SYSTEMATIC REVIEW

Muscular Fitness and Cardiometabolic Variables in Children and Adolescents: A Systematic Review

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Abstract

Background The importance of muscular fitness (MF) in the performance of activities of daily living is unequivocal. Additionally, emerging evidence has shown MF can reduce cardiometabolic risk in children and adolescents.

Objectives The purpose of this study was to examine and summarize the evidence regarding the relationship between MF phenotypes (i.e., maximum muscular strength/power, muscular endurance, and maximum muscular strength/power/endurance) and cardiometabolic variables (obesity, blood pressure, lipids, glucose homeostasis, inflammatory markers, and clustered cardiometabolic variables) in children and adolescents.

Design This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and was registered with PROSPERO, number CRD42020179273.

Data Sources A systematic review was performed on five databases (PubMed, EMBASE, SciELO, Scopus, and Web of Knowledge) from database inception to May 2020, with complementary searches in reference lists.

Eligibility Criteria for Selecting Studies Eligibility criteria included (1) a study sample of youth aged ≤ 19 years, (2) an assessment of MF with individual or clustered cardiometabolic variables derived from adjusted models (regardless of test/measurement adopted or direction of reported association), and (3) a report of the association between both, using observational studies. Only original articles published in peer-reviewed journals in English, Portuguese, and Spanish languages were considered. The quality of the included studies was assessed by using the National Heart, Lung, and Blood Institute checklist. The percentage of results reporting a statistically significant inverse association between each MF phenotype and cardiometabolic variables was calculated.

Results Of the 23,686 articles initially identified, 96 were included (77 cross-sectional and 19 longitudinal), with data from children and adolescents from 35 countries. The score for the quality of evidence ranged from 0.33 to 0.92 (1.00 maximum). MF assessed by maximum muscular strength/power was inversely associated with lower obesity (64/113 total results (56.6%)) and reduction in clustered cardiometabolic risk (28/48 total results (58.3%)). When assessed by muscular endurance, an inverse association with obesity (30/44 total results (68.1%)) and cardiometabolic risk (5/8 total results (62.5%)) was identified. Most of the results for the relationship between MF phenotypes with blood pressure, lipids, glucose homeostasis, and inflammatory markers indicated a paucity of evidence for these interrelationships (percentage of results below 50.0%).

Conclusion MF assessed by maximum muscular strength/power or muscular endurance is potentially associated with lower obesity and lower risk related to clustered cardiometabolic variables in children and adolescents. There is limited support for an inverse association between MF with blood pressure, lipids, glucose homeostasis biomarkers, and inflammatory markers in children and adolescents.

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Key Points

Muscular fitness assessed by maximum muscular strength/power or muscular endurance is potentially associated with lower obesity in children and adolescents. When considering the assessment of maximum muscular strength/power, tests with lower limb demand (e.g., jumps), tests involving recruitment of upper limbs (e.g., handgrip strength) and results normalized for body mass, and/or a combination of tests that evaluate maximum muscular strength/power and results normalized for body mass have been shown to be more sensitive for this interrelation.

Maximum muscular strength/power or muscular endurance are associated with a lower risk related to clustered cardiometabolic variables in children and adolescents, with no differences attributed to the muscular fitness tests/measurements adopted.

The associations between muscular fitness and blood pressure, lipids, glucose homeostasis biomarkers, and inflammatory markers are inconsistent.

1 Introduction

Cardiovascular disease (CVD) is the leading cause of death among adults globally [1], though the manifestations of the disease in children and adolescents are uncommon [2]. However, risk factors associated with the development of CVD begin during childhood and adolescence, and risk exposure can slowly progress towards disease [2]. Thus, the investigation and monitoring of traditional and emerging cardiometabolic disease risk variables have been routinely assessed in the clinic and primary prevention [3–5].

The importance of muscular fitness (i.e., incorporation of phenotypes of muscular strength, including maximum isometric and dynamic strength, muscular power, and muscular endurance) [6–9] in the performance of activities of daily living is unequivocal. Additionally, there is a growing body of evidence reporting an inverse association between muscular fitness with individual [10–14] and clustered cardiometabolic variables among children and adolescents [11, 13–15], suggesting that muscular fitness may have a mitigating effect on the development of CVD. However, the relationship between muscular fitness and cardiometabolic variables in children and adolescents is not clear, with results showing both an absence of association [16–19] and inverse associations [12, 20, 21].

The inconsistency in findings for associations between muscular fitness and cardiometabolic variables may result from the diversity of muscular fitness tests/measurements adopted by studies (e.g., evaluation of upper or lower limbs, static or moving, counter-resistance effort or use of own body) for assessing different phenotypes of muscular fitness (each one with different assessment procedures) [6, 7]. However, although tests/measurements for the assessment of muscular fitness may influence the result of the association with cardiometabolic risk indicators, there is no standardized assessment for muscular fitness in children and adolescents [22]. In addition, it is speculated that such conflicting results may also be related to the different strategies adopted by the studies to consider body size [23, 24]. This is because a portion of the studies normalized the results for body-related indexes, including body mass [10, 11, 16, 21, 25–33], body mass index (BMI) [28, 34], and fat-free mass [34], while others adopted absolute values [18–20, 35–75], muscular fitness scores obtained from the use of two or more tests (and different procedures for considering body size in each test adopted) [76–79] or mathematical models to create muscular fitness indexes uncorrelated with body mass [12, 13, 32, 66, 80, 81]. Finally, some studies described in the literature failed to control for important covariates directly associated with muscular fitness or/and cardiometabolic variables, such as age [16, 18, 39, 48, 61, 66, 82], sex [20, 28, 36, 38–43, 48, 50, 52, 56, 61, 66, 67, 77, 81–86], sexual maturation [11, 13, 18–20, 28, 34–40, 42, 45, 48–52, 54, 55, 57, 60, 62, 66, 77, 81–83, 86, 87], and physical activity [11, 13, 15, 17–20, 26, 27, 34–38, 41–43, 45, 50, 52, 54, 55, 60–62, 65, 66, 76, 77, 81–84, 86], which may have contributed to the divergent associations observed.

Existing reviews on this topic are available in the literature [6, 9, 88, 89], though they explored a limited number of cardiometabolic risk variables. Further, the impact or the heterogeneity of the results according to the tests/measurements adopted to assess muscular fitness across studies, or results described according to sex, were not considered [6, 9, 88, 89]. Furthermore, although adolescent boys have greater muscle mass and lower body fat compared to adolescent girls, aspects that can confound, or even mediate [77] the association between muscular fitness and cardiometabolic variables, the direction of these associations according to sex is not known [6, 9, 88, 89]. Additionally, the information compiled in the previously published reviews [6, 9, 88] was restricted to the extraction of results in which it was identified that muscular fitness was associated with better results for the investigated cardiometabolic variables, although the same studies had identified absence of association or even inverse association of muscular fitness with

the cardiometabolic variable investigated depending on the investigated muscular fitness phenotype [13].

Thus, the aim of this systematic review was to examine the relationship between muscular fitness and cardiometabolic variables among children and adolescents, advancing previous reviews [6, 9, 88, 89], by comprehensively investigating the relationship between muscular fitness and several cardiometabolic risk variables, considering the heterogeneity of the results according to muscular fitness tests/measurements adopted.

