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Review

Low muscle mass and strength in pediatrics patients: Why should we care?

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SUMMARY

Skeletal muscle plays major roles in metabolism and overall health across the lifecycle. Emerging evidence indicates that prenatal (maternal diet during pregnancy and genetic defects) and postnatal factors (physical activity, hormones, dietary protein, and obesity) influence muscle mass acquisition and strength early in life. As a consequence, low muscle mass and strength contributes to several adverse health outcomes during childhood. Specifically, studies demonstrated inverse associations of muscle mass and strength to single and clustered metabolic risk factors. The literature also consistently reports that low muscle mass and strength are associated with reduced bone parameters during growth, increasing the risk of osteoporosis in old age. Furthermore, muscle mass gains are associated with improved neurodevelopment in the first years of life. Given these negative implications of low muscle mass and strength on health, it is crucial to track muscle mass and strength development from childhood to adolescence. Several body composition techniques are currently available for estimation of muscle mass, all with unique advantages and disadvantages. The value of ultrasound as a technique to measure muscle mass is emerging in pediatric research with potential for translating the research findings to clinical settings. For the assessment of muscle strength, the handgrip strength test has been widely employed but without a standardized protocol. Although further research is needed to define normative data and cut points for the low muscle mass and strength phenotype, the use of such non-invasive medical monitoring is a promising strategy to identify early abnormalities and prevent low muscle mass in adulthood.

1. Introduction

Adequate skeletal muscle quantity and "quality" are essential for the maintenance of optimal health throughout life [1]. Besides its contractile function, skeletal muscle plays an essential role in whole-body protein metabolism and is an important determinant of glucose and energy homeostasis [2], directly influencing the development of metabolic diseases [3–5]. During all life stages, several factors have been found that negatively influence skeletal muscle quantity and "quality", such as inactivity, diseases and malnutrition [6]. These factors can generate a phenotype defined as "sarcopenia", which is characterized by low muscle mass and strength and poor physical performance [6].

In 1964, Forbes described for the first time a low muscle mass phenotype in children [7]; nonetheless, very little attention has been paid to the mechanical and metabolic implications of low skeletal muscle mass and strength in pediatrics since this initial publication [8]. Similar to its effects in adulthood and senescence, low muscle mass and strength contribute to adverse health outcomes in childhood. Several studies have described an increased risk of developing metabolic dysfunction and cardiovascular diseases in children and adolescents with low skeletal muscle mass and strength [4,5,9–11]. On the other hand, additional research has shown positive associations between muscle mass and bone

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Abbreviations

ADP	air displacement plethysmography
AGA	appropriate size for gestational age
ASM	appendicular skeletal muscle mass
ASMI	appendicular skeletal muscle index
BIA	bioelectrical impedance analysis
BMC	bone mineral content
BMD	bone mineral density
BMI	body mass index
CT	computerized tomography
DXA	dual energy x-ray absorptiometry
FDG	fluorine 18 (^{18}F) fluorodeoxyglucose
FFM	fat-free mass
FM	fat mass
FT4	free thyroxine
GH	growth hormone
IBD	inflammatory bowel diseases
IGF-1	insulin-like growth factor 1
LST	lean soft tissue
MRI	magnetic resonance imaging
PET	integrated positron emission tomography
PWS	Prader-Willi syndrome
ROC	receiver operating characteristic
SGA	small for gestational age
SMI	skeletal muscle mass index
SMM	skeletal muscle mass
TSH	thyroid-stimulating hormone
%SMM	percentage of skeletal muscle mass

mineral content [12,13], and cognition and motor scores early in life [14,15].

In view of the risks associated with low skeletal muscle mass and strength, the aim of this narrative review is to identify and discuss the factors affecting skeletal muscle development, the impact of low muscle mass and strength on children's health, and to review the latest technology employed in both clinical and research settings to assess muscle mass and strength. For the purpose of this review, we will use the most accurate terminology to describe the body composition measured by the authors (as defined in Table 1), which may vary from the original terminology presented by them.

2. Methods

An unsystematic literature search was performed in PubMed from its inception until December 2018. The search strategy consisted of key words related to the main topics discussed throughout this narrative review involving only the pediatric population: muscle mass and strength, bone and cognitive development, sarcopenic obesity, and techniques to assess body composition and strength. Moreover, the reference list of selected literature was manually searched for additional relevant articles. Articles in languages other than English, conference abstracts, and studies assessing muscle mass using skinfolds were excluded. Titles and abstracts of relevant articles were unsystematically reviewed to select the ones of overall good quality, which addressed a clear focused question, used reliable methods, and described valid results. A critical synthesis of the literature was therefore presented throughout the main text, describing the limitations of included articles.

3. Influences on skeletal muscle development

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) [16–18]. After birth, muscle fibers grow mainly in size and to a much lesser degree in number [19]; therefore, defects in muscle development that occurred during pregnancy may be perpetuated throughout adult life [20]. Besides intrauterine and genetic influences [21], several postnatal environmental factors affect skeletal muscle development, such as dietary protein [22], physical activity [23], chronic diseases [24], and obesity [25]. In this section, we discuss some of the factors known to influence pre- and postnatal skeletal muscle development (Fig. 1).

