Cloutier P, Mallory R, Prud'homme D, Parker T, Doucet E. Validity of foot-to-foot bioelectrical impedance analysis in overweight and obese children and parents. J Sports Med Phys Fitness. 2006;46(3):447-453.
23. González-Ruíz K, Medrano M, Correa-Bautista JE, et al. Comparison of bioelectrical impedance analysis, slaughter skinfold-thickness equations, and dual-energy x-ray absorptiometry for estimating body fat percentage in colombian children and adolescents with excess of adiposity. Nutrients. 2018;10(8):1-14.
24. Haroun D, Wells JCK, Williams JE, Fuller NJ, Fewtrell MS, Lawson MS. Composition of the fat-free mass in obese and nonobese children: Matched case-control analyses. Int J Obes. 2005;29(1):29-36.
25. Haroun D, Croker H, Viner RM, et al. Validation of BIA in obese children and adolescents and re-evaluation in a longitudinal study. Obesity. 2009;17(12):2245-2250.
26. Hofsteenge GH, Chinapaw MJM, Weijs PJM. Fat-free mass prediction equations for bioelectric impedance analysis compared to dual energy X-ray absorptiometry in obese adolescents: A validation study. BMC Pediatr. 2015;15(1).
27. Hui SCN, Zhang T, Shi L, Wang D, Ip CB, Chu WCW. Automated segmentation of abdominal subcutaneous adipose tissue and visceral adipose tissue in obese adolescent in MRI. MagnReson Imaging. 2018;45(January 2017):97-104.
28. Kabiri LS, Hernandez DC, Mitchell K. Reliability, validity, and diagnostic value of a pediatric bioelectrical impedance analysis scale. Child Obes. 2015;11(5):650-655.
29. Kasvis P, Cohen TR, Loiselle SÈ, et al. Foot-to-foot bioelectrical impedance accurately tracks direction of adiposity change in overweight and obese 7- to 13-year-old children. Nutr Res. 2015;35(3):206-213.
30. Koot BGP, Westerhout R, Bohte AE, et al. Ultrasonography is not more reliable than anthropometry for assessing visceral fat in obese children. PediatrObes. 2014;9(6):443-447.
31. Lazzer S, Boirie Y, Meyer M, Vermorel M. Evaluation of two foot-to-foot bioelectrical impedance analysers to assess body composition in overweight and obese adolescents. Br J Nutr. 2003;90(5):987-992.
32. Lazzer S, Bedogni G, Agosti F, De Col A, Mornati D, Sartorio A. Comparison of dual-energy X-ray absorptiometry, air displacement plethysmography and bioelectrical impedance

analysis for the assessment of body composition in severely obese Caucasian children and adolescents. Br J Nutr. 2008;100(4):918-924.
33. Lu K, Quach B, Tong TK, Lau PWC. Validation of leg-to-leg bio-impedance analysis for assessing body composition in obese Chinese children. J Exerc Sci Fit. 2003;1(2):97-103.
34. Luque V, Escribano J, Zaragoza-Jordana M, et al. Bioimpedance in 7-year-old children: Validation by dual X-ray absorptiometry - Part 2: Assessment of segmental composition. Ann NutrMetab. 2014;64(2):144-155.
35. Luque V, Closa-Monasterolo R, Rubio-Torrents C, et al. Bioimpedance in 7-year-old children: Validation by dual X-Ray absorptiometry - Part 1: Assessment of whole body composition. Ann NutrMetab. 2014;64(2):113-121.
36. Lyra A, Bonfitto AJ, Barbosa VLP, et al. Comparison of methods for the measurement of body composition in overweight and obese Brazilian children and adolescents before and after a lifestyle modification program. Ann NutrMetab. 2015;66(1):26-30.
37. Meredith-Jones KA, Williams SM, Taylor RW. Bioelectrical impedance as a measure of change in body composition in young children. PediatrObes. 2015;10(4):252-259.
38. Mooney A, Kelsey L, Fellingham GW, et al. Assessing body composition of children and adolescents using dual-energy X-ray absorptiometry, skinfolds, and electrical impedance. Meas Phys Educ Exerc Sci. 2011;15(1):2-17.
39. Newton RL, Alfonso A, White MA, et al. Percent body fat measured by BIA and DEXA in obese, African-American adolescent girls. Int J Obes. 2005;29(6):594-602.
40. Ohta M, Midorikawa T, Hikihara Y, et al. Validity of segmental bioelectrical impedance analysis for estimating fat-free mass in children including overweight individuals. Appl PhysiolNutrMetab. 2017;42(2):157-165.
41. Pineau JC, Lalys L, Bocquet M, et al. Ultrasound measurement of total body fat in obese adolescents. Ann NutrMetab. 2010;56(1):36-44.
42. Radley D, Fields DA, Gately PJ. Validity of thoracic gas volume equations in children of varying body mass index classifications. Int J PediatrObes. 2007;2(3):180-187.
43. Radley D, Cooke C, Fuller N, et al. Validity of foot-to-foot bio-electrical impedance analysis body composition estimates in overweight and obese children. Int J Body Compos Res. 2009;7(1):15-20.

44. Raschpichler MC, Sorge I, Hirsch W, et al. Evaluating childhood obesity: Magnetic resonance-based quantification of abdominal adipose tissue and liver fat in children. FortschrRöntgenstr. 2012;184(4):324-332.
45. Resende C, Camelo Junior J, Vieira M, et al. Body composition in obese adolescents: Deuterium oxide dilution method, bioelectrical impedance and predictive equations. CurrNutr Food Sci. 2013;9(10):73-81.
46. Rolland-Cachera MF, Brambilla P, Manzoni P, et al. Body composition assessed on the basis of arm circumference and triceps skinfold thickness: A new index validated in children by magnetic resonance imaging. Am J Clin Nutr. 1997;65(6):1709-1713.
47. Samouda H, De Beaufort C, Stranges S, et al. Subtraction of subcutaneous fat to improve the prediction of visceral adiposity: exploring a new anthropometric track in overweight and obese youth. Pediatr Diabetes. 2017;18(5):399-404.
48. Seo YG, Kim JH, Kim YM, et al. Validation of body composition using bioelectrical impedance analysis in children according to the degree of obesity. Scand J Med Sci Sport. 2018;28(10):2207-2215.
49. Shaikh MG, Crabtree NJ, Shaw NJ, Kirk JMW. Body fat estimation using bioelectrical impedance. Horm Res. 2007;68(1):8-10.
50. Shypailo RJ, Butte NF, Ellis KJ. DXA: Can it be used as a criterion reference for body fat measurements in children. Obesity. 2008;16(2):457-462.
51. Springer F, Ehehalt S, Sommer J, et al. Predicting volumes of metabolically important whole-body adipose tissue compartments in overweight and obese adolescents by different MRI approaches and anthropometry. Eur J Radiol. 2012;81(7):1488-1494.
52. Steinberg A, Manlhiot C, Li P, et al. Development and validation of bioelectrical impedance analysis equations in adolescents with severe obesity. J Nutr. 2019;149(7):1288-1293.
53. Stevens J, Cai J, Truesdale K, Cuttler L, Robinson T, Roberts A. Percent body fat prediction equations for 8-to 17-year-old American children. PediatrObes. 2014;9(4):260-271.
54. Thivel D, O'Malley G, Pereira B, Duché P, Aucouturier J. Comparison of total body and abdominal adiposity indexes to dual x-ray absorptiometry scan in obese adolescents. Am J Hum Biol. 2015;27(3):334-338.