2 Methods

2.1 Protocol and Registration

This systematic literature review was registered in the International Prospective Register of Systematic Reviews—PROSPERO (CRD42020179273) and described according to the items suggested by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses—PRISMA [90].

2.2 Eligibility Criteria

Eligible studies for this review included: (i) original articles in Portuguese, Spanish, or English; (ii) observational (cross-sectional, cohort, and case–control) studies; (iii) studies in which the result for the association between muscular fitness (i.e., maximum muscular strength, muscular endurance, and muscular power) and the indicator investigated was derived from adjusted models (i.e., adjusted for covariates); and (iv) studies that investigated muscular fitness (regardless of test/measurement adopted) and individual or clustered cardiometabolic variables in children and adolescents with no diseases or special clinical conditions (e.g., diabetes, kidney disease, HIV/AIDS) and age group and/or mean age ≤ 19 years [91]. The selection of the descriptors regarding included cardiometabolic variables was based on guidelines/studies described in the literature [3–5]. Based on this information, studies that investigated the relationship between muscular fitness with obesity indicators, blood pressure, lipids, glucose homeostasis biomarkers, and inflammatory markers were included. Studies that investigated the relationship between muscular fitness and clusters of cardiometabolic variables (i.e., two or more variables grouped) were also included in this review. Published peer-reviewed original manuscripts and in-press manuscripts were eligible for inclusion. Grey literature and conference abstracts were excluded.

2.3 Information Sources

The systematic search for potential articles for this review took place during May 2020 using five electronic databases: PubMed, EMBASE, SciELO, Scopus, and Web of Knowledge.

2.4 Search

Systematic searches were adjusted and applied to all databases based on the method elaborated for PubMed, combining different terms for muscular fitness, cardiometabolic variables, and children and adolescents. A variety of descriptors related to each of these terms was entered into each database. Further information regarding the systematic search (descriptors used, search strategy for each database and number of papers captured) can be accessed in Electronic Supplementary Material (ESM) File 1. There was no restriction on the period of publication of original articles. Manual searches were conducted in the reference lists of the included studies and in review articles in which themes similar to that investigated in this review were analyzed. Additionally, experts in the field were contacted for additional studies.

2.5 Study Selection

The procedures for searching and evaluating titles, abstracts, and full-text articles, as well as assessing the risk of bias, were completed independently by two researchers (TRL and PCM), with guidance from a senior researcher (DASS), who in addition to supervising the information-gathering process, established consensus and assisted in resolving any disputes.

2.6 Data Collection Process and Data Items

Descriptive and methodological information and results for the relationship between muscular fitness and the outcomes investigated in each study were extracted. It is necessary to emphasize the absence of a test/reference instrument to assess muscular fitness phenotypes [92]. This is because the manifestations of muscular strength encompassed by muscular fitness can manifest in a number of different ways [93], which implies different ways of measuring. Thus, in view of the use of multiple measures to assess muscular fitness (small or large muscle groups, upper or lower limbs, with the need to support or move the body, or the substantial covariance between the results identified in the measurements with parameters related to body composition) [23], results for the associations investigated in the studies were presented considering such specificities. Thus, the summarized information was described as: (i) evidence derived from studies where absolute muscular fitness was adopted in the analyses

(absence of a strategy to consider parameters of the body size in the expression of muscular fitness results); (ii) evidence from studies where normalized muscular fitness was adopted in the analyses (adoption of strategy to consider body-related indexes in the expression of muscular fitness, e.g., body mass) or; (iii) evidence from studies where absolute/normalized muscular fitness (adoption of both absolute and normalized strategy, e.g., results of absolute muscular fitness from one test, and results of normalized muscular fitness from another test—used to create a composite muscular fitness score. To complement the summarized information, the results were also presented as follows: (i) absolute or normalized values for measurements of maximum muscular strength/power according to tests involving upper or lower limbs; (ii) absolute or normalized values for measurements of muscular endurance according to the need or not of support of the body itself; (iii) absolute, normalized, or absolute/normalized values for measurements of composite muscular fitness score (two or more tests/measurements) according to tests involving the evaluation of the phenotypes maximum muscular strength/power, muscular endurance, or a combination of the two described muscular fitness phenotypes—maximum muscular strength/power/endurance (e.g., muscular fitness score derived from the adoption of one test that measured maximum muscular strength/power and another test that assessed muscular endurance).

To provide further investigation regarding the quality of the evidence of the information included, all results analyzed in this review were also described according to the design (reverse-causation bias), participation rate (selection bias—internal validity), and control for confounding variables (i.e., variables that can influence both the outcome and the exposure—confounding bias). Regarding the calculation of participation rate, although a range of definition has been suggested [94, 95], which can cause disagreements when comparing different studies [96], in the present study, participation rate was defined as the number of respondents who have provided a usable response divided by the total number of initial personal invitations requesting participation [95, 96]—to provide results as a percentage (%), the final value was multiplied by 100. Regarding the control of analyses for confounding variables, although there is no consensus regarding the determining variables for the interrelation between muscular fitness and cardiometabolic variables in children and adolescents, or the number of variables needed to be inserted in the adjusted models in order to reduce confounding factors, it is necessary to somehow consider the appropriate control for confounding variables. The available evidence indicated that information related to age, sex, sexual maturation, and body size (e.g., body mass, height, fat mass, fat-free mass) is relevant in this context [24, 93, 97]. Likewise, the performance of physical activity and systematic bodily activities (e.g., engagement in sports

practices—especially those in which counter-resistance efforts are necessary) was directly associated with muscular fitness [98]. Thus, results according to the number of confounding variables ($0, 1, 2, \geq 3$) considered relevant (i.e., age, sex, sexual maturation, body size, and physical activity) for the association between muscular fitness and cardiometabolic variables inserted as control in the adjusted analyses were also considered in the summary of information.

Based on the summarized results regarding the relationship between muscular fitness and the investigated cardiometabolic variable of the included studies, a global percentage score for the relationship between muscular fitness and the investigated cardiometabolic variables was calculated [(number of results indicating an inverse relationship between muscular fitness and the investigated cardiometabolic variable/number of results for the relationship investigated) $\times 100$]. For example, in the relationship between muscular fitness (assessed by maximum muscular strength/power measurements) and obesity indicators, if the study found a result indicating that higher levels of muscular fitness were associated with lower values for the investigated obesity indicator, that result was considered an inverse association.

After the data were extracted in spreadsheets designed specifically for the review, the outcome variable(s) of each study were classified based on available evidence [3–5] and grouped into six broad categories: (i) general (BMI) and central obesity (waist circumference, WC) indicators; (ii) blood pressure (hypertension/high blood pressure, mean arterial pressure, systolic and diastolic blood pressure); (iii) lipids (total cholesterol, HDL-cholesterol, triglycerides, HDL-cholesterol/total cholesterol ratio, total cholesterol/HDL-cholesterol ratio, [(Triglycerides) – (HDL-cholesterol)]/2, triglycerides/HDL-cholesterol ratio, non-HDL-cholesterol, atherogenic index of plasma); (iv) glucose homeostasis biomarkers [2-h glucose, fasting blood glucose, insulin, Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), Homeostatic Model Assessment of B-cell function (HOMA-B), quantitative insulinsensitivity check index (QUICKI), glycated hemoglobin (HbA1c)]; (v) inflammatory markers [C-reactive protein (CRP), complement factor C3, complement factor C4, ceruplasmin, adiponectin, leptin, white blood cells, interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α)]; and (vi) clustered cardiometabolic variables.

