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Review

Metabolic implications of low muscle mass in the pediatric population: a critical review

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ABSTRACT

Skeletal muscle is recognized as a tissue with high metabolic capacity given its key roles in glucose and lipid metabolism. Although low muscle mass has been associated with metabolic disorders in adults, it is not clear if this body composition phenotype is related to metabolic health status earlier in life. In this review, we aim to clarify whether having low muscle mass is associated with increased risk of metabolic dysregulation in the pediatric population. Fifteen original articles investigating the relationship between body composition measures of muscle mass and single or clustered metabolic risk factors in children and adolescents were critically evaluated. Despite a growing body of evidence supporting low muscle mass as a risk factor for metabolic health in children and adolescents, conflicting associations were reported. 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. Moreover, most studies did not control for potential biological and lifestyle confounders. Future studies using precise, reproducible techniques to evaluate body composition and metabolic biomarkers are required to determine the implications of low muscle mass on metabolic health during childhood and adolescence.

Contents

Abbreviations: ADP, air-displacement plethysmography; AUC, area under the curve; BIA, bioelectrical impedance analysis; DXA, dual-energy x-ray absorptiometry; FFM, fat-free mass; GLUT4, glucose transporter type 4; HDL, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment of insulin resistance; LDL, low-density lipoprotein cholesterol; LST, lean soft tissue; MRI, magnetic resonance imaging; mTOR, mammalian target of rapamycin; NHANES, National Health and Nutrition Examination Survey; OGTT, oral glucose tolerance test; pQCT, peripheral quantitative computed tomography; RCT, randomized controlled trial.

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1. Introduction

Skeletal muscle is an important site for glucose uptake and storage [1]; approximately one quarter of all ingested glucose is taken up or stored as glycogen by skeletal muscle to use as an energy source [2]. Additionally, skeletal muscle stores amino acids and lipids in the form of muscle triglycerides to produce energy during periods of starvation [1], and skeletal muscle metabolism also is a determinant of resting energy expenditure [3]. Given these metabolic roles, the skeletal muscle has been characterized as a tissue with high metabolic capacity [4].

Although much of the research in pediatrics has focused on the effects of excess body fat on metabolism, it is likely that a body composition phenotype of low muscle mass is an additional key contributor to metabolic dysregulation early in life [5]. Evidence from studies describing a metabolically healthy phenotype in children with obesity indeed supports the idea that factors other than body fat influence the development of metabolic dysregulation [6]; a low muscle mass phenotype is potentially one of these factors. The relationship between low muscle mass (also termed sarcopenia) and metabolic disorders is well-established in adults and the elderly population [4,7,8]. Whether low muscle mass is also a risk for metabolic dysregulation in children has not been studied in a systematic way [9].

It should be noted that dysregulation of the systemic metabolic state by conditions such as insulin resistance, dyslipidemia, and hypertension are precursors for type 2 diabetes mellitus and cardiovascular disease [10,11]. As the prevalence of these morbidities has increased substantially in children and adolescents around the world [10,11], there is an urgent need for characterization of potential contributors to metabolic dysregulation. In this review, we aim to clarify through a comprehensive search of the literature whether having low muscle mass is associated with increased risk of metabolic dysregulation in the pediatric population. By critically evaluating studies that have investigated this association, we will present existing knowledge, identify strengths and limitations of the research findings, and propose future studies addressing gaps in the current literature. Furthermore, findings of this review may highlight the importance of assessing and treating suboptimal accrual of muscle mass in the pediatric population to prevent the burden of metabolic dysregulation in childhood which tracks into adulthood.

2. Molecular pathways potentially implicated in the association between low muscle mass and metabolic dysregulation

Muscle growth occurs when the rate of protein synthesis is greater than the rate of protein breakdown [12]. Several pre- and postnatal factors (e.g. maternal diet, genetics, lifestyle, and chronic conditions) have been associated with an abnormal accrual of muscle mass during childhood and adolescence, with implication for the development of metabolic disorders early in life [9]. However, the cross talk between low muscle mass and metabolic dysregulation is complex, and diverse mechanisms potentially explain this relationship as muscle mass is regulated by various signals [13]. We hereby briefly describe selected relevant molecular pathways.