55. Thivel D, Verney J, Miguet M, et al. The accuracy of bioelectrical impedance to track body composition changes depends on the degree of obesity in adolescents with obesity. Nutr Res. 2018;54:60-68.
56. Tsang TW, Briody J, Kohn M, Chin MC, Singh MF. Abdominal fat assessment in adolescents using dual-energy X-ray absorptiometry. J Pediatr Endocrinol Metab. 2009;22(9):781-794.
57. Vásquez F, Salazar G, Díaz E, Lera L, Anziani A, Burrows R. Comparison of body fat calculations by sex and puberty status in obese schoolchildren using two and four compartment body composition models. Nutr Hosp. 2016;33(5):1116-1122.
58. Verney J, Metz L, Chaplais E, Cardenoux C, Pereira B, Thivel D. Bioelectrical impedance is an accurate method to assess body composition in obese but not severely obese adolescents. Nutr Res. 2016;36(7):663-670.
59. Wabitsch M, Braun U, Heinze E, et al. Body composition in 5-18-y-old obese children and adolescents before and after weight reduction as assessed by deuterium dilution and bioelectrical impedance analysis. Am J Clin Nutr. 1996;64(1):1-6.
60. Watts K, Naylor L, Davis E, et al. Do skinfolds accurately assess changes in body fat in obese children and adolescents? Med Sci Sport Exerc. 2006;38(3):439-470.
61. Wells JCK, Haroun D, Williams JE, et al. Evaluation of DXA against the four-component model of body composition in obese children and adolescents aged 5-21 years. Int J Obes. 2010;34(4):649-655.
62. Wells JCK, Haroun D, Williams JE, et al. Evaluation of lean tissue density for use in air displacement plethysmography in obese children and adolescents. Eur J Clin Nutr. 2011;65(10):1094-1101.
63. Williams JE, Wells JCK, Wilson CM, Haroun D, Lucas A, Fewtrell MS. Evaluation of Lunar Prodigy dual-energy X-ray absorptiometry for assessing body composition in healthy persons and patients by comparison with the criterion 4-component model. Am J Clin Nutr. 2006;83(5):1047-1054.
64. Wohlfahrt-Veje C, Tinggaard J, Winther K, et al. Body fat throughout childhood in 2647 healthy Danish children: Agreement of BMI, waist circumference, skinfolds with dual X-ray absorptiometry. Eur J Clin Nutr. 2014;68(6):664-670.

65. Woolcott OO, Bergman RN. Relative Fat Mass as an estimator of whole-body fat percentage among children and adolescents: A cross-sectional study using NHANES. Sci Rep. 2019;9(1):1-14.
66. Wosje KS, Knipstein BL, Kalkwarf HJ. Measurement error of DXA: Interpretation of fat and lean mass changes in obese and non-obese children. J Clin Densitom. 2006;9(3):335-340.
67. Slaughter AMH, Lohman TG, Boileau RA, et al. Skinfold equations for estimation of body fatness in children and youth. Hum Biol. 1998;60(5):709-723.
68. Huang TTK, Watkins MP, Goran MI. Predicting total body fat from anthropometry in Latino children. Obes Res. 2003;11(10):1192-1199.
69. Ramírez E, Valencia ME, Bourges H, et al. Body composition prediction equations based on deuterium oxide dilution method in Mexican children: a national study. Eur J Clin Nutr. 2012;66(10):1099-1103.
70. Durnin JVGA, Rahaman MM. The assessment of the amount of fat in the human body from measurements of skinfold thickness. Br J Nutr. 1967;21(3):681-689.
71. Lohman TG. Applicability of body composition techniques and constants for children and youths. In: Pandolf KB, ed. Exercise and Sport Sciences Reviews. New York: Macmillan; 1986:325-357.
72. Dezenberg C V., Nagy TR, Gower BA, Johnson R, Goran MI. Predicting body composition from anthropometry in pre-adolescent children. Int J Obes. 1999;23(3):253-259.
73. Jackson A, Pollock M. Practical assessment of body composition. Physician Sport Med. 1985;13:76–90.
74. Brozek J, Grande F, Anderson JT, Keys A. Densitometric analysis of body composition: revision of some quantitative assumptions. Ann N Y Acad Sci. 1953;110(1):113-140.
75. Bray GA, DeLany JP, Harsha DW, Volaufova J, Champagne CC. Evaluation of body fat in fatter and leaner 10-y-old African American and white children: The Baton Rouge children's study. Am J Clin Nutr. 2001;73(4):687-702.
76. Davies P, Preece MA, Hicks CJ, Halliday D. The prediction of total body water using bioelectrical impedance in children and adolescents. Ann Hum Biol. 1988;15(3):237-240.
77. Deurenberg P, Kusters C, Smit H. Assessment of body composition by bioelectrical impedance in children and young adults is strongly age dependent. Eur J Clin Nutr. 1990;44:261-268.

78. Deurenberg P, van der Kooy K, Leenen R, Weststrate J, Seidell J. Sex and age specific prediction formulas for estimating body composition from bioelectrical impedance: a cross-validation study. Int J Obes. 1991;15:17-25.
79. Gray D, Bray G, Gemayel N, Kaplan K. Effect of obesity on bioelectrical impedance. Am J Clin Nutr. 1989;50:225-260.
80. Goran MI, Kaskoun MC, Carpenter WH, Poehlman ET, Ravussin E, Fontvieille AM. Estimating body composition of young children by using bioelectrical resistance. J Appl Physiol. 1993;75(4):1776-1780.
81. Horie LM, Gonzalez Barbosa-Silva MC, Torrinhas RS, Túlio de Mello M, Cecconello I, Waitzberg DL. New body fat prediction equations for severely obese patients. Clin Nutr. 2008;27(3):350-356.
82. Houtkooper LB, Going SB, Lohman TG, Roche AF, Van Loan M. Bioelectrical impedance estimation of fat-free body mass in children and youth: a cross-validation study. J Appl Physiol. 1992;72(1):366-373.
83. Kushner R, Schoeller D, Fjeld C, Danford L. Is the impedance index (ht2/R) significant in predicting total body water? Am J Clin Nutr. 1992;56:835-839.
84. Kyle U, Genton L, Karsegard L, Slosman D, Pichard C. Single prediction equation for bioelectrical impedance analysis in adults aged 22-94 years. Nutrition. 2001;17(3):248-253.
85. Lazzer S, Boirie Y, Meyer M, Vermorel M. [Which alternative method to dual-energy X-ray absorptiometry for assessing body composition in overweight and obese adolescents?]. Arch Pediatr. 2005;12(7):1094-1101.
86. Lewy V, Danadian K, Arslanian S. Determination of body composition in African-American children: validation of bioelectrical impedence with dual energy X-ray absorptiometry. J Pediatr Endocrinol Metab. 1999;12(3):443-448.
87. Lukaski HC, Bolonchuk WW, Hall CB, Siders WA. Validation of tetrapolar bioelectrical impedance method to assess human body composition. J Appl Physiol. 1986;60(4):1327-1332.
88. Schaefer F, Georgi M, Zieger A, Schärer K. Usefulness of bioelectric impedance and skinfold measurements in predicting fat-free mass derived from total body potassium in children. Pediatr Res. 1994;35(5):617-624.

89. Sun SS, Chumlea WC, Heymsfield SB, et al. Development of bioelectrical impedance analysis prediction equations for body composition with the use of a multicomponent model for use in epidemiologic surveys. Am J Clin Nutr. 2003;77(2):331-340.
90. Suprasongsin C, Kalhan S, Arslanian S. Determination of body composition in children and adolescents: validation of bioelectrical impedance with isotope dilution technique. J Pediatr Endocr Met. 1995;8:103-109.

Appendix B Supporting Information of Chapter 4

Table B1 Comparison of body composition, muscular strength, lifestyle, and metabolic markers between sexual maturation groups, stratified by sex.