2.7 Risk of Bias in Individual Studies

Quality appraisal was based on the National Heart, Lung, and Blood Institute checklist for observational cohort/cross-sectional studies [99]. This instrument is based on the evaluation of 14 items that comprise methodological aspects according to the design of the study. For cross-sectional studies, items 7 ("Was the timeframe sufficient so that

one could reasonably expect to see an association between exposure and outcome if it existed?") and 13 ("Was loss to follow-up after baseline 20% or less?") were recorded as not applicable. With regard to exposure measures and assessment (item 9), muscular fitness tests/measurements obtained from physical test batteries and/or validated for the population (children and adolescents) were considered valid and reliable measures [22]. Regarding outcome measures (item 11), measured and non-self-reported information for anthropometric indicators of obesity, blood pressure levels, and blood (lipids, glucose homeostasis biomarkers, inflammatory markers) were considered valid and reliable measures. Adjustment for confounding (item 14) was considered sufficient if studies adjusted for at least three relevant variables for the interrelationship between muscular fitness and cardiometabolic variables in children and adolescents (i.e., age, sex, sexual maturation, body size, and physical activity) [24, 93, 97, 98]. For each criterion, a score of +1 is assigned when the answer is positive (yes), while a score of zero (0) is assigned otherwise (that is, a "no," "not applicable," "answer not reported," or "cannot be determined"). The specific global score of the study ranges from zero to 14 and a quality score is determined by: number of questions with positive score "+1"/number of questions with a score of zero "0" (ESM File 2). Thus, scores ranging from 0.0 (low methodological quality/high risk of bias) to 1.0 (high methodological quality/low risk of bias) could be assigned to the articles inserted/analyzed in this review. For cases of disagreement between the two researchers assigned to assess the risk of bias (TRL & PCM), a third researcher (DASS) with experience in this type of study was consulted through a consensus meeting.

2.8 Synthesis of Results

Meta-analyses were planned if data could be meaningfully pooled (i.e., if sufficiently homogeneous in terms of statistical, clinical, and methodological characteristics). Narrative syntheses structured around the results for the association between muscular fitness phenotypes (e.g., maximum muscular strength/power, muscular endurance, combination of maximum muscular strength/power/endurance phenotypes) and the cardiometabolic variables were conducted if meta-analyses were not possible.

3 Results

3.1 Overview of Studies

After systematic search of articles in the databases, exclusion of duplicate information, application of inclusion and exclusion criteria, and incorporation of additional articles

(after additional readings – references of included studies) 96 articles were included (Fig. 1).

The studies included in this review gathered information from children and adolescents from 35 countries. Of this total, 77 were cross-sectional [20, 25–31, 33, 37–64, 67–79, 81–87, 100–118] and 19 were longitudinal [10–16, 18, 19, 21, 32, 34–36, 65, 66, 80, 119, 120]. With regard to the quality of the longitudinal information investigated, in 63.1% of the studies [10, 11, 14, 15, 18, 19, 34–36, 66, 119, 120] the baseline value of the analyzed outcome was added to the adjusted models when investigating the possible effect attributed to the exposure variable on the outcome longitudinally. Of the total number of studies included, in 22 [21, 27, 29, 30, 36–38, 41, 46, 50, 51, 53, 57, 60, 62, 65, 72, 79, 81, 82, 105, 118] the described frequency rate (or calculated based on the information available in these studies) was ≥ 80.0%. Additionally, a frequency rate ≥ 50.0% was verified/calculated in ten studies [12, 16, 18, 40, 61, 79, 87, 102, 116, 120], while in another 31 studies [10, 11, 13–15, 19, 26, 32, 33, 35, 39, 66, 67, 74–76, 78, 80, 84, 85, 101, 103, 104, 107, 108, 110, 111, 114, 115, 117, 119] such values were less than 50.0%. It is noteworthy that in 33 studies [20, 25, 28, 31, 34, 42–45, 47–49, 52, 54–56, 58, 59, 63, 64, 68–71, 73, 77, 83, 86, 100, 106, 109, 112, 113], values referring to frequency rate were not described or the information necessary for the calculation of this indicator was not available. With regard to the number of participants included in the studies, only three trials [37, 47, 62] (which supported the results of the interrelationship of muscular fitness and obesity) were conducted with a sample of less than 100 evaluated. In addition, in approximately 50% of the studies ($n = 45$) [10, 11, 13, 15, 19, 26, 27, 30–34, 49, 51, 56, 57, 65, 67, 68, 70–76, 78–80, 87, 100, 102–107, 109, 110, 113, 115, 116, 119, 120] a high number of variables likely to confound the interrelationship of muscular fitness and cardiometabolic variables were considered in the analysis models (≥ 3 variables). Further details regarding the characteristics, muscular fitness tests/measurements and adjustment variables adopted by the included studies in this review are available in ESM Tables S1–S3.

3.2 Risk of Bias

The methodological quality assessment of each of the included studies in this review can be accessed in ESM Table S4. Briefly, values for the methodological quality/risk of bias score ranged from 0.67 to 0.92 for longitudinal studies and from 0.33 to 0.82 for cross-sectional studies.
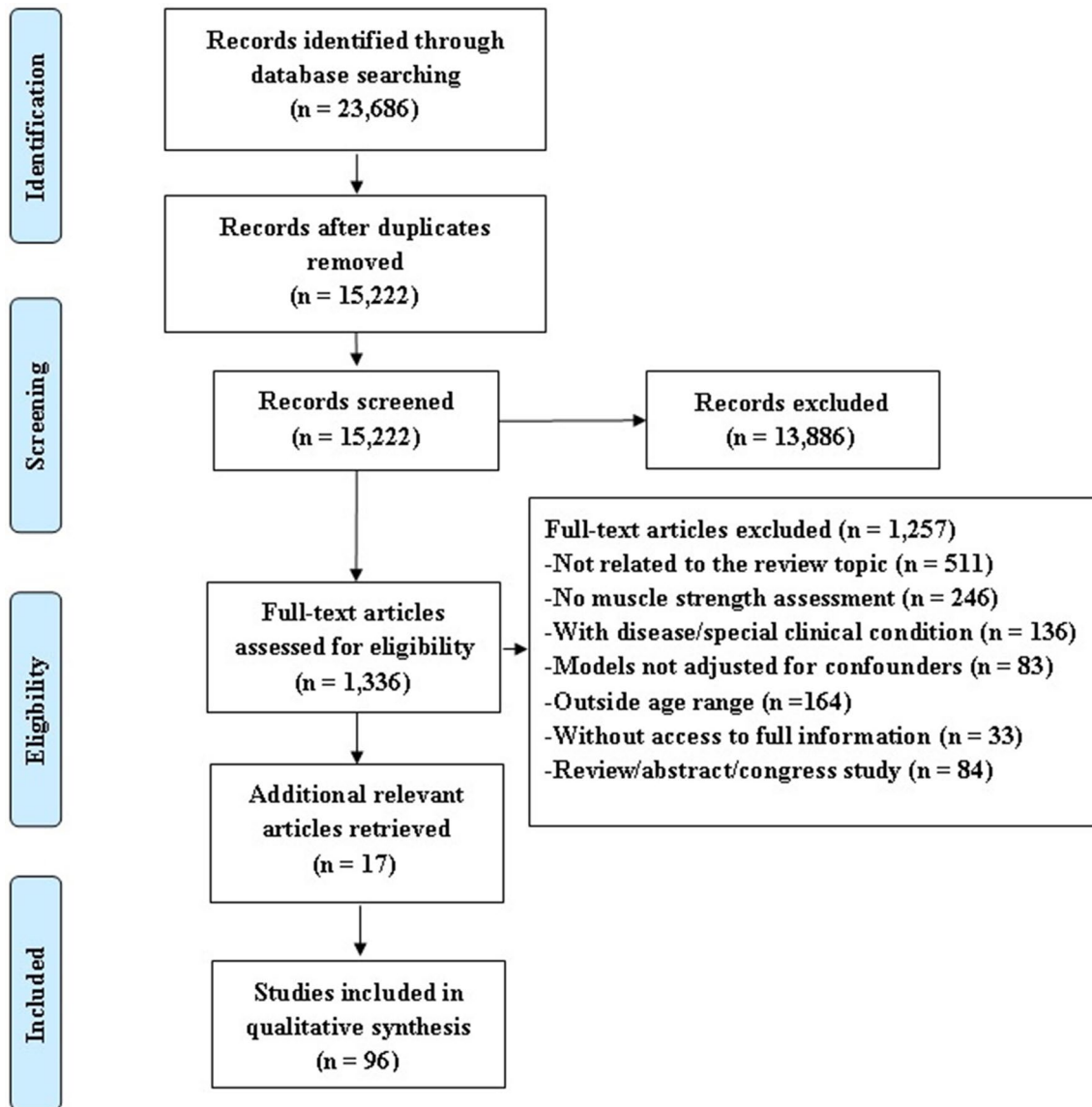
Fig. 1 Results of database searches and criteria used in the selection of studies included to identify the relationship between muscular fitness and cardiometabolic variables among children and adolescents