Myostatin and activin A are examples of negative regulators of muscle growth. By binding with their specific receptors at the muscle surface, these extracellular cytokines activate the phosphorylation of SMADS, known transcription factors [14–16]. Through this mechanism, myostatin and activin A further inhibit protein synthesis by impairing the Akt/mTOR (mammalian target of rapamycin) pathway and promoting protein breakdown by activating the ubiquitin-proteasome pathway [14–16]. Besides controlling muscle growth, evidence from animal studies suggests that myostain and activin also constrain AMP-activated protein kinase activity. This in turn reduces glucose transporter type 4 (GLUT4) expression and translocation and acetyl-CoA carboxylase phosphorylation with adverse effects on insulin sensitivity and lipid oxidation, respectively [14]. Interestingly, a recent study described increased circulating myostatin concentrations in adults with obesity compared to lean controls, and a positive correlation between myostatin and insulin resistance indices [17]. To counteract these effects, an inhibitor of the myostatin and activin A activity, known as follistatin, is secreted from skeletal muscle. As shown in a study using follistatin transfected mice, follistatin overexpression resulted in reductions of whole-body and liver fat and increases in muscle, with further improvements in insulin sensitivity and muscle insulin signalling [18]. Thus, upregulation of myostatin and activin A or downregulation of follistatin may lead to impaired muscle growth and muscle wasting, with implications for metabolic health.

Increased accumulation of adipose tissue within and between muscle fibers also contribute to reductions in muscle mass and development of metabolic disorders. Adipose tissue not only stores energy in form of free fatty acids but also synthesizes and secrets pro-inflammatory cytokines (e.g. tumor necrosis factor alpha, interleukin-6 and -8) that are involved in skeletal muscle inflammation and insulin signaling [19,20]. Infiltration of immune cells in intra- and intermuscular adipose tissue depots, including macrophages and T cells, and their further polarization into pro-inflammatory phenotypes leads to additional increases in circulatory citokines [19,20]. Furthermore, these adipose depots have been shown to reduce the capacity of muscle mitochondria to oxidize fatty acids, which may lead to a specific reduction of type I muscle fibers (slow-twitch fibers containing key elements for the glucose metabolism) [13]. Supporting this altered fiber type profile, the percentage of type I fiber in adults with obesity and metabolic syndrome was indeed lower than in normal weight controls, where both groups had a sedentary lifestyle [21]. Thus, skeletal muscle insulin resistance may also contribute to dyslipidemia development; instead of being used by muscles, glucose is redirected to the liver, where it stimulates hepatic de novo lipogenesis and, consequently, hyperlipidemia [22]. Although the pathophysiology of metabolic disorders in children may differ from adults, other pathways explaining the interplay between adiposity, muscle wasting, and metabolic dysfunction have been suggested; as fully described by Wu & Ballantyne [20].

Potential therapeutic approaches targeting the pathways discussed above have been tested in clinical studies with varied results. For example, a phase 1 randomized controlled trial (RCT) has shown that localized administration of ACE-083 (a modified form of the human follistatin) to the rectus femoris and tibialis anterior muscles of healthy postmenopausal women resulted in greater muscle volume (as assessed by magnetic resonance imaging; MRI) without serious adverse events [23]. In contrast, subcutaneous administration of ACE-031 (modified form of human activin receptor type IIB) to boys with Duchenne muscular dystrophy did not alter lean nor fat mass (by dual-energy x-ray absorptiometry; DXA) after the second dosing regime, when this second phase RCT was terminated due to adverse events not related to muscle health [24]. Several candidate drugs (e.g. including insulin, rosiglitazone, and sex hormones) have also been considered for concurrent treatment of muscle loss and associated metabolic disorders, but beneficial effects remain to be confirmed in clinical studies [25,26].

3. Overview of the current literature

A total of 15 studies, published between July 1996 and October 2017, investigating the associations between muscle mass and metabolic dysregulation in the pediatric population were identified by a comprehensive search of the literature (see details in Supplementary Material). The sample size of studies ranged from 40 to 7321 participants (median of 501 participants), including children and adolescents of both sexes ($n = 12$ studies), only females ($n = 2$), or only males ($n = 1$). Only one study assessed longitudinal changes of muscle mass and its association with measures of metabolic dysregulation; other studies used cross-sectional data of prospective cohort studies ($n = 5$ studies), survey studies ($n = 3$), clinical trials ($n = 2$), or were cross-sectional studies only ($n = 4$). The majority of studies assessed lean soft tissue (LST)

using DXA ($n = 8$ studies) and fat-free mass (FFM) by bioelectrical impedance analysis (BIA; $n = 5$) or air-displacement plethysmography (ADP; $n = 1$). Although LST and FFM provides an estimate of skeletal muscle mass [27], other compartments of the human body are also measured concurrently [28]. For example, the sum of total water, protein, carbohydrate, non-fat lipids, and soft tissue minerals yields LST, and the sum of LST and bone mineral content results in FFM [28]. Only two studies measured skeletal muscle tissue using advanced imaging techniques, such as MRI ($n = 1$) and peripheral quantitative computed tomography (pQCT; $n = 1$). Because each body composition technique estimates a different body compartment containing skeletal muscle, and it is important to understand exactly which compartment was measured by the reviewed studies, precise terminology as measured by the technique employed for body composition assessment is used in this manuscript (possibly differing from original studies) [28].Furthermore, the terms "skeletal muscle" and "muscle mass" are adopted here to generically describe LST, FFM, and skeletal muscle tissue.