3.1. 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 [26]. The mother's nutritional status is one of the aspects already known to affect the programming of the body [27]. Evidence from animal models demonstrate that nutrient restriction during pregnancy, especially protein, impairs skeletal muscle development of the fetus [28,29]. On the other hand, gestational overnutrition and obesity also appear to affect muscle mass of fetus in a negative way [30]. According to Tong et al. [30], myogenesis was downregulated in fetus from sheep with obesity, and this effect was correlated with a pro-inflammatory state.

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 small for gestational age (SGA) with those of appropriate size for gestational age (AGA) have shown that nutritional deprivation during pregnancy may negatively impact muscle development [31–33]. Individuals born SGA had lower amount of lean soft tissue (LST) at birth, reduced muscular growth from two months to eight years of age [32], and lower handgrip strength at 30 years of age compared to those born AGA [33]. Older adults [34] in the lowest quintile of birth weight, compared to the highest quintile, had decreased peripheral skeletal muscle cross-sectional area at 70 years of age. Additionally, a recent meta-analysis found a positive

Table 1
Body composition terminology related to skeletal muscle mass used in this review.

Term	Definition
Skeletal muscle or muscle mass	Generic terms used to describe LST, FFM, and skeletal muscle tissue.
LST	Sum of total body water, total body protein, carbohydrates, non-fat lipids, and soft tissue minerals.
FFM	Sum of lean mass and bone mineral components.
Skeletal muscle tissue	Muscle attached to the bones that provides mechanical, structural, and metabolic functions.

Abbreviations: FFM, fat-free mass; LST, lean soft tissue.

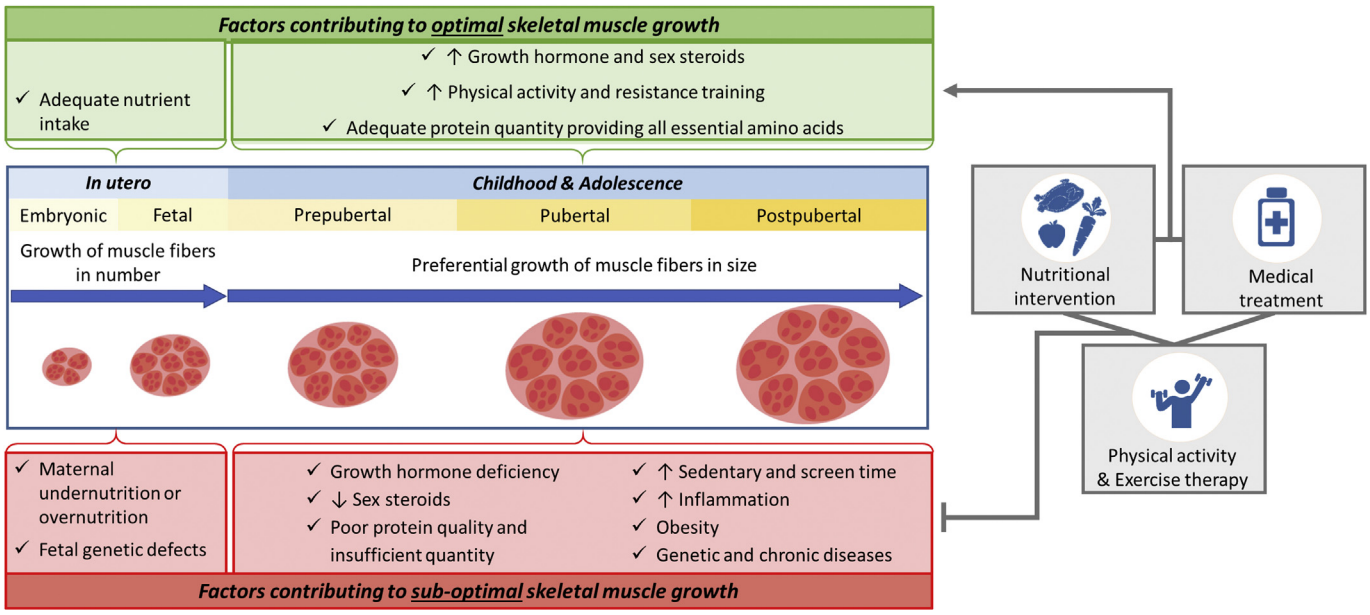

Fig. 1. Summary of factors promoting optimal or sub-optimal skeletal muscle growth during development and strategies to address low muscle mass in childhood and adolescence.

association between birth weight and muscle strength, and this association was maintained across the life cycle [35]. 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 [36].