	Males					Females				
	Pre-early puberty		Mid-late puberty		p-value*	Pre-early puberty		Mid-late puberty		p-value*
	n	Median (IQR)	n	Median (IQR)		n	Median (IQR)	n	Median (IQR)	
Air-displacement plethysmography										
FM (kg)	6	30.8 (24.1-34.4)	9	52.8 (26.5-60.0)	0.224	8	21.6 (20.8-25.6)	8	39.6 (28.3-65.5)	**0.003**
%BF (%)	6	42.1 (40.5-44.9)	9	45.1 (34.3-49.8)	1.000	8	37.7 (30.7-43.5)	8	43.8 (40.1-52.7)	**0.038**
FMI (kg/m^2)	6	12.6 (11.4-14.2)	9	17.2 (9.3-20.3)	0.776	8	9.2 (8.6-11.7)	8	14.0 (11.4-23.7)	**0.010**
FFM (kg)	6	40.0 (34.6-44.7)	9	59.9 (50.6-64.1)	**0.008**	8	36.1 (33.5-43.4)	8	52.7 (39.6-60.0)	**0.015**
FFMI (kg/m^2)	6	16.7 (16.1-18.1)	9	20.0 (18.2-20.9)	**0.026**	8	15.7 (15.2-18.6)	8	19.2 (15.8-21.4)	0.083
LCI by ADP	6	0.73 (0.68-0.82)	9	0.82 (0.52-0.99)	1.000	8	0.61 (0.44-0.77)	8	0.78 (0.67-1.12)	**0.038**
Ultrasound										
SAT (cm)	6	2.0 (1.2-2.3)	5	2.8 (1.5-3.2)	0.247	6	1.9 (1.7-2.2)	8	2.3 (1.9-3.6)	0.108
SAT/ thigh length (cm)	6	0.05 (0.03-0.06)	5	0.06 (0.04-0.07)	0.537	6	0.05 (0.04-0.06)	8	0.05 (0.05-0.09)	0.662
SM (cm)	6	3.9 (3.6-4.2)	5	4.0 (3.4-4.3)	1.000	6	3.8 (3.3-4.2)	7	3.7 (3.7-4.5)	0.534
SM/leg length (cm)	6	0.11 (0.09-0.12)	5	0.09 (0.08-0.10)	0.126	6	0.10 (0.09-0.11)	7	0.09 (0.08-0.10)	0.628
mCSA (cm^2)	6	9.4 (7.9-12.0)	5	14.0 (8.7-16.1)	0.177	6	8.3 (7.5-9.3)	8	11.6 (9.3-16.3)	**0.005**
mEI	6	166.7 (134.7-182.2)	4	174.5 (136.7-220.6)	0.476	6	151.2 (139.2-170.2)	8	169.3 (160.1-233.2)	0.081
LCI by US	6	0.48 (0.29-0.65)	5	0.68 (0.42-0.81)	0.247	6	0.48 (0.45-0.57)	7	0.55 (0.44-0.71)	0.628
Muscular strength										
Right HGS (kg)	6	23 (18-27)	9	**30 (26-37)†**	0.066	8	21 (18-24)	8	24 (19-27)	0.279
Left HGS (kg)	6	20 (18-23)	9	**32 (22-37)†**	**0.050**	8	18 (16-20)	8	21 (15-25)	0.505
Physical activity										
Sedentary time (min/day)	6	562.4 (472.5-614.2)	9	667.9 (540.0-723.6)	0.113	8	557.7 (473.3-658.6)	8	670.2 (628.3-699.2)	0.083
Light intensity (min/day)	6	178.5 (152.6-223.0)	9	135.8 (90.3-180.9)	0.088	8	183.3 (127.6-249.8)	8	121.0 (93.5-147.2)	**0.050**
MVPA (min/day)	6	48.6 (43.7-57.2)	9	50.4 (33.3-55.3)	1.000	8	34.3 (17.9-57.7)	8	30.1 (22.8-34.0)	0.574
Dietary intake										

	Males					Females				
	Pre-early puberty		Mid-late puberty		p-value*	Pre-early puberty		Mid-late puberty		p-value*
	n	Median (IQR)	n	Median (IQR)		n	Median (IQR)	n	Median (IQR)	
TEI (kcal/day)	5	1933 (1702-2012)	9	1848 (1519-2318)	0.699	8	1853 (1517-2491)	8	1796 (970-2129)	0.645
Fat (g/1,000 kcal)	5	39.5 (37.1-41.2)	9	35.8 (30.4-43.7)	0.190	8	39.8 (36.5-43.8)	8	38.0 (26.7-44.5)	0.442
Protein (g/1,000 kcal)	5	46.2 (41.7-58.8)	9	42.3 (37.5-47.6)	0.147	8	41.3 (37.2-42.7)	8	44.5 (40.7-50.6)	0.195
CHO (g/1,000 kcal)	5	116.9 (103.9-127.1)	9	128.1 (106.6-141.3)	0.438	8	127.2 (113.3-133.8)	8	123.6 (98.9-160.3)	0.878
Fiber (g/1,000 kcal)	5	9.1 (7.6-10.5)	9	7.8 (7.2-11.2)	0.606	8	10.3 (7.7-12.0)	8	8.3 (7.8-11.0)	0.234
Metabolic markers										
Glucose (mg/dL)	6	87.3 (81.0-92.7)	9	91.8 (88.2-93.6)	0.388	6	87.3 (84.6-88.7)	7	90.0 (86.4-90.0)	0.234
Insulin (pmol/L)	6	82.6 (60.6-122.9)	9	116.0 (88.9-147.6)	0.328	8	103.8 (68.2-120.0)	8	160.1 (133.3-210.6)	**0.010**
HOMA-IR	6	2.59 (1.79-3.78)	9	3.78 (2.84-4.90)	0.181	6	3.16 (2.02-3.95)	7	5.67 (4.18-7.09)	0.035
HDL-C (mg/dL)	6	42.7 (39.9-46.8)	9	39.4 (32.7-44.7)	0.145	6	41.0 (36.6-55.8)	7	40.6 (38.3-54.1)	0.945
LDL-C (mg/dL)	6	94.0 (75.6-124.6)	9	85.5 (65.7-100.7)	0.328	6	88.7 (71.6-115.4)	7	92.8 (82.4-98.2)	1.000
TG (mg/dL)	6	1.9 (1.8-2)	9	2.1 (1.9-2.1)	0.181	6	2 (1.9-2.1)	7	2.1 (2-2.2)	0.181
hs-CRP (mg/dL)	5	3.5 (1.3-7.5)	7	1.8 (0.8-7.4)	0.530	6	1.9 (1.1-5.2)	5	13.9 (1.5-18.3)	0.247
TNF-α (pg/mL)	5	43.0 (27.5-67.1)	7	10.6 (1.8-30.3)	**0.048**	8	7.4 (1.0-84.6)	8	15.5 (1.0-34.5)	0.721
IL-6 (pg/mL)	5	9.6 (7.0-30.6)	7	9.3 (4.7-35.1)	0.876	8	27.3 (3.2-89.2)	8	9.4 (5.3-19)	0.645
SBP (mmHg)	6	117 (111-127)	9	121 (115-130)	0.328	8	119 (109-132)	8	121 (115-130)	1.000
SBP percentile	6	90 (77-94)	9	92 (59-96)	1.000	8	91 (70-99)	8	88 (79-98)	0.721
DBP (mmHg)	6	65 (54-80)	9	70 (62-75)	0.607	8	68 (57-77)	8	75 (70-90)	0.161
DBP percentile	6	57 (24-89)	9	74 (31-81)	0.864	8	82 (55-98)	8	85 (72-96)	0.798

Abbreviations: %BF, percent body fat; CHO, carbohydrate; ADP, air-displacement plethysmography; DBP, diastolic blood pressure; FFM, fat-free mass; FFMI, fat-free mass index; FM, fat mass; FMI, fat mass index; HDL-C, high-density lipoprotein cholesterol; HGS, handgrip strength; HOMA-IR, homeostatic model assessment of insulin resistance; hs-CRP, high sensitivity c-reactive protein; IL-6, interleukin-6; IQR, interquartile range; LCI, load-capacity index; LDL-C, low-density lipoprotein cholesterol; mCSA, muscle cross-sectional area; mEI, muscle echo intensity; MVPA, moderate-to-vigorous physical activity; n, number of participants included in the analysis; SAT, subcutaneous adipose tissue; SBP, systolic blood pressure; SM, skeletal muscle; TEI, total energy intake; TG, triglycerides; TNF-α, tumor necrosis factor alpha; US, ultrasound.

* Statistically significant difference between sexual maturation stages within sex group by Mann-Whitney U test, $p<0.05$.

† Statistically significant difference between males and females within sexual maturation stage group by Mann-Whitney U test, $p<0.05$.

Table B2 Comparison of body composition, muscular strength, lifestyle, and inflammatory markers between children with insulin resistance versus without, stratified by sex.