Inconsistent associations between muscle mass and metabolic dysregulation were reported by these studies in unadjusted and adjusted analyses (Table 1; Fig. 1). Muscle mass was inversely associated with at least one metabolic risk factor in six studies, positively associated in eight studies and not associated with any metabolic risk factors in one study. As these studies evaluated distinct single (i.e. glucose metabolism, lipid profile, and blood pressure) or clustered (i.e. composite metabolic risk score and metabolic syndrome) components of the metabolic profile, results assessing the associations of muscle mass with each of these components are discussed below.

4. Implications of muscle mass on single metabolic risk factors

4.1. Glucose metabolism

Skeletal muscle is the primary site for insulin-stimulated glucose uptake, contributing directly to the maintenance of glucose homeostasis [29]. When sensitivity to the effects of insulin is reduced, circulating glucose concentrations increase and chronic conditions such as type 2 diabetes likely manifest [30]. From the studies reviewed, eight evaluated the relationship between measures of muscle mass and fasting glucose or insulin sensitivity in the pediatric population [31–38].

Regarding the concentration of circulating glucose, one cross-sectional survey including 1420 participants described a more than three times increase in the likelihood of having hyperglycemia in Korean boys and girls with a body composition phenotype of low muscle mass [38]. In this study, participants were defined as having low muscle mass if the sum of LST from their arms and legs (i.e. appendicular LST; Table 2) adjusted for body weight was below the lower quintile of the studied population [38]. 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 ($\beta = -0.017$; 95% CI -0.027, -0.008) and girls ($\beta = -0.018$; 95% CI -0.034, -0.002) [32]. In contrast, results from another cross-sectional survey (the US National Health and Nutrition Examination Survey; NHANES) with a greater sample size ($n = 3004$) indicated a positive, but weak correlation of fasting glucose with whole-body LST (by DXA), divided by squared height in boys ($r = 0.149$) [35]. 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 [39].

The contradictory findings above can be partially attributed to the methodological differences in the assessment of muscle mass. Despite using the same body composition technique (DXA, which is considered the reference method for LST measurements), indices of muscle mass were calculated employing two different approaches with none of them being free from flaws. Correcting muscle mass measures for differences in body weight and stature standardizes body composition data and is a common practice in the reviewed studies (Table 3). However, 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) [5]. Another limitation of using weight-adjusted indices is that the level of adiposity can influence the associations between muscle mass and metabolic risk factors; in fact, the ratio of muscle mass to body weight decreases as body fat percentage increases. According to the authors of the first study, this approach was used because previous research in the Korean population found a greater association between metabolic dysregulation and weight-adjusted muscle mass compared to other indices [38]. A more appropriate strategy for correcting differences in growth among children and adolescents with reduced statistical bias is to adjust muscle mass for height, which is an independent component of body composition [5]. Although Weber et al. has attempted to use a height-adjusted index [35], correcting muscle mass for squared height appears to be incorrect in adolescents because body weight is not proportional to squared height during pubertal growth [40]. As confirmed by a recent study using data from the NHANES, body weight is more proportional to the cube of the height in non-Hispanic white individuals aged 8 to 17 years [41]; further studies are required to evaluate whether muscle mass is also similarly more proportional to the cube of the height in children and adolescents. It is also relevant to note that body fat and anthropometrics vary by ethnicity, with Hispanic boys and girls having greater body fat percentage (using DXA) than non-Hispanic white and black individuals, although they are shorter and weigh less [42,43]. Thus, adjustments of muscle mass may be ethnic specific.

A greater number of studies investigated the associations between muscle mass and insulin sensitivity [31–37]. 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 [36]. 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 insulin resistance (HOMA-IR) in boys ($\beta = -0.203$; 95% CI -0.245, -0.161) and girls ($\beta = -0.111$; 95% CI -0.172, -0.049) [32]. The association between these measures remained significant ($\beta = -0.178$; 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 [32]. Given the large sample size of these studies, adjustments for multiple factors were possible while maintaining statistical power to provide stronger evidence that low muscle mass influences insulin sensitivity in individuals with different biological characteristics and lifestyles. However, a cross-sectional study assessing FFM by BIA in 1089 European individuals of similar age described opposite results [31]. 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 $p < 0.001$ [31]; but limitations inherent to the body technique employed may have contributed to inaccurate measurements of FFM. Bioelectrical impedance analysis is highly sensitive to hydration status requiring individuals to be in a euhydrated state [44], a standardized clinical condition hardly obtained in large-scale observational studies. Moreover, a cross-sectional study of 215 adolescents found that the likelihood of having hyperinsulinemia increased by a factor of 0.92 (odds ratio [95%CI = 0.86–0.99], $p = 0.03$) when weight adjusted FFM (measured by ADP) was included in the model [37].