Although evidence suggests that a diet containing adequate nutrients for healthy growth during pregnancy would also favor optimal skeletal muscle development in the fetal stage and throughout life, causality cannot be inferred. One study indeed failed to show associations between maternal protein intake (as estimated by a Food-Frequency Questionnaire) and muscle mass of the fetus measured by ultrasound at 28 and 36 weeks' gestation in overweight and obese pregnant women [37]. Inherent limitations of these methodologies, such as recall bias and underreporting of dietary intake [38] and poor accuracy of the ultrasound in estimating fetal body composition in a scenario of maternal obesity [39], may partially explain the absence of an association between prenatal protein ingestion and newborns' muscle mass [37]. Therefore, future studies using more accurate body composition techniques are required to elucidate the effect of fetal programming on muscle mass of the fetuses and newborns.

3.2. Genetic and chronic diseases

Genetic diseases affect skeletal muscle development [40], with muscular dystrophy being the most commonly encountered group of myogenic disorders in pediatrics [41,42]. 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 [41,42]. As a consequence of this disorder, most of the patients face serious problems with locomotion, breathing and feeding, which ultimately leads to premature death [41]. More than 50 forms and sub-forms of muscular dystrophies have been recognized, with Duchenne muscular dystrophy being the most prevalent pediatric myopathy (1/5000 boys) [43]. Although knowledge on the etiology of muscular dystrophies is rapidly evolving, a cure still does not exist and treatment is aimed at delaying disease progression and relieving symptoms [41].

Prader-Willi syndrome (PWS) is a disorder resulting from inactivation of paternal genes on the chromosome 15q11.2-q13, affecting 1/10,000 to 1/30,000 individuals [44]. Despite not recognized as a genetic disorder of the skeletal muscle system, infants present with hypotonia (or low muscle tone), developmental delay and endocrine dysfunctions, including growth hormone (GH) deficiency [44]. In children with PWS, a body composition phenotype characterized by low muscle mass combined with high fat mass (FM) is a common feature, which is related to reduced muscle strength and physical performance [45]. Besides the multifactorial etiology of hypotonia and low muscle mass in PWS, it has been suggested recently that a lack of the Magel2 gene expression in developing mesodermal tissues results in abnormalities of skeletal muscle tissue [46]. As a consequence, patients have complications with postural stability, are diagnosed with scoliosis, osteopenia/osteoporosis, and have an increased risk of developing chronic diseases. Similar to muscular dystrophies, there is no cure for PWS [44]; however, treatment options comprised of medications (e.g. GH), diet and physical activity can help manage its complications [47,48].

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 [24,49–51]. Studies in children with acute lymphoblastic leukemia, a common form of cancer during childhood, reveal substantial reductions in appendicular LST (as measured by dual energy x-ray absorptiometry [DXA]) [49] and psoas muscle cross-sectional area (by computerized tomography [CT]) [50] 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 [52]. 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 [53].

Other common chronic diseases affecting skeletal muscles during childhood are inflammatory bowel diseases [51], chronic kidney [51] and liver diseases [54], and type 1 diabetes [55]. In inflammatory bowel diseases (IBD), 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 [56]. The deficits in muscle mass and strength observed in children with IBD can be attributed to several factors, including steroid therapy, protein malabsorption, inflammatory cytokines, and possibly vitamin D deficiency [51,57]. Specifically, inflammatory cytokines (e.g. tumor necrosis factor-alpha and interleukin-6) inhibit protein synthesis, mitochondrial biogenesis, and expression of the anabolic insulin-like growth factor 1 (IGF-1) [58]. 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 [49,51,59].

3.3. 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 [60]. Although the exact mechanisms of interaction between GH/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 [60]. Before the onset of puberty in healthy boys and girls, muscle mass and fat-free mass (FFM) increase slowly and proportionally to body growth [60–62]; however, during the pubertal growth spurt, GH and sex steroids undergo a dramatic activation, which rapidly increases the percentage of muscle mass [63]. Hormonal changes also affect skeletal muscle in a sex-dependent manner [60]; boys synthesize more muscle mass for a longer duration when compared with girls during this stage of life [64]. 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 [65], 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 (FT4), but not with thyroid-stimulating hormone (TSH) [62].

Considering the impact hormones have on skeletal muscle development, hormonal deficiencies negatively influence individual's health status, especially during growth [60]. Research has demonstrated that GH and sex steroid deficiencies impair the development of LST as measured by DXA [66]. The crux of therapy for these conditions revolves around hormone replacement, which has been shown to increase skeletal muscle mass [67,68]. In adolescents with GH deficiency, discontinuation of hormone replacement reduced LST by 2 kg over a two-year period [69]. Findings from clinical trials demonstrate that GH replacement therapy (0.67–1 mg/m^2 per day) in PWS increased muscle thickness by ultrasound in infants [47] and LST by DXA in adolescents [70]. Furthermore, in boys with delayed puberty, three months of testosterone replacement therapy significantly increased FFM (measured by bioelectrical impedance analysis [BIA]) and height velocity [71]. 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 [72].