3.3 Association Between Muscular Fitness and Investigated Outcomes

3.3.1 Muscular Fitness and Obesity Indicators

3.3.1.1 Maximum Muscular Strength/Power and Obesity Indicators The relationship between maximum muscular strength/power and obesity indicators (BMI and WC) has been investigated in 43 studies; seven studies with a longitudinal design [11, 15, 18, 19, 34, 65, 66] and 36 studies with a cross-sectional design [20, 25–28, 37–41, 44, 45, 47, 48, 51, 52, 54–64, 67, 76, 77, 81–84, 86, 87] (ESM Table S5). Considering all the information available in the studies (Table 1, ESM Tables 6 and 7), 56.6% of the evidence indicated that

maximum muscular strength/power was inversely associated with obesity indicators in children and adolescents. In this context, tests where maximum muscular strength/power was evaluated by jumps (78.1%; 34/43 results), upper limbs and values normalized for body-related indexes (93.7%; 15/16 results) and/or a combination of tests that evaluated maximum muscular strength/power and results normalized for body related indexes (88.9%; 8/9 results) presented a greater number of results indicating an inverse relationship of maximum muscular strength/power with obesity indicators. However, it is necessary to highlight that evidence from 19 studies, 28.7% of the evidence [20, 34, 37, 40, 41, 44, 51, 52, 54, 56, 57, 60, 61, 63, 64, 66, 83, 86, 87], identified a direct relationship between muscular fitness and obesity

Table 1 Summary of results assessing the relationship between maximum muscular strength/power[a] with cardiometabolic variables, and global percentage of findings related to the inverse association with cardiometabolic variables among children and adolescents

Cardiometabolic variables	Combined evidence			Longitudinal evidence			Cross-sectional evidence		
	n/N for inverse association[b] (%)			n/N for inverse association[b] (%)			n/N for inverse association[b] (%)		
	Boys	Girls	Total	Boys	Girls	Total	Boys	Girls	Total
Maximum muscular strength/power measurements[a]									
Obesity indicators	16/29 (55.2)	16/29 (55.2)	64/113 (56.6)	1/1 (100.0)	0/1 (0.0)	8/14 (57.1)	15/28 (53.6)	16/28 (57.1)	56/99 (56.6)
BMI	13/21 (61.9)	11/21 (52.4)	46/84 (54.8)	1/1 (100.0)	0/1 (0.0)	3/7 (42.8)	12/20 (60.0)	11/20 (55.5)	43/77 (55.8)
WC	3/8 (37.5)	5/8 (62.5)	18/29 (62.1)	–	–	5/7 (71.4)	3/8 (37.5)	5/8 (62.5)	13/22 (59.1)
Blood pressure	2/15 (13.3)	5/14 (35.7)	17/66 (25.7)	0/6 (0.0)	2/5 (40.0)	3/26 (11.5)	2/9 (22.2)	3/9 (33.3)	13/39 (33.3)
Hypertension/ high BP	0/2 (0.0)	0/1 (0.0)	0/3 (0.0)	0/1 (0.0)	–	0/1 (0.0)	0/1 (0.0)	0/1 (0.0)	0/2 (0.0)
Mean arterial pressure	2/3 (66.7)	2/3 (66.7)	6/13 (46.1)	–	–	0/2 (0.0)	2/3 (66.6)	2/3 (66.6)	6/11 (54.5)
SBP	0/7 (0.0)	2/7 (28.6)	5/29 (17.2)	0/4 (0.0)	2/4 (50.0)	2/15 (13.3)	0/3 (0.0)	0/3 (0.0)	3/14 (21.4)
DBP	0/3 (0.0)	1/3 (33.3)	6/21 (28.6)	0/1 (0.0)	0/1 (0.0)	1/8 (12.5)	0/2 (0.0)	1/2 (50.0)	4/12 (33.3)
Lipids	6/17 (35.3)	4/17 (23.5)	15/59 (25.4)	4/8 (50.0)	4/8 (50.0)	11/26 (42.3)	2/9 (22.2)	0/9 (0.0)	4/33 (12.1)
Total cholesterol	2/5 (40.0)	0/5 (0.0)	2/10 (20.0)	0/1 (0.0)	0/1 (0.0)	0/2 (0.0)	2/4 (50.0)	0/4 (0.0)	2/8 (25.0)
HDL-C[c]	0/3 (0.0)	0/3 (0.0)	1/12 (8.3)	0/1 (0.0)	0/1 (0.0)	1/4 (25.0)	0/2 (0.0)	0/2 (0.0)	0/8 (0.0)
Triglycerides	2/3 (66.7)	2/3 (66.7)	7/15 (46.7)	2/3 (66.6)	2/3 (66.6)	5/10 (50.0)	–	–	2/5 (40.0)
HDL-C/total cholesterol ratio	0/1 (0.0)	0/1 (0.0)	0/2 (0.0)	0/1 (0.0)	0/1 (0.0)	0/2 (0.0)	–	–	–
Total cholesterol/ HDL-C ratio	2/4 (50.0)	2/4 (50.0)	4/11 (36.4)	2/2 (100.0)	2/2 (100.0)	4/6 (66.6)	0/2 (0.0)	0/2 (0.0)	0/5 (0.0)
[(Triglycerides) – (HDL-C)] / 2	–	–	1/2 (50.0)	–	–	1/2 (50.0)	–	–	–
Triglycerides/ HDL-C ratio	0/1 (0.0)	0/1 (0.0)	0/3 (0.0)	–	–	–	0/1 (0.0)	0/1 (0.0)	0/3 (26.9)
Non-HDL-C	–	–	0/4 (0.0)	–	–	–	–	–	0/4 (0.0)
Atherogenic index of plasma	–	–	–	–	–	–	–	–	–
Glucose homeostasis biomarkers	8/24 (33.3)	4/24 (16.7)	24/76 (31.6)	6/10 (60.0)	1/10 (10.0)	13/34 (38.2)	2/14 (14.3)	3/14 (21.4)	11/42 (26.2)
Fasting blood glucose	2/5 (40.0)	0/5 (0.0)	2/16 (12.5)	0/2 (0.0)	0/2 (0.0)	0/7 (0.0)	2/3 (66.7)	0/3 (0.0)	2/9 (22.2)
Insulin	2/6 (33.3)	1/6 (16.7)	6/16 (37.5)	2/2 (100.0)	0/2 (0.0)	3/6 (50.0)	0/4 (0.0)	1/4 (25.0)	3/10 (30.0)
HOMA-IR	3/7 (42.9)	2/7 (28.6)	11/27 (40.7)	3/4 (75.0)	1/4 (25.0)	7/15 (46.7)	0/3 (0.0)	1/3 (33.3)	4/12 (33.3)
HOMA-B	1/2 (50.0)	0/2 (0.0)	3/6 (50.0)	1/2 (50.0)	0/2 (0.0)	3/6 (50.0)	–	–	–
2-h glucose	–	–	1/1 (100.0)	–	–	–	–	–	1/1 (100.0)
QUICKI	0/3 (0.0)	1/3 (33.3)	1/6 (16.7)	–	–	–	0/3 (0.0)	1/3 (33.3)	1/6 (16.7)
Glycated hemoglobin	0/1 (0.0)	0/1 (0.0)	0/4 (0.0)	–	–	–	0/1 (0.0)	0/1 (0.0)	0/4 (0.0)
Inflammatory markers	0/1 (0.0)	0/1 (0.0)	17/36 (47.2)	–	–	1/1 (100.0)	0/1 (0.0)	0/1 (0.0)	16/35 (45.7)
C-reactive protein	0/1 (0.0)	0/1 (0.0)	5/9 (55.6)	–	–	1/1 (100.0)	0/1 (0.0)	0/1 (0.0)	4/8 (50.0)
C3	–	–	2/5 (40.0)	–	–	–	–	–	2/5 (40.0)
C4	–	–	1/5 (20.0)	–	–	–	–	–	1/5 (20.0)
Ceruloplasmin	–	–	1/1 (100.0)	–	–	–	–	–	1/1 (100.0)
Adiponectin	–	–	2/4 (50.0)	–	–	–	–	–	2/4 (50.0)
Leptin	–	–	5/5 (100.0)	–	–	–	–	–	5/5 (100.0)
White blood cells	–	–	0/1 (0.0)	–	–	–	–	–	0/1 (0.0)
Interleukin-6	–	–	1/3 (33.3)	–	–	–	–	–	1/3 (33.3)