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 oral glucose tolerance test (OGTT) [33]. Although MRI provides a more accurate and direct measure of the skeletal muscle tissue and fat infiltration within muscles [28], findings from the study revealed no associations between total skeletal muscle tissue, insulin sensitivity, or any OGTT

Table 1
Characteristics and main outcomes of the included studies assessing muscle mass and metabolic risk factors in children and adolescents.

Author, year (Ref.)	Study design	Population characteristics						BC techniques	Outcomes
		Sample size (n)	Age (years)[a]	Sex (M/F)	BMI (kg/m^2)[a]	Ethnicity/Race (n)	Sexual maturation		
Daniels et al., 1996 [63]	Cross-sectional	201	11.7 ± 2.7	105/96	NR	Black: 98 White: 103	NR	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 et al., 2003 [66]	Cross-sectional	384	♂: 13.52 ± 1.60 ♀: 13.49 ± 1.69	179/205	♂: 22.13 ± 4.61 ♀: 22.68 ± 5.67	Black: 141 Hispanic: 117 White: 116 Other: 10	Assessed, but NR	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 et al., 2006 [34]	Cohort	234	5.9 ± 0.3	133/101	Z-score ♂: 0.14 (−0.04, 0.33) [b] ♀: 0.50 (0.32, 0.67) [b]	European, mostly White of mixed SES	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 et al., 2009 [65]	Cross-sectional	425	♂: 14.6 ± 1.9; ♀: 14.7 ± 1.9	200/225	♂: 21.5 ± 3.9; ♀: 21.4 ± 3.7	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 et al., 2012 [33]	Cross-sectional	40	15 ± 1.6	40/0	35.0 ± 4.6	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)
Hou et al., 2015 [32]	Cohort	501	15	278/223	NR	Hong Kong Chinese	NR	DXA[c]	↑ Appendicular LST[c] was associated with ↓ glucose, insulin and HOMA-IR
Weber et al., 2014 [35]	Cross-sectional	3004	16.1 ± 2.5	1738/1266	Z-score All: 0.44 ± 1.2; ♂: 0.51 ± 1.2 ♀: 0.39 ± 1.0	Non-Hispanic White: 71.9% Non-Hispanic black: 16% Mexican American: 12.1%	NR	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 [36]	Cross-sectional	7321	8-20[f]	4316/3005	NR	Black: 1685 White: 1931 Mexican-American: 2009	NR	DXA[g]	For each quartile[g] 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 [75]	Cross-sectional	667	16.8 ± 0.3	348/319	Z-score All: 0.65 ± 1.2 ♂: 0.58 ± 1.2 ♀: 0.73 ± 1.2	Chilean of low to middle SES	All post puberty (Tanner V)	DXA[h]	Having low relative FFM[h] was associated with risk of having MetS[e] 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 [64]	RCT (baseline data)	730	12.1 ± 0.7	0/730	23.5 ± 6.0 Z-score: 1.00 ± 1.04	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)
Garcia-Marco et al., 2016 [31]	Cross-sectional	1089	14.8 ± 1.2	509/580	All: 21.4 ± 3.7 ♂: 21.4 ± 4.0 ♀: 21.3 ± 3.4	European	NR	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 ≥63.5 kg of FFM was associated with an unhealthier clustered CVD risk[i] in boys, and ≥ 46.1 kg in girls
Kim & Park, 2016 [38]	Cross-sectional	1420	12-19[f]	749/671	Low muscle mass[j]: 24.7 ± 0.4 Normal muscle mass: 20.4 ± 0.1	Korean	NR	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 [37]	Clinical trial (baseline data)	215	15.4 ± 1.4	97/118	Z-score 0.64 ± 0.99	Black: 65 White: 127	Prepubertal/ early-mid	ADP	The odds of being classified as hyperinsulinemic ↑ by a factor of 0.92

(continued on next page)

Table 1 (*continued*)

Author, year (Ref.)	Study design	Population characteristics						BC techniques	Outcomes
		Sample size (*n*)	Age (years)[a]	Sex (M/F)	BMI (kg/m^2)[a]	Ethnicity/Race (*n*)	Sexual maturation		
						Asian: 11 Multiracial: 6 Other: 6	pubertal/ late pubertal (*n*) ♂: 5/60/30 ♀: 3/53/61		(OR, 95%CI 0.86–0.99; $p = 0.03$) when relative FFM[k] was included in the analysis
Brion et al., 2007 [62]	Cross-sectional	6863	9.9 (9.7, 10.1)[b]	3401/3462	All: 17.5 (15.7, 19.0)[b] ♂: 17.3 (15.6, 18.7)[b] ♀: 17.7 (15.7, 19.4)[b]	European	Assessed, but NR	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 [73]	Longitudinal	236	11-18[f]	0/236	Pre-menarche: 18.3 ± 2.9 Post-menarche: 20.7 ± 3.4 Early adulthood: 21.9 ± 3.2	European	All prepuberty at baseline	DXA and pQCT[l],	↑ 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 computed tomography; SBP, systolic blood pressure; SES, socioeconomic status; SM, skeletal muscle; SMI, skeletal muscle index; TG, triglycerides; Total-C; total cholesterol; WC, waist circumference.
Data on ethnicity was reported in Jeffery et al. [77]
[a] Values are expressed as mean ± standard deviation unless otherwise stated.
[b] Values are expressed as geometric mean and interquartile range (IQR, 25th–75th).
[c] Appendicular LST was calculated as {1.13 × appendicular LST (kg) – [0.02 × age (years) + (0.61 × sex)] + 0.97}/ total weight [kg] × 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) × 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, VO2max, 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) × 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) × 100.