3.4. 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 [73]. Indeed, a recent study including 3991 children aged 8 years found an association between higher protein intake and higher FFM measured by DXA [74]; similar associations were also described in adolescents with normal [75,76] and high FM [77]. 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 [78]. 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 [79]. 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 [79,80]. In very low birth weight infants, for example, a protein intake of 4.2 g/kg/day promoted FFM (measured using BIA) accretion compared to a standard pre-term formula providing 3.7 g/kg/day of protein [22]. 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 [22].

On the other hand, one study revealed that a higher protein intake was associated with increased FM [81] and risk of obesity in early childhood [82]. Divergent from adults [83], protein intake above the amount needed for maintenance and growth appears to stimulate adipogenesis and inhibit lipolysis in children [84,85]. 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 [82,84–86]. According to this hypothesis, children who are genetically predisposed to obesity [87] and the ones who experienced catch-up growth in early childhood [88] 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 [75] and using skinfolds in young adulthood [76] 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 [89]. Additionally, animal protein has a greater content of leucine, which is a key amino acid in stimulating post-prandial anabolism [89]. 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 [74]. A German cohort study including children aged 5–6 years also supports this contradictory finding [90]. 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 [91]. 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.

3.5. 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 [92,93]. 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 [94,95]. Although some of the metabolic and hormonal responses to long-term exercise in the pediatric population differ from adults [94], children and adolescents most likely increase muscle mass through similar mechanisms to adults when skeletal muscle is subjected to a mechanical stimulus [96,97]. 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 muscle cross-sectional area (known as hypertrophy) [98]. For a detailed description of the mechanisms through which exercise promotes hypertrophy, see Watson & Baar [98].

Several observational studies highlight the benefits of physical activity in promoting optimal muscle mass development. In a recent study, 138 healthy Swedish preschoolers were assessed for physical activity using accelerometry and FFM by air displacement plethysmography (ADP) at the age of 4 years (baseline) and again at 5.5 years old [99]. Children who performed greater vigorous-intensity and moderate-to-vigorous physical activity at baseline had higher FFM index at 5.5 years of age [99]. A larger study conducted in Brazil, in which 3176 adolescents were followed for seven years to evaluate the associations between self-reported physical activity during growth and body composition at the age of 18 years, described similar findings. Moderate- and vigorous-intensity physical activity at the ages of 11, 15 and 18 years were positively associated with body weight adjusted LST (assessed by DXA) at the age of 18 years old in girls and boys (except for boys at 11 years old) [100].

Gains in muscle mass, however, do not necessarily translate into improvements in muscle strength or vice-versa [101]. 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 [97,101]. Additionally, low concentrations of GH 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 [68]. 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 [102]. 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 [102]. Thus, in children and adolescents, resistance training is important to ensure optimal muscle mass accrual.

3.6. Obesity

The prevalence of childhood obesity has increased substantially around the world [103]. Research has shown that obesity contributes to low muscle mass and weakness [104]; children and adolescents with obesity exhibit low relative strength to body mass [105], impaired muscular fitness [106], and reduced neuromuscular activation capacity [107] 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 to -0.12; $p = 0.001$) in children aged 4–19 years old [108]. 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 [106,109].

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 [107]. 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 [110]. The researchers indeed found that overweight children had smaller motor units than children with healthy weight [110], 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 [25,111,112]. Chronic positive energy balance leads to excessive fat accumulation in adipose tissue and between skeletal muscle fibers or surrounding muscle [113]. 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 [25]. 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 [112].

4. Impact of low muscle mass and strength in pediatrics

Previous studies have established that low muscle mass and strength contribute to adverse health outcomes in childhood [4,5,9–13]. Here, we discuss this evidence by highlighting the implications of low muscle mass and strength on metabolic homeostasis, bone health, and neurodevelopment as summarized in Fig. 2.

4.1. Metabolic health

Evidence from several studies suggest low muscle mass as a contributing factor to an unfavourable metabolic profile in pediatric populations [4,9,10,114–116]. Using data from the National Health and Nutrition Examination Survey, Kim et al. [4] found an inverse association between relative LST (assessed by DXA) and risk factors for cardiovascular disease and diabetes in children aged 8–20 years. Moreover, the authors reported that the odds of having an adverse level of any of the metabolic risk factors gradually decreased as relative LST increased in this population [4]. Similarly, low skeletal muscle mass (defined as the lower quintile of appendicular LST adjusted for body weight, age, and sex) was associated with metabolic syndrome and its components in Koreans aged 12–19 years [9]. Interestingly, even after controlling for confounders (i.e. age, sex, energy intake, protein intake, resistance exercise, equivalent income, and alcohol consumption) the risk of developing metabolic syndrome was higher in those adolescents