Table 1 (continued)

Cardiometabolic variables	Combined evidence			Longitudinal evidence			Cross-sectional evidence		
	n/N for inverse association[b] (%)			n/N for inverse association[b] (%)			n/N for inverse association[b] (%)		
	Boys	Girls	Total	Boys	Girls	Total	Boys	Girls	Total
TNF-α	–	–	0/3 (0.0)	–	–	–	–	–	0/3 (0.0)
Clustered variables	5/11 (45.4)	6/11 (54.5)	28/48 (58.3)	2/3 (66.6)	2/3 (66.6)	9/14 (64.3)	3/8 (37.5)	4/8 (50.0)	19/34 (55.9)

BMI body mass index, *WC* waist circumference, *BP* blood pressure, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *HDL-C* high-density lipoprotein cholesterol, *TC* total cholesterol, *TC/HDL-C* total cholesterol/cholesterol HDL ratio, *TG/HDL-C* triglycerides/cholesterol HDL-C ratio, HOMA-IR homeostatic model assessment of insulin resistance, *HOMA-B* beta cell function, *LDL-C* low-density lipoprotein cholesterol, *C3* complement factor C3, *C4* complement factor C4, *QUICKI* quantitative insulin sensitivity index, *Non-HDL-C* non- high-density lipoprotein cholesterol, *TNF-α* tumor necrosis factor

[a]Absolute or normalized values for measurements of maximum muscular strength/power according to tests involving upper or lower limbs

[b]Considering the results from the totality of tests/measurements used by the studies included in this review

[c]Results regarding the direct association between maximum muscular strength/power with the investigated variable

indicators (32.1%—BMI; 19.3%—WC). Such associations were predominantly identified when maximum muscular strength/power was measured by handgrip strength, or tests in which body-related indexes were not considered in determining the results obtained. When muscular fitness was normalized for body size, no direct association with obesity was identified. Additional information for the association between maximum muscular strength/power and obesity indicators is available in the ESM (Tables S8–S11).

3.3.1.2 Muscular Endurance and Obesity Indicators The evidence available in the literature regarding the association of muscular endurance and obesity indicators is based on two longitudinal studies [35, 36] and 19 cross-sectional studies [25, 37–39, 41–43, 46, 48–50, 53, 55, 58, 61, 64, 82, 83, 87] (ESM Table S5). Of the total information analyzed (ESM Tables S6 and S7), 68.1% of the evidence indicated that muscular endurance was inversely associated with obesity indicators (Table 2). In addition, similar results regarding the inverse relationship between muscular endurance and obesity indicators were verified for boys (61.5%) and girls (64.3%) (Table 1). With regard to each obesity indicator investigated, although tests requiring body support (e.g., pull-ups, push-ups) have generally been inversely associated with BMI, longitudinal evidence consistently indicated no association for this interrelationship (muscular endurance and BMI) [35, 36]. Additionally, regardless of how muscular fitness was measured (e.g., sit-ups, curl-ups, push-ups), muscular endurance was inversely associated with WC (evidence derived exclusively from cross-sectional studies [25, 53, 61]). Detailed information regarding the association between muscular endurance and obesity indicators according to design and tests/measurements can be found in ESM Tables S8–S11.

3.3.1.3 Maximum Muscular Strength/Power/Endurance and Obesity Indicators The longitudinal evidence for the association between the combination of maximum muscular strength/power/endurance phenotypes and obesity [13] (ESM Table S5) indicated that higher values of the score derived from assessments of maximum muscular strength/power/endurance phenotypes was inversely associated with obesity (1/1 results; Table 3 and ESM Table S7). General and specific information for this association is available in ESM Tables S9 and S11.

3.3.2 Muscular Fitness and Blood Pressure

3.3.2.1 Maximum Muscular Strength/Power and Blood Pressure The relationship between maximum muscular strength/power and blood pressure (hypertension, high blood pressure, mean arterial pressure, systolic and diastolic blood pressure) was investigated in 23 studies, ten with a longitudinal design [11–16, 19, 21, 65, 120] and 13 with a cross-sectional design [25, 26, 30, 31, 61, 68–71, 76, 77, 82, 84] (ESM Table S5). In view of the results described in each investigated study (Table 1, ESM Tables S6 and S7), the overall percentage of results for the inverse association between maximum muscular strength/power and blood pressure was 25.7%. When considering sex in this interrelationship, the percentage for the inverse association among boys was 13.3% and among girls was 35.7% (Table 1). Additionally, 16.7% of the evidence (derived from seven studies [12, 21, 26, 29, 65, 70, 71]), indicated that maximum muscular strength/power was directly associated with blood pressure. Such results were mostly identified when absolute muscular fitness values were analyzed [12, 65, 70, 71]. Detailed information according to the study design and tests/measurements adopted by the studies are available in ESM Tables S12–S19.