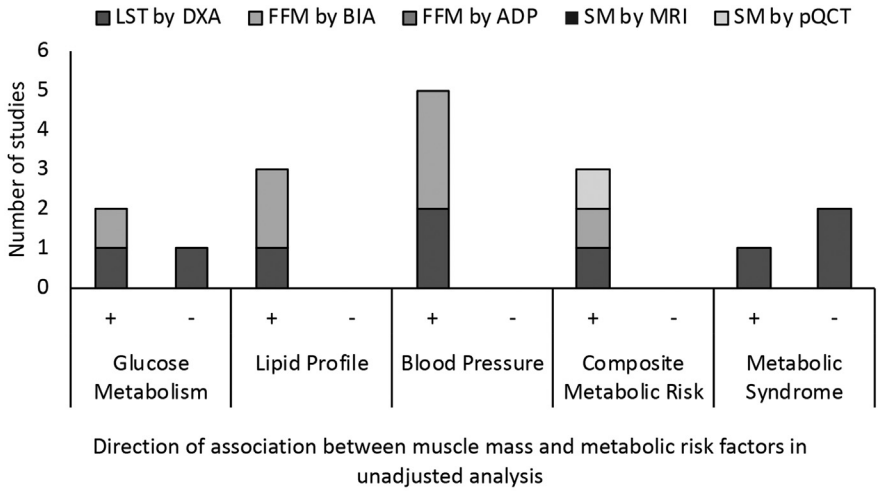
parameters. By contrast, increased intramuscular fat was associated with decreased insulin sensitivity ($r = -0.53$) and increased OGTT-insulin area under the curve (AUC) ($r = 0.31$) [33]. Briefly, intramuscular fat depots release fatty acids and cytokines that impair the signaling mechanisms of insulin on muscles, contributing to the development of insulin resistance [45].

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 covariates found inverse associations between muscle mass and indirect measures of insulin resistance [32,36]. However, other studies provide evidence of positive associations between these variables [31,35,37]. 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 [46]; and a more adequate and widely accepted measure (reference standard) is the glucose clamp method [47]. Of the studies reviewed here, only one attempted to use logarithmic transformation of HOMA-IR [34], an approach that corrects the skewed distribution of fasting insulin, providing a stronger correlation of this index with the glucose clamp [47]. In this study of prepubertal children, however, FFM by BIA was neither significantly associated with log (HOMA-IR) nor fasting glucose concentrations ($p > 0.05$) [34]. 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.

4.2. Lipid profile

Abnormalities of lipid metabolism lead to an increased risk for development of premature cardiovascular dysfunction in children and adolescents [48]. These abnormalities are often characterized by measuring components of the plasma/serum lipid profile, such as total cholesterol, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol, and triglycerides concentration [49]. The associations between these components and measures of muscle mass were investigated in five of the reviewed studies [31,34–36,38].

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 [36,38]. 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