	Overall Sample					With IR				Without IR			
	With IR		Without IR		p-value	Male		Female		Male		Female	
	n	Median (IQR)	n	Median (IQR)		n	Median (IQR)	n	Median (IQR)	n	Median (IQR)	n	Median (IQR)
Air-displacement plethysmography													
FM (kg)	17	37.2 (25.5-58.5)	11	26.5 (23-34.2)	0.066	8	43.8 (27.7-58.5)	9	37.2 (22.4-61.3)	7	27.5 (24.5-34.3)	4	24.7 (22.1-26.9)
%BF (%)	17	45.1 (38.3-49.8)	11	40.6 (38.9-44.3)	0.264	8	44.7 (36.6-48.5)	9	45.3 (38.3-51.9)	7	40.6 (36.9-46.7)	4	40 (38.9-43.5)
FMI (kg/m^2)	17	14.5 (10.4-19.2)	11	11.2 (9.5-13.6)	0.147	8	15.7 (10.9-19.3)	9	14.5 (9.7-22.0)	7	11.4 (9.5-14.2)	4	10.8 (9.6-11.8)
FFM (kg)	17	**52.3 (40.2-62.3)**	11	39.1 (33.3-48.0)	**0.013**	8	60.5 (45.8-64.2)	9	**48.2 (38.0-59.6)***	7	40.9 (35.8-49.0)	4	33.8 (33.2-40.2)
FFMI (kg/m^2)	17	**19.7 (16.5-20.9)**	11	16.7 (15.2-18.5)	**0.019**	8	20.1 (17.8-20.9)	9	18.5 (15.7-20.9)	7	16.8 (16.2-19.1)	4	15.3 (14.7-16.8)
LCI by ADP	17	0.82 (0.62-0.99)	11	0.68 (0.64-0.80)	0.264	8	0.81 (0.58-0.94)	9	0.83 (0.62-1.08)	7	0.68 (0.59-0.88)	4	0.67 (0.64-0.77)
Ultrasound													
SAT (cm)	12	2.3 (1.8-2.9)	11	1.9 (1.7-2.2)	0.190	4	2.4 (1.4-2.9)	8	2.3 (1.9-3.6)	7	2 (1.2-2.5)	4	1.9 (1.7-2.0)
SAT/thigh length	12	0.06 (0.05-0.07)	11	0.05 (0.04-0.06)	0.190	4	0.06 (0.04-0.07)	8	0.05 (0.05-0.09)	7	0.05 (0.03-0.06)	4	0.05 (0.04-0.05)
SM (cm)	11	3.7 (3.7-4.1)	11	3.9 (3.3-4.3)	0.898	4	4 (3.7-4.3)	7	3.7 (3.6-4.1)	7	3.8 (3.3-4.3)	4	4 (3.3-4.4)
SM/thigh length	11	0.09 (0.09-0.10)	11	0.10 (0.09-0.11)	1.000	4	0.10 (0.09-0.12)	7	0.09 (0.08-0.10)	7	0.09 (0.09-0.11)	4	0.10 (0.09-0.11)
mCSA (cm^2)	12	11.4 (9.1-13.8)	11	8.6 (8.0-11.8)	0.235	4	12.7 (8.0-13.8)	8	10.4 (9.1-15.4)	7	10.3 (8.3-14.5)	4	8.3 (7.8-11.0)
mEI	11	169.0 (163.2-209.2)	11	148.6 (139.7-177.9)	0.401	3	135.2-209.2†	8	169.3 (164.6-233.2)	7	170.1 (135.7-201.8)	4	148.6 (142.0-170.5)
LCI by US	11	0.55 (0.45-0.70)	11	0.44 (0.42-0.66)	0.193	4	0.60 (0.36-0.69)	7	0.55 (0.45-0.71)	7	0.44 (0.41-0.66)	4	0.45 (0.43-0.62)
Muscular strength													
Right HGS (kg)	17	24 (22-32)	11	20 (18-30)	0.306	8	29 (20-36)	9	**24 (22-28)***	7	**26 (20-30)**‡	4	18 (18-19.5)
Left HGS (kg)	17	24 (19-31.5)	11	19 (16-22)	0.073	8	29 (19.5-35.5)	9	**22 (19-25)***	7	20 (19-26)	4	16 (15-18)
Physical activity													

	Overall Sample					With IR				Without IR			
	With IR		Without IR		p-value	Male		Female		Male		Female	
	n	Median (IQR)	n	Median (IQR)		n	Median (IQR)	n	Median (IQR)	n	Median (IQR)	n	Median (IQR)
Sedentary time (min/day)	17	**667.9 (598.9-709.9)**	11	537.2 (488.1-628.3)	**0.029**	8	670.4 (562.6-725.2)	9	645.1 (606.3-699.0)	7	537.2 (488.1-589.9)	4	611.3 (480.9-745.2)
Light intensity (min/day)	17	122.5 (90.3-166.2)	11	171.4 (161.4-200.0)	0.053	8	117.3 (90.1-185.8)	9	129.5 (99.7-166.2)	7	171.4 (161.7-200.0)	4	163.6 (98.2-214.5)
MVPA (min/day)	17	34.2 (24.7-52.7)	11	44.9 (31.9-52.8)	0.458	8	48.6 (30.1-53.9)	9	28.5 (18.0-45.8)	7	**48.9 (44.9-59.4)**‡	4	31.8 (14.8-37.6)
Dietary intake													
TEI (kcal/day)	17	1731 (1349-2119)	10	1957 (1797-2249)	0.243	8	1812 (1381-1985)	9	1706 (1065-2210)	6	1927 (1797-2171)	4	2017 (1638-2491)
Fat (g/1,000 kcal)	17	35.9 (32.3-42.1)	10	39.8 (35.8-43.4)	0.243	8	35.9 (31.0-40.6)	9	36.2 (32.7-43.9)	6	38.6 (35.8-42.9)	4	41.7 (29.3-43.8)
Protein (g/1,000 kcal)	17	43.4 (40.2-47.8)	10	41.3 (34.7-47.9)	0.286	8	44.5 (40.0-48.7)	9	42.0 (40.2-48.2)	6	43.9 (36.9-55.7)	4	36.5 (27.0-41.3)
CHO (g/1,000 kcal)	17	129.0 (108.4-135.9)	10	115.3 (110.2-135.0)	0.675	8	126.2 (108.6-135.4)	9	132.4 (103.6-135.9)	6	114.6 (103.2-134.4)	4	122.7 (113.3-159.0)
Fiber (g/1,000 kcal)	17	9.1 (7.7-11.5)	10	8.7 (7.4-10.2)	0.639	8	9.3 (7.4-12.5)	9	8.5 (7.9-11.5)	6	8.2 (6.2-9.1)	4	10.4 (8.4-12.)
Inflammatory markers													
IL-6 (pg/mL)	15	9.3 (6.1-20.6)	10	21.4 (8.5-58.6)	0.103	6	9.5 (4.5-43.3)	9	9.3 (6.7-17.5)	6	13.5 (7.4-25.8)	4	**71.8 (27.6-117.9)*** ‡
TNF-α (pg/mL)	15	24.4 (1.8-42.2)	10	27.5 (4.5-86.9)	0.428	6	20.5 (1.6-45.4)	9	24.4 (3.9-38.8)	6	27.5 (14.5-59.2)	4	49.8 (1.0-103.9)
CRP (mg/L)	13	2.0 (1.5-11.8)	10	2.8 (1.0-5.5)	0.563	5	2.1 (1.2-8.6)	8	1.9 (1.3-15)	7	2.0 (0.8-5.3)	3	1.3-5.9†

Abbreviations: %BF, percent body fat; CHO, carbohydrate; ADP, air-displacement plethysmography; FFM, fat-free mass; FFMI, fat-free mass index; FM, fat mass; FMI, fat mass index; HGS, handgrip strength; hs-CRP, high sensitivity c-reactive protein; IL-6, interleukin-6; IQR, interquartile range; IR, insulin resistance; LCI, load-capacity index; mCSA, muscle cross-sectional area; mEI, muscle echo intensity; MVPA, moderate-to-vigorous physical activity; n, number of participants included in the analysis; SAT, subcutaneous adipose tissue; SM, skeletal muscle; TEI, total energy intake; TNF-α, tumor necrosis factor alpha; US, ultrasound.

***** Statistically significant difference between insulin resistance status within sex group by Mann-Whitney U test, $p < 0.05$.