Table 2 Summary of results assessing the relationship between muscular endurance with cardiometabolic variables, and global percentage of findings related to the inverse association with cardiometabolic variables among children and adolescents

Cardiometabolic variables	Combined evidence			Longitudinal evidence			Cross-sectional evidence		
	n/N for inverse association[a] (%)			n/N for inverse association[a] (%)			n/N for inverse association[a] (%)		
	Boys	Girls	Total	Boys	Girls	Total	Boys	Girls	Total
Muscular endurance measurements									
Obesity indicators	8/13 (61.5)	9/14 (64.3)	30/44 (68.1)	0/4 (0.0)	0/4 (0.0)	0/8 (0.0)	8/9 (88.9)	9/10 (57.1)	30/36 (83.3)
BMI	7/12 (58.3)	8/13 (61.5)	26/40 (65.0)	0/4 (0.0)	0/4 (0.0)	0/8 (0.0)	7/8 (87.5)	8/9 (88.9)	26/32 (81.2)
WC	1/1 (100.0)	1/1 (100.0)	5/5 (100.0)	–	–	–	1/1 (100.0)	1/1 (100.0)	4/4 (100.0)
Blood pressure	0/2 (0.0)	0/2 (0.0)	0/10 (0.0)	–	–	0/2 (0.0)	0/2(0.0)	0/2 (0.0)	0/8 (0.0)
Hypertension/high BP	–	–	–	–	–	–	–	–	–
Mean arterial pressure	–	–	0/2 (0.0)	–	–	–	–	–	0/2 (0.0)
SBP	0/1 (0.0)	0/1 (0.0)	0/4 (0.0)	–	–	0/1 (0.0)	0/1 (0.0)	0/1 (0.0)	0/3 (0.0)
DBP	0/1 (0.0)	0/1 (0.0)	0/4 (0.0)	–	–	0/1 (0.0)	0/1 (0.0)	0/1 (0.0)	0/3 (0.0)
Lipids	2/3 (66.7)	0/3 (0.0)	5/13 (38.5)	–	–	1/2 (50.0)	2/3 (66.7)	0/3 (0.0)	4/11 (36.4)
Total cholesterol	0/1 (0.0)	0/1 (0.0)	0/2 (0.0)	–	–	–	0/1 (0.0)	0/1 (0.0)	0/2 (0.0)
HDL-C	1/1 (100.0)	0/1 (0.0)	1/4 (25.0)	–	–	0/1 (0.0)	1/1 (100.0)	0/1 (0.0)	1/3 (33.3)
Triglycerides	–	–	1/2 (50.0)	–	–	1/1 (100.0)	–	–	0/1 (0.0)
HDL-C/total cholesterol ratio	–	–	–	–	–	–	–	–	–
Total cholesterol/HDL-C ratio	1/1 (100.0)	0/1 (0.0)	1/2 (50.0)	–	–	–	1/1 (100.0)	0/1 (0.0)	1/2 (50.0)
[(Triglycerides) – (HDL-C)]/2	–	–	–	–	–	–	–	–	–
Triglycerides/HDL-C ratio	–	–	–	–	–	–	–	–	–
Non-HDL-C	–	–	1/2 (50.0)	–	–	–	–	–	1/2 (50.0)
Atherogenic index of plasma	–	–	1/1 (100.0)	–	–	–	–	–	1/1 (100.0)
Glucose homeostasis bio-markers	0/2 (0.0)	0/2 (0.0)	4/10 (40.0)	–	–	4/5 (80.0)	0/2 (0.0)	0/2 (0.0)	0/5 (0.0)
Fasting blood glucose	0/1 (0.0)	0/1 (0.0)	0/3 (0.0)	–	–	0/1 (0.0)	0/1 (0.0)	0/1 (0.0)	0/2 (0.0)
Insulin	–	–	1/1 (100.0)	–	–	1/1 (100.0)	–	–	–
HOMA-IR	–	–	2/2 (100.0)	–	–	2/2 (100.0)	–	–	–
HOMA-B	–	–	1/1 (100.0)	–	–	1/1 (100.0)	–	–	–
2-h glucose	–	–	–	–	–	–	–	–	–
QUICKI	–	–	–	–	–	–	–	–	–
Glycated hemoglobin	0/1 (0.0)	0/1 (0.0)	0/3 (0.0)	–	–	–	0/1 (0.0)	0/1 (0.0)	0/3 (0.0)
Inflammatory markers	0/1 (0.0)	0/1 (0.0)	2/4 (50.0)	–	–	1/1 (100.0)	0/1 (0.0)	0/1 (0.0)	1/3 (33.3)
C-reactive protein	0/1 (0.0)	0/1 (0.0)	2/4(50.0)	–	–	1/1 (100.0)	0/1 (0.0)	0/1 (0.0)	1/3 (33.3)
C3	–	–	–	–	–	–	–	–	–
C4	–	–	–	–	–	–	–	–	–
Ceruloplasmin	–	–	–	–	–	–	–	–	–
Adiponectin	–	–	–	–	–	–	–	–	–
Leptin	–	–	–	–	–	–	–	–	–
White blood cells	–	–	–	–	–	–	–	–	–
Interleukin-6	–	–	–	–	–	–	–	–	–
TNF-α	–	–	–	–	–	–	–	–	–
Clustered variables	–	1/1 (100.0)	5/8 (62.5)	–	–	0/1 (0.0)	–	1/1 (0.0)	5/7 (71.4)

BMI body mass index, *WC* waist circumference, *BP* blood pressure, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *HDL-C* high-density lipoprotein cholesterol, *TC* total cholesterol, *TC/HDL-C* total cholesterol/cholesterol HDL ratio, *TG/HDL-C* triglycerides/cholesterol HDL-C ratio, HOMA-IR homeostatic model assessment of insulin resistance, *HOMA-B* beta cell function, *LDL-C* low-density lipoprotein cholesterol, *C3* complement factor C3, *C4* complement factor C4, *QUICKI* quantitative insulin sensitivity index, *Non-HDL-C* non- high-density lipoprotein cholesterol, *TNF-α* tumor necrosis factor

[a]Considering the results from the totality of tests/measurements used by the studies included in this review

[b]Results regarding the direct association between muscular endurance with the investigated variable

Table 3 Summary of results assessing the relationship between the combination of maximum muscular strength/power/endurance[a] with cardiometabolic variables, and global percentage of findings related to the inverse association with cardiometabolic variables among children and adolescents