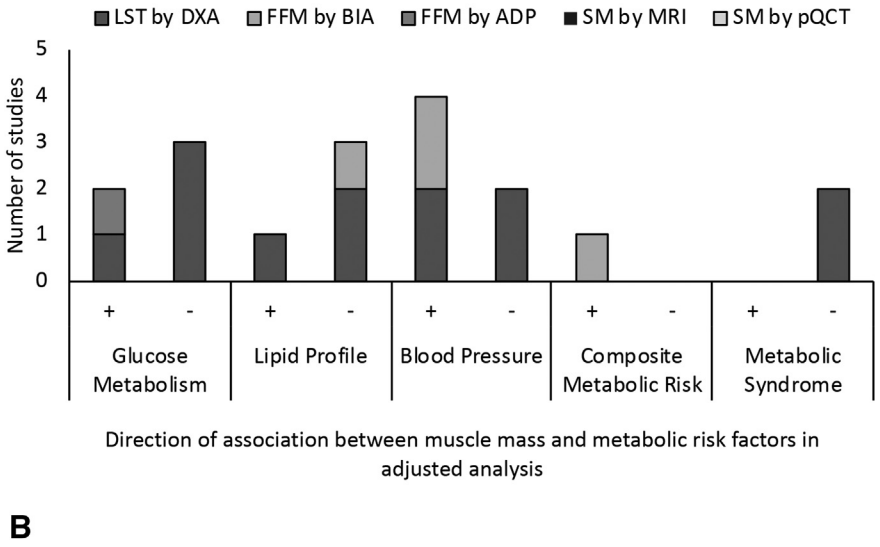


Fig. 1. Number of reviewed studies evaluating the associations between muscle mass and single or clustered metabolic risk factors in (A) unadjusted analysis and (B) adjusted analysis according to body composition technique. Studies were adjusted differently for several covariates, including personal (e.g. age, sex, birth weight, fat mass or body mass index, race/ethnicity, and pubertal stage), lifestyle (e.g. physical activity or sedentary behaviors, dietary intake, alcohol experience, and smoking), and parental factors (e.g. family history of disease, maternal smoking, household income, and education). **Symbols:** +, positive associations; −, negative associations; **Abbreviations:** ADP, air displacement plethysmography; BIA, bioelectrical impedance analysis; DXA, dual-energy x-ray absorptiometry; FFM, fat-free mass; LST, lean soft tissue; MRI, magnetic resonance imaging; pQCT, peripheral quantitative computed tomography; SM, skeletal muscle.

cholesterol (OR = 0.67; 95% CI 0.61–0.75), and low HDL cholesterol (OR = 0.55; 95% CI 0.49–0.61), all $p < 0.001$, independently of age, sex, and race/ethnicity [36]. 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 triglycerides and low HDL cholesterol [38]. As physical activity and dietary intake are known factors to play a role on muscle mass and metabolic conditions [50–52], 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) [38], they have inherent limitations [53–55]. 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 [55]; however, this approach was not adopted by the authors [38]. 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 [31] or LST divided by squared height (using DXA) [35] were associated with improved lipid metabolism in adolescents. Age- and sex- specific measures of muscle mass were positively associated with triglycerides levels in boys of both studies ($r = 0.173$–0.278) [31,35] and in girls of one study ($r = 0.123$) [31], and inversely correlated with HDL cholesterol ($r = -0.310$ and $r = -0.233$, for boys and girls, respectively) [35]. After further adjustment for fat mass, only the relationship with HDL cholesterol remained significant (OR = 1.5 95% CI 1.2–1.9), suggesting that associations between LST divided by squared height and triglycerides is partially mediated by fat mass [35]. In fact, fat mass is a predictor of triglycerides concentrations in overweight children and

Table 2
Definition used in the reviewed studies to classify children and adolescents as exhibiting a body composition phenotype of low muscle mass.

Definition of low muscle mass	Cut points	Author, year (Reference)
Children in the lowest quintile of LST for the study population	NR	Brion et al., 2007 [62]
Adolescents with relative FFM[a] ≤ 25th percentile of the study population adjusted for sex	NR	Burrows et al., 2016 [75]
Adolescents in the lowest quintile of appendicular LST[b] according to sex and age group	NR	Kim & Park, 2016 [38]
Children and adolescents in the lowest quartile of relative LST[c]	≤64.2%	Kim & Valdez, 2015 [36]

Abbreviations: LST, lean soft tissue; FFM, fat-free mass, FM, fat mass; NR, not reported.
[a] Definition of FFM is not clearly stated in the original article.
[b] Appendicular LST is defined as Appendicular LST/body weight.
[c] Relative LST is defined as (LST/LST + FM) × 100.

adolescents [56]. Obesity can result in a low-grade chronic inflammation state characterized by increased production of pro-inflammatory cytokines [57]. These cytokines are known to not only impair the regenerative capacities of skeletal muscle, but also contribute to dyslipidemia and insulin resistance. Interestingly, opposing results were found by Murphy et al. in prepubertal children (mean age = 5.9 years old) [34]. Unadjusted analysis revealed slightly greater positive association between FFM (as measured by BIA) and triglycerides in girls only ($r = 0.21$), but adjustments for fat mass 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 cholesterol and girls in early puberty have higher HDL cholesterol concentrations; however, no differences were observed in triglycerides concentrations [58].

Another factor that may influence the association between muscle mass and lipid profile is 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 [59]. Children of Black African origin had lower mean systemic concentrations of total and LDL cholesterol and triglyceride than white Europeans; compared to white Europeans, South Asians had similar total and LDL cholesterol concentrations, but lower HDL and higher triglycerides [59]. Despite these known ethnic differences in lipid profile, none of the studies discussed above [31,35] (with heterogeneous study samples from the US [20] and European countries [16]) 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 body fat 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.

4.3. Blood pressure

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 on in life [60,61]. 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 [31,34–36,38,62–66].