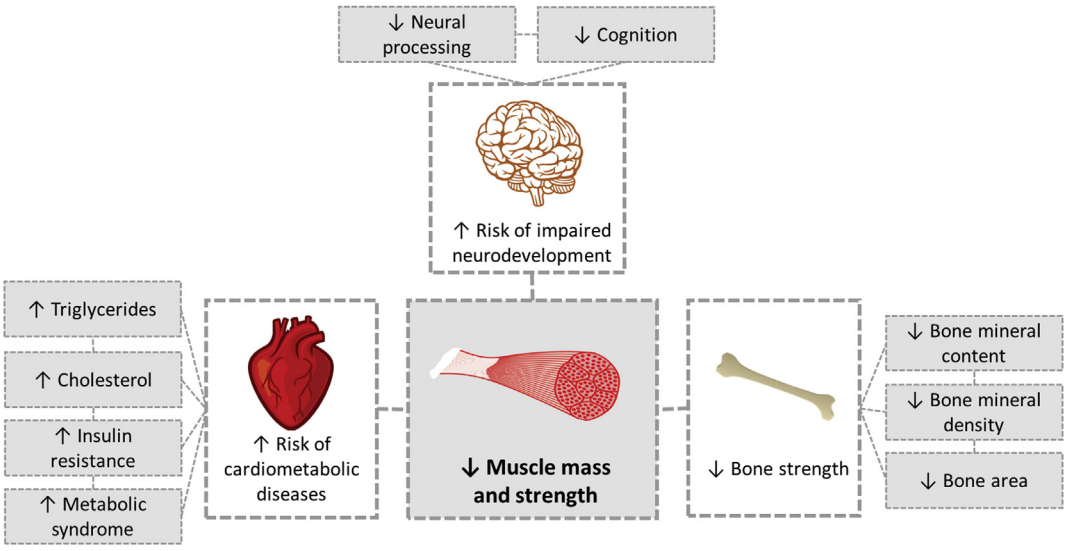

Fig. 2. Low muscle mass and strength in childhood and adolescence are associated with increased risk for cardiometabolic diseases and impairments in bone parameters and neurodevelopment.

exhibiting low muscle mass (OR, 5.28; 95% CI, 2.76–10.13)[9]. A recent observational study including 660 adolescents found that those in the 25th percentile of muscle mass (assessed using DXA and adjusted for sex) had higher waist circumference, arterial blood pressure, triglycerides, total cholesterol/high-density lipoprotein-cholesterol, homeostatic model assessment for insulin resistance, and metabolic syndrome z-score than their peers in other percentiles [114]. Moreover, those adolescents exhibiting low muscle mass combined with obesity had the most unfavourable cardiometabolic risk profile [114].

Besides muscle mass, muscle strength is also an important aspect of physical fitness [117] and a protective factor for health across populations [118], being defined as the ability to produce force against a resistance. Handgrip strength is a non-invasive field test used to assess muscle strength and predict health in different population groups [119]. Although widely used to measure muscle strength in older adults, this technique is also gaining popularity in pediatric populations [119,120]; associations between handgrip strength, chronic diseases [5,118,121–123] and mortality risk [121,124] have indeed been reported. A prospective cohort study involving more than one million male adolescents demonstrated that those with muscle strength (as measured by handgrip and knee extension tests) equal or greater than the 40th percentile of the studied population had a 20 and 35% lower risk of all-cause premature mortality and cardiovascular disease, respectively, as compared to those in the 10th percentile [124]. In addition, a negative association between muscle strength and occurrence of coronary heart disease and stroke was also shown in these individuals after a 24-year follow-up [125]. Another study found that boys and girls aged 11 years and in the highest tertile of strength adjusted for body weight had lower body mass index and FM, smaller waist circumference, higher levels of cardiorespiratory fitness, and lower clinical markers of risk compared to the first and second tertiles [126]. Similarly, two other studies with schoolchildren [118] and adolescents [127] found associations between low muscle strength and unfavourable metabolic risk profile. Moreover, Peterson et al. [5] observed that for every 5% decrease in muscle strength, there was a 1.48 increased odds of having a high cardiometabolic risk score in boys and 1.45 in girls. Collectively, these studies suggest that both low muscle mass and low muscle strength are important contributors to metabolic dysfunction in children and adolescents.

4.2. 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 [12,13,128]. 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 [129,130]; therefore, muscle mass and strength are considered important predictors of bone strength [131]. 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 [130,132,133]. As bone and muscle function synergistically and “peak” bone mass during growth partially determines osteoporosis risk in adulthood and old age [131], “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 [128]. The majority of the reviewed studies found positive associations between muscle mass and bone mineral content (BMC), bone mineral density (BMD) and bone area [128]. A cross-sectional study evaluating 254 girls aged 16–20 years, for example, observed a strong correlation between LST, BMC, and BMD (all measured by DXA); moreover, 30% of the variability observed in BMD was predicted by LST [134]. Similarly, a longitudinal study on 370 children of both sexes aged 8–18 years found a positive association between LST (assessed using DXA), and BMC and bone area (by peripheral quantitative CT) [135]. 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 BMC, 19.9 cm^2 in bone area, and 0.007 g/cm^2 in BMD [136].