Cardiometabolic variables	Combined evidence			Longitudinal evidence			Cross-sectional evidence		
	n/N for inverse association[b] (%)			*n/N* for inverse association[b] (%)			*n/N* for inverse association[b] (%)		
	Boys	Girls	Total	Boys	Girls	Total	Boys	Girls	Total
Maximum muscular strength/power/endurance measurements[a]									
Obesity indicators	–	–	1/1 (100.0)	–	–	1/1 (100.0)	–	–	–
BMI	–	–	–	–	–	–	–	–	–
WC	–	–	1/1 (100.0)	–	–	1/1 (100.0)	–	–	–
Blood pressure	–	–	1/2 (50.0)	–	–	1/2 (50.0)	–	–	–
Hypertension/high BP	–	–	–	–	–	–	–	–	–
Mean arterial pressure	–	–	–	–	–	–	–	–	–
SBP	–	–	0/1 (0.0)	–	–	0/1 (0.0)	–	–	–
DBP	–	–	1/1 (100.0)	–	–	1/1 (100.0)	–	–	–
Lipids	–	–	2/2 (100.0)	–	–	2/2 (100.0)	–	–	–
Total cholesterol	–	–	–	–	–	–	–	–	–
HDL-C	–	–	1/1 (100.0)	–	–	1/1 (100.0)	–	–	–
Triglycerides	–	–	1/1 (100.0)	–	–	1/1 (100.0)	–	–	–
HDL-C/total cholesterol ratio	–	–	–	–	–	–	–	–	–
Total cholesterol/HDL-C ratio	–	–	–	–	–	–	–	–	–
[(Triglycerides) – (HDL-C)]/2	–	–	–	–	–	–	–	–	–
Triglycerides/HDL-C ratio	–	–	–	–	–	–	–	–	–
Non-HDL-C	–	–	–	–	–	–	–	–	–
Atherogenic index of plasma	–	–	–	–	–	–	–	–	–
Glucose homeostasis biomarkers	–	–	–	–	–	–	–	–	–
Fasting blood glucose	–	–	–	–	–	–	–	–	–
Insulin	–	–	–	–	–	–	–	–	–
HOMA-IR	–	–	–	–	–	–	–	–	–
HOMA-B	–	–	–	–	–	–	–	–	–
2-h glucose	–	–	–	–	–	–	–	–	–
QUICKI	–	–	–	–	–	–	–	–	–
Glycated hemoglobin	–	–	–	–	–	–	–	–	–
Inflammatory markers	–	–	3/3 (100.0)	–	–	–	–	–	3/3 (100.0)
C-reactive protein	–	–	1/1 (100.0)	–	–	–	–	–	1/1 (100.0)
C3	–	–	–	–	–	–	–	–	–
C4	–	–	–	–	–	–	–	–	–
Ceruloplasmin	–	–	–	–	–	–	–	–	–
Adiponectin	–	–	–	–	–	–	–	–	–
Leptin	–	–	2/2 (100.0)	–	–	–	–	–	2/2 (100.0)
White blood cells	–	–	–	–	–	–	–	–	–
Interleukin-6	–	–	–	–	–	–	–	–	–
TNF-α	–	–	–	–	–	–	–	–	–
Clustered variables	0/1 (0.0)	0/1 (0.0)	2/4 (50.0)	–	–	1/1 (100.0)	0/1 (0.0)	0/1 (0.0)	1/3 (33.3)

BMI body mass index, *WC* waist circumference, *BP* blood pressure, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *HDL-C* high-density lipoprotein cholesterol, *TC* total cholesterol, *TC/HDL-C* total cholesterol/cholesterol HDL ratio, *TG/HDL-C* triglycerides/cholesterol HDL-C ratio, HOMA-IR homeostatic model assessment of insulin resistance, *HOMA-B* beta cell function, *LDL-C* low-density lipoprotein cholesterol, *C3* complement factor C3, *C4* complement factor C4, *QUICKI* quantitative insulin sensitivity index, *Non-HDL-C* non- high-density lipoprotein cholesterol, *TNF-α* tumor necrosis factor

[a]Absolute, normalized or absolute/normalized values for measurements of composite (two or more tests/measurements) of muscular fitness score according to tests involving the evaluation of the combination of maximum muscular strength/power/endurance (e.g., muscular fitness score derived from the use of one test that measured maximum muscular strength/power and another test that assessed muscular endurance)

[b]Considering the results from the totality of tests/measurements used by the studies included in this review

3.3.2.2 Muscular Endurance and Blood Pressure Evidence regarding the association between muscular endurance and blood pressure derived from one longitudinal study [12] and four cross-sectional studies [25, 29, 61, 82] (ESM Table S5). None of the evidence available in the literature and analyzed in this review (Table 2, ESM Tables S6 and S7) reported an inverse association between muscular endurance and blood pressure (including longitudinal and cross-sectional evidence). Lack of statistical significance [12, 25, 61, 82] and direct association [12] were identified for 90.0% (9/10 results) and 10.0% (1/10 results) of the evidence, respectively. Additional information for the interrelationship between muscular endurance and blood pressure can be found in ESM Tables S15–S19.

3.3.2.3 Maximum Muscular Strength/Power/Endurance and Blood Pressure The results for the relationship between the combination of maximum muscular strength/power/endurance phenotypes and blood pressure derived from one longitudinal study [13] (ESM Tables S5, S14, and S15), the results of which indicated a global percentage for the inverse association of 50.0% (Table 3, ESM Tables S7, S18, and S19).

3.3.3 Muscular Fitness and Lipids

3.3.3.1 Maximum Muscular Strength/Power and Lipids Information from 15 studies described in the literature—six longitudinal [11, 12, 14–16, 19] and nine cross-sectional [25–27, 30, 61, 69, 77, 82, 84]—underpin the relationship between maximum muscular strength/power and lipids in children and adolescents (ESM Table S5). In view of the results described according to the tests/measurements for muscular fitness (ESM Tables S6 and S7), the global percentage for the inverse relationship between maximum muscular strength/power and lipids was 25.4% (Table 1). Additionally, the global percentage for the inverse association among boys was 35.3%, whereas among girls the percentage was 23.5% (Table 1). It is noteworthy that the results for this inverse interrelationship (considering all analyzed results, or according to sex) were consistent regardless of the lipid analyzed, test adopted to assess maximum muscular strength/power, or whether the results were normalized for body size or not. Detailed information regarding the relationship between maximum muscular strength/power and lipids is available in ESM Tables S20–S37.

3.3.3.2 Muscular Endurance and Lipids One longitudinal study [12] and four cross-sectional studies [25, 61, 82, 115] referring to the association between muscular endurance and lipid markers have been identified in the literature (ESM Table S5). Based on the results synthesized according to the tests/measurements (ESM Tables S6 and S7), the global

percentage for the inverse relationship between muscular endurance and lipids was 38.5%. When considering sex, the percentage identified for boys was 66.7%. For girls, this percentage was 0.0% (Table 2). Results for the association between muscular endurance and individual lipid indicators, according to the design and tests/measurements are available in ESM Tables S20–S37.

3.3.3.3 Maximum Muscular Strength/Power/Endurance and Lipids The evidence supporting the relationship between the combination of maximum muscular strength/power/endurance phenotypes and lipids in children and adolescents was derived from one longitudinal study [13] (ESM Table S5). Based on the summary of results (ESM Table S7), the global percentage for the inverse relationship for this association was 100.0% (2/2 results, Table 3).