Regarding each component of blood pressure alone, muscle mass was moderately positively associated with systolic blood pressure in unadjusted ($r = 0.27$–0.60) [31,34,35,63,64] and adjusted analyses ($r = 0.29$–0.41) [62,65,66] in both boys and girls. Indeed, there was a difference of nearly 8 mmHg (95% CI 6.78–9.13, $p < 0.001$) in systolic blood pressure between children of young age (mean 9.9 years) in the highest and lowest quintiles of LST as measured by DXA [62]. 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 systolic blood pressure 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 [36]. In this study, children and adolescents with values of systolic blood pressure 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 [67].

Only four studies found weak to moderate positive correlations of diastolic blood pressure to measures of muscle mass [62–65] ($r = 0.14$–0.50). It is important to note that results from one of these studies [64] are questionable because it employed the bipolar impedance technique, also known as foot-to-foot BIA, in children with overweight and obesity (>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 [68]. After controlling for several confounding factors (e.g.: sex, age, height, and puberty stage), diastolic blood pressure remained significantly associated to muscle mass in one study in adolescents ($r = 0.32$) [65], but not in children [62]. 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 [69], adolescents in a more advanced pubertal stage could have greater

Table 3
Indices of muscle mass reported by the reviewed studies according to body composition technique.

Body composition technique	Indices	Author, year (Reference)
DXA	**Relative LST**	
	(LST/body weight) × 100	Cheng & Wiklund, 2018; [73]
	(LST/LST + FM) × 100	Kim & Valdez, 2015 [36]
	LST adjusted to height	
	LST/height^2	Weber et al., 2014 [35]
	Appendicular LST	
	{1.13 × appendicular LST - [0.02 × age (years) + (0.61 × sex)] + 0.97}/total body weight × 100	Hou et al., 2015 [32]
	Appendicular LST/body weight	Kim & Park, 2016 [38]
MRI	**Relative SM**	
	(SM/body weight) × 100	Lee et al., 2012 [33]
ADP	**Relative FFM**	
	(FFM/body weight) × 100	Schvey et al., 2016 [37]

Abbreviations: ADP, air displacement plethysmography; DXA, dual-energy x-ray absorptiometry; FFM, fat-free mass; FM, fat mass; LST, lean soft tissue; MRI, magnetic resonance imaging; SM, skeletal muscle.

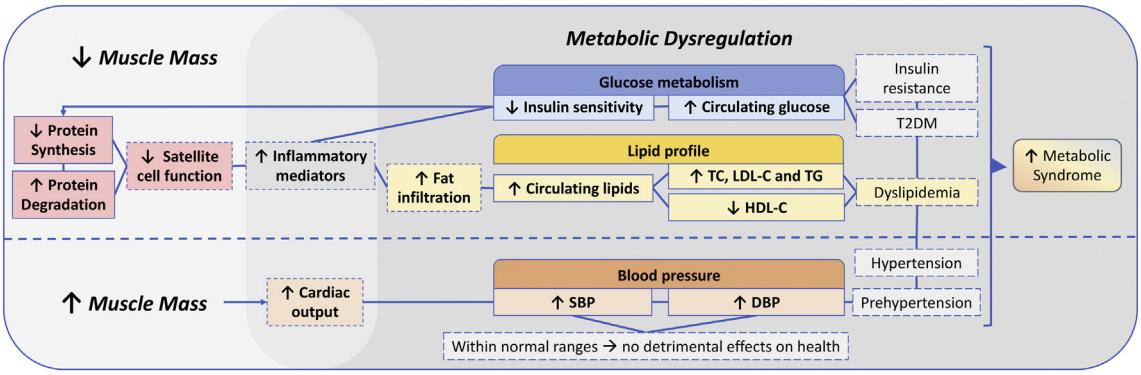


Fig. 2. Schematic explanation of the associations between low muscle mass and metabolic dysregulation in pediatrics. **Symbols:** ↑, increased; ↓, decreased **Abbreviations:** HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density cholesterol; TC, total cholesterol; TG, triglycerides; T2DM, type 2 diabetes mellitus.

amounts of muscle mass than their peers. Specifically, there is a marked activation of the growth hormone/insulin-like growth factor 1 (GH/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 [69]. 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 [35,38]. 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) [38], 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) [35]. 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 diastolic blood pressure 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 [38]. In the second study, individuals with elevated blood pressure were those with systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg [35]. According to the most recent American Academy of Pediatrics Clinical Practice Guidelines, children older than 13 years with systolic blood pressure ranging from 120 to 129, but diastolic blood pressure < 80 mmHg, are categorized as elevated blood pressure [70]; 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 hinder comparison of findings. Results from a study conducted in the US, for example, demonstrated that non-Hispanic black boys had on average 2 mmHg higher DBP than Asians boys and non-Hispanic black girls had on average 3 mmHg SBP than non-Hispanic whites; however, there were no ethnic differences for SBP and DBP within each pubertal stage [71].

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, the majority of 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 [63]. 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 [72]. 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.