† Variable is expressed using range (minimum – maximum).

‡ Statistically significant difference between males and females within insulin resistance group by Mann-Whitney U test, $p < 0.05$.

Table B3 Comparison of body composition, muscular strength, and lifestyle characteristics between children with dyslipidemia versus without, stratified by sex.

	Overall sample					Children with dyslipidemia				Children without dyslipidemia			
	With dyslipidemia		Without dyslipidemia		p-value	Males		Females		Males		Females	
	n	Median (IQR)	n	Median (IQR)		n	Median (IQR)	n	Median (IQR)	n	Median (IQR)	n	Median (IQR)
Air-displacement plethysmography													
FM (kg)	16	30.0 (23.5-57.1)	13	34.2 (24.0-36.7)	0.779	9	27.8 (24.0-60.0)	7	32.1 (23.0-52.8)	6	34.2 (26.9-40.6)	7	27.0 (21.8-37.2)
%BF (%)	16	43.4 (37.7-49.9)	13	40.6 (39.0-46.3)	0.531	9	42.5 (35.5-49.8)	7	44.3 (40.9-50.3)	6	43.0 (39.1-46.0)	7	40.0 (38.9-47.2)
FMI (kg/m^2)	16	12.4 (9.8-18.6)	13	13.5 (10.4-14.7)	0.914	9	11.7 (9.3-18.9)	7	12.7 (10.7-18.7)	6	13.9 (11.2-15.9)	7	11.0 (9.3-15.2)
FFM (kg)	16	50.6 (34.7-60.8)	13	42.2 (36.5-52.7)	0.589	9	56.2 (36.6-62.6)	7	48.2 (33.3-58.6)	6	45.8 (38.3-56.5)	7	41.6 (35.2-53.1)
FFMI (kg/m^2)	16	18.5 (15.5-20.1)	13	17.2 (16.1-19.9)	0.914	9	18.5 (16.2-20.4)	7	18.5 (15.4-19.8)	6	18.4 (16.6-21.2)	7	17.0 (15.3-19.8)
LCI by ADP	16	0.77 (0.61-1.00)	13	0.68 (0.64-0.86)	0.559	9	0.74 (0.55-0.99)	7	0.80 (0.69-1.01)	6	0.75 (0.64-0.85)	7	0.67 (0.64-0.90)
Ultrasound													
SAT (cm)	13	2.1 (1.8-2.9)	11	2.0 (1.8-2.5)	0.649	7	1.9 (1.2-3.0)	6	2.1 (2.0-3.2)	4	2.1 (1.4-2.4)	7	1.9 (1.8-2.5)
SAT/thigh length	13	0.06 (0.04-0.07)	11	0.05 (0.04-0.06)	0.691	7	0.06 (0.03-0.07)	6	0.05 (0.05-0.07)	4	0.05 (0.04-0.06)	7	0.05 (0.04-0.06)
SM (cm)	13	3.7 (3.6-4.0)	10	4.1 (3.7-4.6)	0.067	7	4.0 (3.7-4.3)	6	3.7 (3.5-3.8)	4	3.9 (3.4-4.4)	6	**4.3 (3.9-4.7)**[†]
SM/thigh length	13	0.09 (0.08-0.1)	10	0.1 (0.09-0.12)	0.067	7	0.10 (0.09-0.11)	6	0.05 (0.05-0.07)	4	0.10 (0.09-0.12)	6	**0.10 (0.10-0.12)**[†]
mCSA (cm^2)	13	10.3 (7.9-14.3)	11	11.3 (8.5-13.0)	0.910	7	12.3 (6.5-14.5)	6	9.4 (7.9-13.9)	4	10.1 (8.4-12.7)	7	11.3 (8.6-14.9)
mEI	12	166.6 (141.9-202.8)	11	167.7 (139.8-175.7)	0.695	6	151.4 (135.1-213.0)	6	173.7 (159.9-206.2)	4	172.9 (143.9-195.3)	7	159.0 (139.8-169.0)
LCI by US	13	0.57 (0.43-0.70)	10	0.45 (0.43-0.56)	0.691	7	0.53 (0.41-0.70)	6	**0.62 (0.52-0.87)**[†]	4	0.54 (0.33-0.66)	6	0.45 (0.43-0.51)
Muscular strength													
Right HGS (kg)	16	25.0 (19.0-33.8)	13	22.0 (19.0-27.5)	0.308	9	30.0 (20.0-37.0)	7	24.0 (18.0-28.0)	6	27.0 (19.5-30.0)	7	20.0 (18.0-24.0)

	Overall sample					Children with dyslipidemia				Children without dyslipidemia			
	With dyslipidemia		Without dyslipidemia		p-value	Males		Females		Males		Females	
	n	Median (IQR)	n	Median (IQR)		n	Median (IQR)	n	Median (IQR)	n	Median (IQR)	n	Median (IQR)
Left HGS (kg)	16	22.0 (18.0-31.8)	13	20.0 (16.0-25.0)	0.351	9	24.0 (18.5-35.0)	7	22.0 (16.0-26.0)	6	24.0 (19.0-30.1)	7	18.0 (14.0-20.0)
Physical activity													
Sedentary time (min/day)	16	589.1 (534.1-715.2)	13	639.8 (598.6-684.1)	0.559	9	546.9 (510.6-694.2)	7	624.5 (547.3-740.5)	6	618.9 (559.5-686.3)	7	645.1 (629.6-695.4)
Light intensity (min/day)	16	145.4 (88.2-186.3)	13	151.0 (114.2-194.0)	0.398	9	161.4 (90.3-185.7)	7	129.5 (85.9-191.3)	6	174.1 (129.9-223.0)	7	135.9 (112.5-163.0)
MVPA (min/day)	16	48.5 (24.1-55.4)	13	39.6 (28.4-46.6)	0.531	9	49.1 (37.5-55.3)	7	31.9 (13.8-57.4)	6	**46.6 (40.0-58.2)***	7	28.5 (26.3-33.3)
Dietary intake													
TEI (kcal/day)	16	1870 (1617-2120)	12	1855 (1402-2109)	0.802	9	1892 (1755-2320)	7	1665 (1391-2127)	5	1803 (1275-1975)	7	1908 (1685-2613)
Protein (g/1,000 kcal)	16	42.0 (37.9-45.9)	12	43.9 (39.7-53.0)	0.423	9	42.3 (36.5-47.8)	7	41.4 (40.1-45.2)	5	46.2 (42.4-58.8)	7	41.5 (36.2-49.1)
Fat (g/1,000 kcal)	16	36.5 (32.1-42.5)	12	39.8 (36.0-42.3)	0.507	9	37.0 (33.1-43.7)	7	35.9 (29.8-43.2)	5	39.5 (25.9-41.2)	7	40.1 (36.2-44.0)
CHO (g/1,000 kcal)	16	129.7 (112.6-136.2)	12	116.8 (106.2-134.3)	0.599	9	128.1 (106.6-134.2)	7	131.7 (113.6-136.8)	5	116.9 (103.9-151.1)	7	116.7 (113.0-134.9)
Fiber (g/1,000 kcal)	16	8.7 (7.3-11.2)	12	9.0 (8.0-11.7)	0.580	9	7.8 (6.8-10.4)	7	10.6 (8.3-12.1)	5	9.1 (8.1-11.3)	7	8.5 (7.9-11.8)

Abbreviations: %BF, percent body fat; CHO, carbohydrate; ADP, air-displacement plethysmography; FFM, fat-free mass; FFMI, fat-free mass index; FM, fat mass; FMI, fat mass index; HGS, handgrip strength; IQR, interquartile range; LCI, load-capacity index; mCSA, muscle cross-sectional area; mEI, muscle echo intensity; MVPA, moderate-to-vigorous physical activity; n, number of participants included in the analysis; SAT, subcutaneous adipose tissue; SM, skeleta1 muscle; TEI, total energy intake; US, ultrasound.

* Statistically significant difference between males and females within dyslipidemia group by Mann-Whitney U test, $p < 0.05$

† Statistically significant difference between dyslipidemia status within sex group by Mann-Whitney U test, $p < 0.05$.

Table B4 Comparison of body composition, muscular strength, and lifestyle characteristics between children with versus without hypertension, stratified by sex.