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 handgrip strength and bone mass at hip, spine and whole body; moreover, the authors reported handgrip strength as an independent predictor of bone mass [137]. In young athletes, handgrip strength was

a determinant factors of radial BMD [138]. A recent study evaluating 1427 adolescent students of both sexes aged 11–18 years demonstrated that handgrip strength was associated with the BMD and BMC. Moreover, a cross-sectional analysis of girls aged 13–15 years showed a strong association between handgrip strength and BMD [139]. In support of the association between muscle strength and bone health, the Institute of Medicine has recommended the handgrip strength test to be used as part of school-based fitness testing to monitor adequate levels of muscle strength for optimal bone health [140]. To this end, cut points for handgrip strength were recently developed in order to facilitate the implementation of the use of handgrip strength in assessment of bone health in youth [141].

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.

4.3. 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 [142], impacting academic performance and later productivity in adulthood [143]. Although birth weight has been identified as a strong predictor of child neurodevelopment [144,145], children in the same birth weight range can have different neurodevelopmental progress; this suggests that there are other factors playing a role on neurodevelopment [144]. Considering that body composition is highly variable in children with the same body weight [146,147], 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 [14]. 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 [148]. In addition to this finding, the authors observed a greater absolute value of FFM associated with faster neuronal processing [148]. Furthermore, a prospective cohort study measured the body composition of 227 Ethiopian children within 48 h of birth also using ADP [149]. 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 [149]. 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 [150]. Interestingly, it was demonstrated that fetal FFM accretion was associated with developmental progression, but not postnatal FFM accretion [150]. For each kg increase in FFM at birth, global development progression increased 1.8 points from 1 to 5 years of age [150].

In contrast, Scheurer et al. found that body composition changes (also assessed by ADP) continue to induce neurodevelopmental benefit beyond infancy [151]. In a prospective, observational design, a cohort of preterm infants was followed from infancy through preschool age [151]. The authors observed that greater FFM gains from infancy to preschool age were associated with improved overall cognition and processing speed task performance [151]. 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 [152]. 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.

5. Sarcopenic obesity in pediatrics

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 greater health risks than either compartment alone [153,154]. 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 [155]. 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 body fat to muscle mass represents the metabolic load-capacity index. A lay video explanation of this concept can be found in the YouTube channel: U of A Nutrition (https://youtu.be/SY2IaktOuZM).

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 metabolic syndrome z-score, triglycerides, insulin resistance and systolic blood pressure compared to adolescents with either obesity or low muscle mass alone [114].

We therefore propose that the metabolic load-capacity index could be applied in research and clinical settings to discriminate metabolic dysregulation also during childhood (Fig. 3). Current studies in our group will investigate whether this index is a better discriminator of an unfavourable metabolic profile in children, as compared to age and sex-specific body mass index (BMI z-score). The main limitation of BMI is its inability to distinguish between different body composition components, which leads to

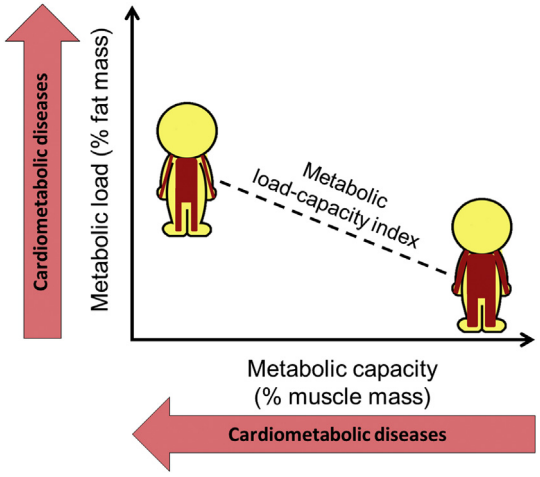

Fig. 3. The model of metabolic load-capacity in childhood. A body composition phenotype of concurrent high body fat and low lean mass (on the left) results in a higher metabolic load-capacity index. Conversely, having low body fat and high lean mass results in a lower index. Children and adolescents with a high metabolic load-capacity index may be at increased risk for cardiometabolic diseases.

misclassifications particularly in those individuals with short stature or high muscle mass [8]. Although BMI has high specificity to identify children with excess body fat, sensitivity is lower with 25% of children with excess FM being misclassified as having a healthy body weight [156]. Thus, an individual with a BMI z-score in the healthy category may actually have low muscle mass with high FM and an increased risk for cardiometabolic diseases. Future prospective studies must be conducted to evaluate the predictive value of the metabolic load-capacity index in prediction of cardiometabolic risks.

6. Tracking muscle mass and strength throughout development

Measurement of muscle mass and strength are fundamental to identify relevant health outcome measures and functional status, establish nutritional recommendations, and monitor the effectiveness of interventions aiming to promote health and prevent diseases [157]. In pediatric patients with chronic diseases, an accurate bedside evaluation of muscle mass and strength provide further support to clinicians in planning ongoing care of patients [24,158,159]. These high-risk children usually require targeted nutritional and occupational therapy interventions to reduce muscle wasting and improve clinical outcomes [158,159]. In this section, we discuss the body composition techniques most commonly used in pediatrics to estimate muscle mass and measure strength, as well as normative data developed for this population group.