5. Implications of muscle mass on clustered metabolic risk factors

5.1. Composite metabolic risk score

Two 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

Table 4
Summary of findings describing the associations between muscle mass and single or clustered metabolic risk factors in children and adolescents.

Metabolic risk factors	Key findings
Glucose metabolism	Due to inconsistent approaches to quantify muscle mass and glucose metabolism, it is unclear whether those presenting with low muscle mass have a decreased responsiveness to the actions of insulin
Lipid profile	There is a limited understanding on whether low muscle mass is associated with an increased risk of lipid abnormalities; reviewed studies have inconsistently controlled for the influence of body fat or the variability of including children with diverse ethnic origins and pubertal stages
Blood pressure	Most studies described a positive association between muscle mass and blood pressure, within the reference range, in children and adolescents. However, comparison of results among studies is challenging as authors have used diverse methodologies to assess muscle mass or have failed to control for key confounders
Composite Metabolic Risk Score	Evidence of positive association between muscle mass and composite metabolic score is limited after including body fat as a covariate in the analysis
Metabolic Syndrome	Low muscle mass appears to be characteristic of a more detrimental metabolic condition with several risk factors clustered together. Nevertheless, after controlling for body fat, one study failed to show association between metabolic syndrome and muscle mass

et al., composite risk scores are useful in pediatric studies because variations in individual risk factors can be compensated [50], with higher scores indicating a worse metabolic profile. Although these studies calculated composite scores slightly differently, positive association with measures of muscle mass was reported in boys [31] and girls [31,73] with healthy body weights. Specifically, Gracia-Marco created a composite score based on the levels of systolic blood pressure, cardiovascular fitness ($VO_{2\ max}$), HOMA-IR, C-reactive protein, total cholesterol to HDL ratio, and triglycerides [31]; 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 cholesterol, and triglycerides [73]; increases in muscle cross-sectional area as measured by pQCT ($r = 0.32$) 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 fat mass in one study [73], but remained in the other study with FFM explaining nearly 57% of the variation in the composite score in girls [31].

5.2. Metabolic syndrome

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 metabolic syndrome. Despite the lack of definitive criteria for establishment of metabolic syndrome in the pediatric population [74], three reviewed studies investigated the implications of muscle mass on this condition. In two cross-sectional surveys [35,38], metabolic syndrome was defined as the presence of three or more of the following factors: abdominal obesity, hyperglycemia, high triglycerides, low HDL cholesterol and hypertension. Using this criteria, prevalence of metabolic syndrome 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%), $p < 0.001$ [38]. Additionally, multiple logistic regressions adjusted for several confounding variables, but not fat mass, revealed an odds of 5.28 (95% CI 2.76–10.13) for the presence of metabolic syndrome in children with low muscle mass [38]. 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 metabolic syndrome; however, multivariate regression including measures of fat mass in the model removed the associations between muscle mass and metabolic syndrome [35]. In the third study [75], where cross-sectional data of a prospective cohort study in older adolescents (aged 16 to 17 years, all postpubertal stage) were evaluated, metabolic syndrome was defined as the presence of abdominal obesity and two of the following: high fasting glucose, high triglycerides, low HDL, and hypertension. According to the authors, there was a greater likelihood of metabolic syndrome 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.

6. Conclusion and future directions

A growing body of evidence supports low muscle mass as a risk factor for child metabolic health (Fig. 2, Table 4). However, contradictory results were found in large observational studies, with increased muscle mass being associated with increased risk for single or clustered metabolic risk factors. These inconsistent results may be partially explained by the heterogeneity of techniques used to assess body composition and metabolic markers and the lack of statistical control for important confounders, such as physical activity, diet, ethnicity, pubertal stage, and body fat. Clearly, more research is required.

To advance the field, there is an urgent need to clarify the best index of muscle mass in children and adolescents. Perhaps muscle mass scales more accurately to the cubed height (and not to the squared height) in this population. Then future longitudinal studies using precise techniques may investigate whether small changes in muscle mass during growth are related to the development of metabolic dysregulation. Another study design that may provide some insight into causal relationship is the case-control design, with participants matched for pubertal stage, sex, and body fat index (i.e. body fat adjusted for squared height) [76]. Ongoing studies in our group will assess whether children with metabolic dysregulation (cases) have lower muscle mass than children without metabolic dysregulation (controls) independent of obesity status, physical activity levels, and dietary intake. As establishing a cause-effect relationship is challenging, animal models may provide further mechanistic explanations for the associations between skeletal muscle and metabolic dysregulation early in life. Thus, more research is needed to confirm the optimal skeletal muscle mass in childhood that confers metabolic health, physical function, and well-being in adulthood.

Author contributions

CEO and JRBT performed the literature search. CEO drafted the manuscript. DAR, CJF, SBH, CMP, AMH provided critical intellectual contributions. All authors have read and approved the final manuscript.

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Declaration of Competing Interest

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.metabol.2019.153949.

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