	Overall sample					Children with hypertension				Children without hypertension			
	With hypertension		Without hypertension		p-value	Males		Females		Males		Females	
	n	Median (IQR)	n	Median (IQR)		n	Median (IQR)	n	Median (IQR)	n	Median (IQR)	n	Median (IQR)
Air-displacement plethysmography													
FM (kg)	12	36.7 (20.9-65.5)	19	27.6 (23.4-34.7)	0.617	3	24.5-67.8†	9	36.2 (20.8-56.3)	12	31.0 (25.8-48.3)	7	26.5 (23.0-32.1)
%BF (%)	12	41.5 (33.2-51.9)	19	41.6 (38.9-45.3)	0.889	3	40.6-54.7†	9	40.5 (31.2-50.4)	12	42.1 (35.2-46.3)	7	40.9 (39.0-45.3)
FMI (kg/m^2)	12	14.0 (9.1-23.3)	19	11.7 (10.2-14.2)	0.484	3	11.4-24.1†	9	13.5 (8.8-20.3)	12	12.6 (9.8-16.5)	7	11.0 (10.2-12.7)
FFM (kg)	12	50.6 (38.3-60.0)	19	42.2 (34.3-52.3)	0.205	3	35.8-69.2†	9	**48.2 (39.4-59.6)‡**	12	48.5 (39.6-60.8)	7	35.2 (33.3-42.2)
FFMI (kg/m^2)	12	19.7 (16.8-21.4)	19	17.2 (15.4-19.1)	0.059	3	16.8-24.7†	9	**19.7 (16.5-20.9)‡**	12	**18.2 (16.3-20.1)***	7	15.4 (15.2-17.2)
LCI by ADP	12	0.71 (0.50-1.09)	19	0.71 (0.64-0.83)	0.889	3	0.68-1.21†	9	0.68 (0.45-1.02)	12	0.73 (0.54-0.86)	7	0.69 (0.64-0.83)
Ultrasound													
SAT (cm)	9	**2.5 (2-3.8)**	16	1.9 (1.7-2.4)	**0.049**	2	2.2-3.5†	7	2.5 (1.9-4.0)	9	1.9 (1.2-2.6)	7	1.9 (1.8-2.1)
SAT/ thigh length (cm)	9	0.06 (0.05-0.09)	16	0.05 (0.04-0.06)	0.065	2	0.06-0.08†	7	0.06 (0.05-0.10)	9	0.05 (0.03-0.06)	7	0.05 (0.04-0.06)
SM (cm)	8	3.7 (3.5-4.4)	16	4.0 (3.7-4.3)	0.569	2	3.3-3.8†	6	3.7 (3.6-4.7)	9	4.0 (3.7-4.3)	7	3.9 (3.6-4.1)
SM/leg length (cm)	8	0.09 (0.09-0.11)	16	0.10 (0.09-0.11)	0.350	2	0.09-0.09†	6	0.09 (0.08-0.12)	9	0.10 (0.09-0.11)	7	0.10 (0.08-010)
mCSA (cm^2)	9	11.3 (8.4-17.3)	16	9.8 (8.1-12.2)	0.276	2	8.3-17.8†	7	11.3 (8.5-16.7)	9	11.7 (7.5-13.5)	7	9.1 (8.0-11.4)
mEI	9	169.6 (156.4-237.0)	15	163.2 (139.7-177.9)	0.155	2	175.7-224.3†	7	167.7 (153.8-249.7)	8	151.4 (135.3-193.9)	7	163.6 (148.5-177.9)
LCI by US	8	0.54 (0.50-0.86)	16	0.45 (0.42-0.67)	0.106	2	0.66-0.92†	6	0.53 (0.49-0.75)	9	0.44 (0.36-0.66)	7	0.45 (0.44-0.68)
Muscular strength													
Right HGS (kg)	12	24 (21-28)	19	24 (18-30)	0.952	3	20-30†	9	24 (21-26)	12	28 (19.5-36)	7	18 (18-24)
Left HGS (kg)	12	20 (19-24)	19	22 (16-26)	0.984	3	20-43†	9	20 (17-23)	12	**25 (18.3-34)***	7	16 (14-22)
Physical activity													
Sedentary time (min/day)	12	606.3 (536.6-661.1)	19	628.3 (527.3-720.4)	0.484	3	533.1-672.8†	9	624.5 (522.0-654.0)	12	599.7 (500.4-707.3)	7	695.4 (527.3-740.5)

	Overall sample					Children with hypertension				Children without hypertension			
	With hypertension		Without hypertension		p-value	Males		Females		Males		Females	
	n	Median (IQR)	n	Median (IQR)		n	Median (IQR)	n	Median (IQR)	n	Median (IQR)	n	Median (IQR)
Light intensity (min/day)	12	166.2 (113.4-196.4)	19	151.0 (90.5-191.3)	0.459	3	135.8-200.0†	9	163.0 (112.4-217.2)	12	161.5 (95.9-194.8)	7	135.9 (85.9-191.3)
MVPA (min/day)	12	40.9 (26.8-58.9)	19	39.8 (28.5-49.1)	0.704	3	44.9-59.4†	9	33.3 (23.6-60.6)	12	**48.6 (39.9-54.5)***	7	31.7 (13.8-34.2)
Dietary intake													
TEI (kcal/day)	11	1685 (1391-2279)	19	1908 (1731-2097)	0.328	2	1243-2634†	9	1685 (1449-2140)	12	1870 (1743-2005)	7	2097 (1548-2140)
Fat (g/1,000 kcal)	11	37.3 (35.7-42.5)	19	37.8 (34.9-43.2)	0.933	2	15.8-31.2	9	**39.5 (36.1-45.6)***	12	**37.5 (35.9-41.5)**‡	7	40.2 (25.7-44.0)
Protein (g/1,000 kcal)	11	43.2 (39.2-51.1)	19	42.3 (40.3-46.2)	0.832	2	35.7-39.2†	9	43.8 (40.8-55.6)	12	**45.9 (41.8-52.3)***	7	41.1 (31.8-42.0)
CHO (g/1,000 kcal)	11	130.5 (94.2-134.9)	19	123.4 (112.3-131.7)	0.800	2	**145.1-177.8***,†,‡	9	122.6 (91.0-133.3)	12	120.2 (103.8-128.8)	7	131.7 (113.2-168.1)
Fiber (g/1,000 kcal)	11	8.5 (7.4-11.8)	19	8.9 (7.7-11.1)	0.899	2	7.8-12.9†	9	8.5 (7.2-11.7)	12	8.7 (7.2-9.6)	7	8.9 (8.3-11.9)

Abbreviations: %BF, percent body fat; CHO, carbohydrate; ADP, air-displacement plethysmography; FFM, fat-free mass; FFMI, fat-free mass index; FM, fat mass; FMI, fat mass index; HGS, handgrip strength; IQR, interquartile range; LCI, load-capacity index; mCSA, muscle cross-sectional area; mEI, muscle echo intensity; MVPA, moderate-to-vigorous physical activity; n, number of participants included in the analysis; SAT, subcutaneous adipose tissue; SM, skeletal muscle; TEI, total energy intake; US, ultrasound.

* Statistically significant difference between males and females within hypertension group by Mann-Whitney U test, $p < 0.05$

† Variable is expressed using range (minimum – maximum).

‡ Statistically significant difference between hypertension status within sex group by Mann-Whitney U test, $p < 0.05$.

Table B5 Comparison of body composition, muscular strength, and lifestyle characteristics between children with versus without metabolic syndrome as defined by IDF, stratified by sex.