6.1. Body composition techniques for the assessment of muscle mass in pediatrics

As summarized in Table 2 diverse body composition techniques (e.g. ADP, BIA, DXA, CT, magnetic resonance imaging [MRI], and ultrasound) are current available in both research and clinical settings for estimation of muscle mass in infants, children and adolescents.

Air displacement plethysmography and BIA are safe, non-invasive, and simple techniques to evaluate whole-body FFM in the pediatric population [160,161]. 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 $\leq$ 10 kg) [162]. Both ADP and BIA use age- and sex-specific equations to estimate FFM based on body density [163] and impedance (and/or its components - resistance and reactance) to an electrical current that passes through the body [161], respectively. Most of these predictive equations, however, do not account for sexual maturation status and could, consequently, under or overestimate FFM; therefore, using raw data on body density from ADP or conductivity from BIA in selected equations is an alternative approach [161]. Another limitation of these techniques is its sensitivity to hydration status, which is known to vary in children [164,165]. As children

Table 2
Summary of commonly used techniques for assessment of muscle mass.

Technique, (References)	Level, Compartment Being Measured	Advantages	Limitations
Dual energy x-ray absorptiometry, [172–175]	Molecular, LST and FFM	Non-invasive, minimal radiation exposure, and rapid whole-body scan (newer equipment 2–3 min). Regional measurements allow calculation of appendicular skeletal muscle index. High precision and accuracy.	Sensitive to tissue hydration. Compared to 4C 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, [161,166]	Molecular, 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, [162,176],	Molecular (density), 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.
Computerized tomography scans, [177]	Tissue, SM tissue	Reference method as it provides quantitative and qualitative measures of SM tissue. Single slices can be used to estimate whole-body SM. 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, [178]	Tissue, 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, [179,180]	Tissue, SM tissue	Real-time measurement of SM thickness and 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: BIA, bioelectrical impedance imaging; CT, computerized tomography; FFM, fat-free mass; LST, lean soft tissue; SM, skeletal muscle.

with chronic diseases can exhibit an altered fluid state, the accuracy of impedance measurements may be compromised [24,165]. 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 [24]. 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 [166].

Dual-energy X-ray absorptiometry is a widely used method to estimate both whole-body and regional 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 [167]. This index has been used to assess sarcopenia in adults and elderly population [168,169], 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 [170,171]. Newer DXA instruments allow quick whole-body scans (2–3 min), 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 [172].

Computerized tomography and MRI are considered the reference imaging methods for body composition assessment at the tissue level; both provide accurate measures of skeletal muscle cross-sectional area and volume using single or multislice images [181,182]. 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 [51]. Another feature of CT and MRI techniques is the characterization of “muscle quality” due to their ability to detect intramuscular adipose tissue, which is the adipose tissue within the skeletal muscle. As a predictor of health, low muscle “quality” (or increased infiltration of adipose tissue in muscles) has been associated with metabolic dysregulation, reduced muscle strength, and impaired skeletal development in children and adolescents [183–185]. Furthermore, integrated positron emission tomography (PET)/CT and PET/MRI can provide information on skeletal muscle glucose metabolism in research settings [186,187]. By using a specific PET tracer, commonly the fluorine 18 (^{18}F) fluorodeoxyglucose (FDG), and the hyperinsulinemic euglycemic clamp, researchers are able to characterize the dynamics of glucose uptake by skeletal muscles to develop and evaluate the efficacy of new treatments for metabolic abnormalities [186,187].

Ultrasound is another imaging modality that allows assessment of skeletal muscle in the pediatric population [188]. It provides real-time measurement of muscle thickness and cross-sectional area with low cost and in a relatively fast manner without any radiation exposure [189]. Measurements of rectus femoris and vastus intermedius muscles taken at the mid point of the anterior superior iliac spine to the superior aspect of the patella (mid-thigh) have been used in pediatrics, especially to track changes of muscle thickness over time [190]. In addition to muscle thickness and cross-sectional area, ultrasound is a valuable technique for quantification of muscle echo intensity, which is currently used for evaluation of muscle diseases in children and adolescents [188,189]. In diseases such as inflammatory myopathies, fasciculation, and neuromuscular diseases, a greater muscle echo intensity has been observed [158,188,189]. Given these features and advantages over other imaging techniques, the value of ultrasound 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 may be an issue when evaluating muscle thickness in pediatric patients with chronic conditions [158]. Future research is required to support the use of ultrasound when characterizing sarcopenia in the young population.

Given the advantages and limitations of each body composition technique (Table 2), 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 muscle mass at the individual or population level, which body compartment containing 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.

6.2. Measuring muscle strength by the handgrip strength test

The handgrip strength test is used worldwide in the pediatric population to assess upper body muscle strength due to its simplicity, portability and low cost. It is also a good proxy of whole-body muscle strength as confirmed by strong correlations between the handgrip test and measures of whole-body muscular strength ($r = 0.736–0.890$) in children and adolescents aged 8–20 years [191]. As recently proposed, the index of handgrip strength to body mass may be useful to screen children and adolescent at a high risk for cardiometabolic diseases [192]. In clinical settings, the handgrip strength test has also been employed to evaluate muscle functionality [193,194]. Diverse protocols for measuring handgrip strength in children and adolescents are described in the literature with variances on body position, dynamometer handle positions, hand dominance, number of assessments, and interval between measures [192,195–197]. Because this diversity in the administration of the test may affect the results, a standardized method is required for the pediatric population as it was recently proposed for adults [198].

6.3. Normative data for muscle mass and handgrip strength

Development of normative data for muscle mass and handgrip strength in pediatrics is essential to identify perturbations in these variables throughout growth. Population-based studies conducted in different countries have attempted to establish reference curves for skeletal muscle mass and handgrip strength in children and adolescents (see Table 3 for details of the studies on normative data for muscle mass and Bohannon et al. [197] for handgrip strength). These studies have characterized the “normal distribution” of muscle mass for the growth trajectory; however, classification of low muscle mass using defined cut points is limited in pediatrics. Current studies have used population derived values to rank participants into the lowest quartiles or quintiles of muscle mass for sex and age [4,9]. Another method employed to identify optimal cut points for skeletal muscle is using receiver operating characteristic (ROC) curves; to our knowledge, only two studies have used this method and defined cut points for skeletal muscle that were sensitive to predict metabolic syndrome or other cardiovascular risk factors in pediatric patients [114,199]. Although most of these studies have included a large sample size, they have not accounted for puberty stages and results cannot be transferred to other

Table 3
Normative data for lean mass across childhood and adolescence.

Author, reference	Country	Age group (years)	BC technique	Indices
Kelly, Wilson & Heymsfield, 2009, [201]	United States	8 to 20	DXA	SMI (kg/m^2), LST (kg)
Webber & Barr, 2011, [61]	Canada	3.1 to 18.8	DXA	ASM and derived values of SMM
McCarthy et al., 2013, [62]	United Kingdom	5 to 18.8	Segmental BIA	%FFM and ASM (kg)
Weber et al., 2013, [202]	United States	8 to 20	DXA	SMI (kg/m^2)
Guo et al., 2016, [203]	China	5 to 19	DXA	Lean mass (%), SMI (kg/m^2), ASMI (kg/m^2)
Kim, Hong & Kim, 2016, [204]	Korea	10 to 18	DXA	ASMI (kg/m^2), %SMM and ASM (kg)
Chiplonkar et al., 2017, [205]	India	5 to 17	BIA (foot-to-foot)	%FFM
Marwaha et al., 2017, [200]	India	5 to 18	DXA	Total LST (kg), ASMI (kg/m^2), arm LST (kg), leg LST (kg), trunk LST (kg)

Abbreviations: ASM, appendicular skeletal muscle mass; ASMI, appendicular skeletal muscle index (calculated as ASM/height^2); BC, body composition; BIA, bioelectrical impedance imaging; DXA, dual energy x-ray absorptiometry; %SMM, percentage of skeletal muscle mass (calculated as ASM/weight x 100); SMI, skeletal muscle mass index (calculated as total LST/height^2); SMM, skeletal muscle mass (calculated from ASM using specific equations for prepubertal and pubertal children).

populations (country/origin-specific) or other methods of body composition assessment (Table 2). Only one study of Indian children and adolescents has reported measures of whole-body and regional LST according to pubertal stages [200]. Therefore, these curves and cut points should be interpreted with caution to prevent misclassification of children with delayed or advanced pubertal maturation [201].

7. Conclusion and perspectives

Growing evidence suggests that several pre- and postnatal factors influence the development of suboptimal muscle mass and strength, fostering the development of a sarcopenic-like phenotype in childhood and adolescence. Inadequate maternal intake along with genetics and hormonal disorders, physical inactivity and obesity, can limit the growth of skeletal muscle as expected for an individual's age, pubertal stage and sex. In addition, current literature confirms that low muscle mass and strength might impair metabolic and bone health even before adulthood.

Taken together, these findings highlight the importance of measuring and monitoring skeletal muscle mass and function from early in life to young adulthood in clinical settings. Although further research is needed to define normative data and cut points for the low muscle mass phenotype, using body composition techniques for the evaluation of health status of pediatric patients is a promising strategy. These studies should incorporate techniques of body composition assessment that are transferable to pediatric clinical settings. Given the advantages and limitations of each one of these techniques (as discussed above and in Table 2), we propose the use of ultrasound as a promising technique to accurately measure skeletal muscle and FM and calculate the metabolic load-capacity index in pediatric clinical settings. Through such non-invasive medical monitoring, health care professionals may identify and evaluate the necessary strategies to improve muscle mass and strength while treating associated pediatric diseases. Personalized approaches including dietary recommendations, medical, nutrition, and exercise therapies might maximize muscle mass and strength in youth to prevent the burden of sarcopenia in adulthood and in older age.

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Conflict of interest

The authors declare no conflict of interest.

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