	Overall sample					Children with MetS				Children without MetS			
	With MetS		Without MetS		p-value	Males		Females		Males		Females	
	n	Median (IQR)	n	Median (IQR)		n	Median (IQR)	n	Median (IQR)	n	Median (IQR)	n	Median (IQR)
Air-displacement plethysmography													
FM (kg)	4	**63.2 (46.9-72)**	20	27.2 (23.1-35.7)	**0.005**	2	58.6-67.8	2	42.9-73.4	9	18.9-61.5	11	21.4-69.8
%BF (%)	4	**51.5 (44.1-54.4)**	20	40.8 (38.9-46.4)	**0.023**	2	49.4-54.7	2	42.3-53.6	9	30.3-50.1	11	36.5-53.5
FMI (kg/m^2)	4	**21.9 (15.8-25)**	20	11.6 (9.7-14)	**0.007**	2	19.6-24.1	2	14.5-25.3	9	7.9-18.1	11	9.2-31
FFM (kg)	4	**59.3 (56.8-62.6)**	20	40 (34.5-51.4)	**0.018**	2	56.2-59.9	2	58.6-63.5	9	30.8-64	11	33.2-60.5
FFMI (kg/m^2)	4	**20 (19.9-21.5)**	20	16.7 (15.4-18.5)	**0.010**	2	20-20.1	2	19.8-21.9	9	13.6-20.7	11	14.6-26.9
LCI by ADP	4	**1.1 (0.8-1.2)**	20	0.7 (0.6-0.9)	**0.027**	2	1-1.2	2	0.7-1.2	9	0.4-1	11	0.6-1.2
Ultrasound													
SAT (cm)	4	**3.2 (2.3-4.7)**	19	2 (1.8-2.5)	**0.027**	2	3-3.5	2	2-5	8	1.2-2.8	11	1.6-4
SAT/ thigh length (cm)	4	0.07 (0.05-0.09)	19	0.05 (0.04-0.06)	0.054	2	0.07-0.08	2	0.05-01	8	0.03-0.06	11	0.04-0.14
SM (cm)	4	3.8 (3.7-4.2)	18	3.9 (3.6-4.3)	0.902	2	3.8-4.4	2	3.7-3.7	8	3-4.5	10	3-5
SM/leg length (cm)	4	0.09 (0.08-0.10)	18	0.1(0.09-0.11)	0.166	2	0.09-0.10	2	0.07-0.09	8	0.07-0.12	10	0.08-0.12
mCSA (cm^2)	4	**15.9 (10.6-20.4)**	19	9.3 (8.3-11.8)	**0.035**	2	14-17.8	2	9.4-21.3	8	5.2-14.5	11	7.8-16.7
mEI	3	169.6-224.3	19	163.6 (139.8-177.9)	0.053	1	224.3-224.3	2	169.6-273.9	8	133.2-209.2	11	137.6-249.7
LCI by US	4	**0.80 (0.58-1.25)**	18	0.48 (0.43-0.65)	**0.014**	2	0.68-0.92	2	0.55-1.36	8	0.28-0.70	10	0.42-0.71
Muscular strength													
Right HS	4	32 (26-34)	20	23 (18-28)	0.097	2	30-34	2	24-33	9	12-40	11	18-28
Left HS	4	27 (21-33)	20	20 (16-26)	0.157	2	20-34	2	22-31	9	15-38	11	14-26
Physical activity													
Sedentary time (min/day)	4	585.9 (536.6-657.1)	20	634.7 (529.7-699.2)	0.525	2	533.1-667.9	2	547.3-624.5	9	464.8-755.2	11	465.5-761.8
Light intensity (min/day)	4	130.0 (88.1-192.3)	20	143.5 (112.3-169.3)	0.970	2	90.5-200.0	2	87.3-169.4	9	87.6-284.5	11	85.6-222.3
MVPA (min/day)	4	42.1 (22.4-58.9)	20	33.7 (26.8-48.7)	0.682	2	26.8-59.4	2	21.0-57.4	9	**23.2-81.8***	11	9.2-39.6

	Overall sample					Children with MetS				Children without MetS			
	With MetS		Without MetS		p-value	Males		Females		Males		Females	
	n	Median (IQR)	n	Median (IQR)		n	Median (IQR)	n	Median (IQR)	n	Median (IQR)	n	Median (IQR)
Dietary intake													
Total energy intake (kcal/day)	4	2005 (1681-2545)	19	1892 (1685-2097)	0.611	2	1731-2634	2	1665-2279	8	1601-2017	11	713-2786
Fat intake (g/1,000 kcal)	4	33.6 (30-45.5)	19	39.5 (36.2-43.2)	0.366	2	29.6-31.2	2	35.9-48.7	8	34.9-53.2	11	17.4-45.2
Protein intake (g/1,000 kcal)	4	46.6 (37.7-50.7)	19	41.6 (37.2-46.2)	0.505	2	35.7-49.5	2	43.8-51.1	8	34.5-63.3	11	25.4-67.2
CHO intake (g/1,000 kcal)	4	129.7 (102.9-141.4)	19	116.9 (112.3-134.9)	0.907	2	129.0-145.1	2	94.2-130.5	8	97.9-137.5	11	87.7-175.8
Fiber intake (g/1,000 kcal)	4	7.5 (6.4-9.9)	19	8.9 (7.9-11.5)	0.138	2	7.2-7.8	2	6.1-10.6	8	5.9-15.7	11	7.8-12.1

Abbreviations: %BF, percent body fat; CHO, carbohydrate; ADP, air-displacement plethysmography; FFM, fat-free mass; FFMI, fat-free mass index; FM, fat mass; FMI, fat mass index; HGS, handgrip strength; IQR, interquartile range; LCI, load-capacity index; mCSA, muscle cross-sectional area; mEI, muscle echo intensity; MetS, metabolic syndrome; MVPA, moderate-to-vigorous physical activity; n, number of participants included in the analysis; SAT, subcutaneous adipose tissue; SM, skeletal muscle; TEI, total energy intake; US, ultrasound.

* Statistically significant difference between males and females within metabolic syndrome group by Mann-Whitney U test, $p < 0.05$

Table B6 Comparison of body composition, muscular strength, and lifestyle characteristics between children with metabolically unhealthy obesity (MUO) versus metabolically healthy obesity (MHO), stratified by sex.

	Overall sample					Children with MUO				Children with MHO			
	Children with MUO		Children with MHO		p-value*	Males		Females		Males		Females	
	n	Median (IQR)	n	median (IQR)		n	Range	n	Range	n	Range	n	Range
Air-displacement plethysmography													
FM (kg)	26	30.0 (22.9-54.2)	5	27.0 (22.6-34.5)	0.480	13	18.9-67.8	13	13.5-73.4	2	34.2-34.7	3	21.8-27.0
%BF (%)	26	42.4 (36.0-47.8)	5	40.0 (39.0-43.0)	0.448	13	30.3-54.7	13	27.8-53.6	2	41.6-44.3	3	38.9-40.0
FMI (kg/m^2)	26	12.4 (9.4-18.2)	5	11.0 (9.7-13.9)	0.514	13	7.9-24.1	13	5.9-31.0	2	13.6-14.2	3	9.3-11.0
FFM (kg)	26	48.6 (36.8-60.1)	5	42.2 (34.7-45.8)	0.257	13	30.8-69.2	13	33.2-63.5	2	43.6-48.0	3	34.3-42.2
FFMI (kg/m^2)	26	18.5 (15.9-20.1)	5	17.2 (14.9-18.4)	0.176	13	13.6-24.7	13	15.2-26.9	2	17.8-19.1	3	14.6-17.2
LCI by ADP	26	0.74 (0.56-0.92)	5	0.67 (0.64-0.75)	0.480	13	0.44-1.21	13	0.39-1.16	2	0.71-0.80	3	0.64-0.67
Ultrasound													
SAT (cm)	20	2.1 (1.8-2.7)	5	1.8 (1.5-1.9)	0.060	9	1.2-3.5	11	1.6-5.0	2	1.2-2.0	3	1.8-1.9
SAT/ thigh length (cm)	20	0.06 (0.05-0.07)	5	0.04 (0.04-0.05)	0.083	9	0.03-0.08	11	0.04-0.14	2	0.03-0.05	3	0.04-0.05
SM (cm)	19	3.7 (3.6-4.0)	5	**4.1 (4.0-4.5)**	**0.036**	9	3.0-4.4	10	3.0-5.0	2	4-4.5	3	4.1-4.5
SM/leg length (cm)	19	0.09 (0.09-0.10)	5	0.10 (0.10-0.11)	0.063	9	0.07-0.12	10	0.07-0.12	2	0.10-0.12	3	0.10-0.11
mCSA (cm^2)	20	9.8 (8.1-14.4)	5	11.7 (8.8-12.4)	0.717	9	5.2-17.8	11	6.8-21.3	2	11.7-13.0	3	8.6-11.8
mEI	19	167.7 (148.6-201.8)	5	148.5 (137.5-169.6)	0.235	8	133.2-224.3	11	137.6-273.9	2	135.2-170.1	3	139.8-169.0
LCI by US	19	**0.55 (0.45-0.68)**	5	0.44 (0.36-0.44)	**0.012**	9	0.28-0.92	10	0.44-1.36	2	0.30-0.44	3	0.42-0.45
Muscular strength													
Right HGS (kg)	26	24 (20-30)	5	18 (18-23)	0.081	13	12-40	13	14-33	2	18-26	3	18-20
Left HGS (kg)	26	**21 (18-27)**	5	16 (14-20)	**0.026**	13	15-43	13	14-31	2	16-22	3	14-18
Physical activity													
Sedentary time (min/day)	26	607.2 (524-698.7)	5	628.3 (568.4-670.2)	0.897	13	464.8-755.2	13	454-761.8	2	609.5-628.3	3	527.3-695.4
Light intensity (min/day)	26	148.6 (106.8-186.9)	5	162.7 (143.5-212.4)	0.305	13	87.6-284.5	13	85.6-267.1	2	162.7-202.5	3	135.9-222.3
MVPA (min/day)	26	42.3 (26.7-55.2)	5	39.6 (30.1-44.2)	0.658	13	23.2-81.8	13	9.2-77.9	2	40.1-48.2	3	28.5-39.6
Dietary intake													
TEI (kcal/day)	25	1778 (1528-2052)	5	2017 (1920-2377)	0.085	12	1243-2907	13	713-2786	2	1933-2017	3	1908-2613

	Overall sample					Children with MUO				Children with MHO			
	Children with MUO		Children with MHO		p-value*	Males		Females		Males		Females	
	n	Median (IQR)	n	median (IQR)		n	Range	n	Range	n	Range	n	Range
Air-displacement plethysmography													
Fat (g/1,000 kcal)	25	37.3 (35.3-41.3)	5	41.7 (33.2-44.6)	0.300	12	15.8-53.2	13	17.4-61.0	2	40.7-41.7	3	25.7-45.2
Protein (g/1,000 kcal)	25	43.2 (39.6-49.3)	5	42.0 (33.2-50.3)	0.872	12	34.5-63.3	13	31.8-67.2	2	46.2-54.3	3	25.4-42.0
CHO (g/1,000 kcal)	25	128.1 (108.1-134.6)	5	113.2 (108.4-142.5)	0.552	12	97.9-177.8	13	55.4-175.8	2	103.7-116.9	3	113-168.1
Fiber (g/1,000 kcal)	25	8.6 (7.3-11.4)	5	8.9 (8-10.5)	0.872	12	5.9-15.7	13	6.1-12.1	2	8.9-9.1	3	7.8-11.9

Abbreviations: %BF, percent body fat; CHO, carbohydrate; ADP, air-displacement plethysmography; FFM, fat-free mass; FFMI, fat-free mass index; FM, fat mass; FMI, fat mass index; HGS, handgrip strength; IQR, interquartile range; LCI, load-capacity index; mCSA, muscle cross-sectional area; mEI, muscle echo intensity; MHO, metabolically healthy obesity; MUO, metabolically unhealthy obesity; MVPA, moderate-to-vigorous physical activity; n, number of participants included in the analysis; SAT, subcutaneous adipose tissue; SM, skeletal muscle; TEI, total energy intake; US, ultrasound.
* Statistically significant difference between children with MUO and MHO by Mann-Whitney U test, $p<0.05$.

Appendix C Study Report Form for Participants

UNIVERSITY OF ALBERTA

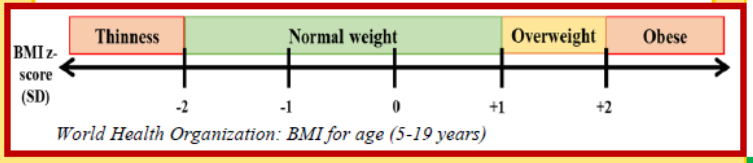
PARTICIPANT RESULTS

Thank-you again for participating in our study "A model of metabolic load-capacity in pediatric obesity: implications for metabolic health and interactions with gut microbiota".
Here you will find your child's data collected on _____, as part of this research study.

→ Anthropometrics

Height (cm)	
Weight (kg)	
BMI z-score	

The body mass index (BMI) used for children is called BMI z-score, and is determined based on children's age and sex. When we place the z-score into the right group below, it helps us understand children's health risks.



World Health Organization: BMI for age (5-19 years)

→ Body composition

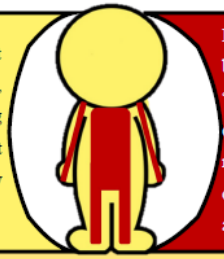
Many aspects of the body, in particular the amount and distribution of fat mass and fat-free mass, are known to be important for good health.

→ Body composition

Body Compartments	BodPod®	BIA	TBK
Fat Mass (%)			
Fat Mass (kg)			
Fat-Free Mass (kg)			
Body Cell Mass			

BIA, bioelectrical impedance analysis; TBK, total body potassium.

Fat Mass plays an important role in protecting internal organs, providing energy, and regulating hormones. If too much fat accumulates over time, health may be compromised.



Fat-Free Mass includes muscles, water, bone, and internal organs. Muscles are the "metabolic engine" of the body that burns calories and plays an important role in maintaining strength and energy. Muscles can also be estimated by measuring the amount of **Body Cell Mass.**

→ Grip Strength

Right hand (kg)	
Left hand (kg)	

Grip strength is an important indicator of how well people perform activities during the day (such as walking or climbing stairs). Values of grip strength obtained from healthy Canadian children and adolescents are described below.

Boys	Age (years)	
	6 to 11	12 to 19
Grip strength (kg) 	13.6 to 14.5	35.6 to 37.7

Girls	Age (years)	
	6 to 11	12 to 19
Grip strength (kg) 	12.8 to 13.7	25.0 to 26.1

Statistics Canada. Health Reports, 27(10), pp. 3-10, October 2016.

→ Physical activity

Physical activity (PA) refers to any movement produced by the skeletal muscles. Physical inactivity or low PA levels is linked to increased risk of metabolic issues in children.

Physical activity level	
Frequency (days/week)	
Types of physical activity	

Based on the *Canadian Physical Activity Guidelines*, children aged 5 to 17 years should perform physical activity as follows:

Once again, **THANK YOU** for participating in our study. We hope you found this information useful. Please do not hesitate to contact us if you have any further questions.

Camila Estefani Orsso
(587) 936-9627 / orsso@ualberta.ca

UNIVERSITY OF ALBERTA

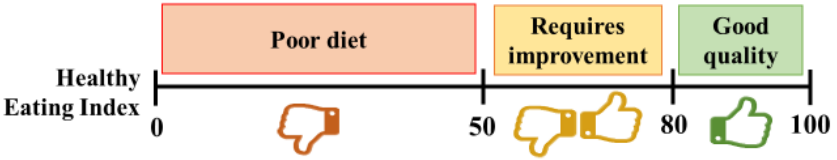
→ Dietary Intake

Dietary management is important to prevent and treat obesity. With the information written down in your child's 3-day food records, we estimated the average of total energy from food and nutrients consumed during those 3 days.

Component	g/day	% kcal
Total energy intake		
Total Fat		
Saturated Fat		
Trans Fat		
Carbohydrate		
Fiber (g/1,000 kcal)		
Protein		

We also calculated the Healthy Eating Index (HEI), which scores from 0 to 100, to estimate the diet quality.

Healthy eating index	



Canadian adaptation of the American Healthy Eating Index.

We encourage children and adolescents to follow the *Eating Well with Canada's Food Guide* to meet their minimum nutritional needs. The recommendations of servings are:

Age (years)	Vegetables and Fruit	Grain Products	Milk and Alternatives	Meat and Alternatives
9 to 13	6	6	3 to 4	1 to 2
14 to 18 (boys)	7	6	3 to 4	2
14 to 18 (girls)	8	7	3 to 4	3