3.3.4 Muscular Fitness and Glucose Homeostasis Biomarkers

3.3.4.1 Maximum Muscular Strength/Power and Glucose Homeostasis Biomarkers Eight longitudinal studies [10–12, 14, 15, 19, 32, 80] and ten cross-sectional studies [26, 30, 61, 72, 77, 78, 82, 84, 100, 104] investigated the relationship between maximum muscular strength/power and glucose homeostasis biomarkers in children and adolescents (ESM Table S5). According to the summarized findings (ESM Tables S6 and S7), the global percentage for the inverse relationship between maximum muscular strength/power and glucose homeostasis biomarkers was 31.6% (Table 1). Additionally, 67.1% of the evidence indicated an absence of association, while one study (1.3% of the evidence analyzed) [32] identified that maximum muscular strength/power (assessed by lower limb test—standing long jump) was directly associated with glucose homeostasis biomarkers (fasting blood glucose). The calculated percentages for the inverse relationship between maximum muscular strength/power and glucose homeostasis biomarkers according to sex were 33.3% for boys and 16.7% for girls. Additional information for this interrelation can be found in ESM Tables S38–S51.

3.3.4.2 Muscular Endurance and Glucose Homeostasis Biomarkers The relationship between muscular endurance and glucose homeostasis biomarkers has been investigated in four studies; two studies with a longitudinal design [12, 80] and two studies with a cross-sectional design [61, 82] (ESM Table S5). Considering general (ESM Tables S38–S51) and specific information (ESM Tables S6 and S7), the global percentage for the inverse association between muscular endurance and glucose homeostasis biomarkers was 40.0%—4/10 results (Table 2). Regarding the summary of evidence according to the evaluated glucose homeostasis

biomarker, consistent results (100.0%) pointed to an inverse association between muscular endurance (assessed by push-up or trunk extension) with insulin, HOMA-IR and HOMA-B [12, 80].

3.3.5 Muscular Fitness and Inflammatory Markers

3.3.5.1 Maximum Muscular Strength/Power and Inflammatory Markers One longitudinal study [12] and 11 cross-sectional studies [30, 61, 73–75, 79, 103, 105, 107, 113, 118] investigated the relationship between maximum muscular strength/power and inflammatory markers in children and adolescents (ESM Table S5). In view of the general (ESM Tables S52–S60) and specific results (ESM Tables S61–S69), in addition to the evidence analyzed according to tests adopted by the studies (ESM Tables S6 and S7), the global percentage for the inverse relationship between maximum muscular strength/power and inflammatory markers was 47.2% (Table 1). Although less than half of the evidence analyzed identified an inverse association between maximum muscular strength/power and inflammatory markers, results according to each inflammatory marker analyzed indicated that muscular fitness (maximum muscular strength/power) was consistently inversely associated with leptin (100.0% – 5/5 results) [75, 79, 103, 105, 113], regardless of the test used to assess muscular fitness or strategy adopted to consider body size (absolute or normalized results). Furthermore, in 55.5% of the evidence, maximum muscular strength/power was inversely associated with CRP [12, 30, 73, 74, 113].

3.3.5.2 Muscular Endurance and Inflammatory Markers The results described in this review regarding the interrelationship between muscular endurance and inflammatory markers derived children and adolescents. Of the from three studies; one study with longitudinal design [12] and two cross-sectional studies [61, 118] (ESM Table S5). According to the results summarized—essentially derived from studies investigating the association between muscular endurance and CRP (ESM Tables S6 and S7; Supplementary Tables S52–S69), the percentage for the inverse relationship between muscular endurance and inflammatory markers was 50.0% (2/4 results) (Table 2).

3.3.5.3 Maximum Muscular Strength/Power/Endurance and Inflammatory Markers Two cross-sectional studies [79, 105] that reported results for the association between the combination of maximum muscular strength/power/endurance phenotypes and inflammatory markers were included in this review (ESM Table S5). Based on the results described by the studies (ESM Tables S6 and S7, and S52–S69), the percentage for the inverse relationship between the combination of maximum muscular strength/power/endurance

phenotypes and inflammatory markers was 100.0% (3/3 results—Table 3). These results were verified regardless of the inclusion or not of body size as an adjustment in the expression of muscular fitness values.

3.3.6 Muscular Fitness and Clustered Cardiometabolic Variables

3.3.6.1 Maximum Muscular Strength/Power and Clustered Cardiometabolic Variables According to the findings described in the literature, 24 studies aimed to investigate the relationship between maximum muscular strength/power and clustered cardiometabolic variables in children and adolescents. Of the total number of studies, seven were longitudinal [11, 13–16, 19, 119] and 17 were cross-sectional [25, 26, 30, 33, 75, 77, 82, 84, 85, 102, 106, 108, 110–114] (ESM Table S5). Based on the evidence summarized in this review (ESM Tables S6 and S7) and available in Table 1, the percentage for the inverse relationship between maximum muscular strength/power and clustered cardiometabolic variables in children and adolescents was 58.3%. When considering the results according to sex, the overall percentage for the inverse association between boys was 45.4%, while for girls a percentage of 54.5% was identified. It is noteworthy that the results obtained by normalized handgrip strength [14, 15, 26, 30, 33, 82, 84, 85, 108, 110, 111, 113] indicated a percentage for the inverse association between maximum muscular strength/power and clustered cardiometabolic variables of 78.2%, suggesting that this test/procedure may be superior to the others when investigating the relationship between muscular fitness (maximum muscular strength/power) and clustered cardiometabolic variables in children and adolescents. Detailed information for the described results can be found in ESM Tables S70 and S71.

3.3.6.2 Muscular Endurance and Clustered Cardiometabolic Variables One longitudinal study [13] and six cross-sectional studies [25, 43, 82, 109, 116, 117] that investigated the relationship between muscular endurance and clustered cardiometabolic variables in children and adolescents were identified in the literature and included in this review (ESM Table S5). Based on the analyzed (ESM Tables S70 and S71) and summarized (ESM Tables S6 and S7) results, the global percentage for the inverse relationship between muscular endurance and clustered cardiometabolic variables in children and adolescents was 62.5%—although the only longitudinal study analyzed [13] reported no significant association for this interrelationship (push-up and clustered cardiometabolic variables) (Table 2, ESM Tables S70 and S71).

3.3.6.3 Maximum Muscular Strength/Power/Endurance and Clustered Cardiometabolic Variables Three studies evaluated the relationship between the combination of maximum muscular strength/power/endurance phenotypes and clustered cardiometabolic variables; one longitudinal study [13] and two cross-sectional studies [79, 101] (ESM Table S5). Finally, according to the results analyzed (ESM Tables S6, S7, S70, and S71), the global percentage for the inverse relationship between the combination of maximum muscular strength/power/endurance and clustered cardiometabolic variables in children and adolescents was 50.0% (Table 3).

4 Discussion

This systematic review synthesized evidence from 96 studies of which the objective was to verify the association between muscular fitness and cardiometabolic variables in children and adolescents. The included studies mainly consisted of cross-sectional (79.8%) studies that involved participants from 35 countries. This systematic review showed that maximum muscular strength/power and muscular endurance phenotypes were inversely associated with obesity indicators and clustered cardiometabolic variables among children and adolescents.

This study found that muscular fitness investigated by maximum muscular strength/power was associated with lower obesity indicators in 56.6% of the evidence, whereas when investigated by muscular endurance, the calculated percentage was 68.1%. However, it is necessary to emphasize that important factors, such as age [16, 18, 39, 48, 61, 66, 82], sex [20, 28, 36, 38–43, 48, 50, 52, 56, 61, 66, 67, 77, 81–86], sexual maturation [11, 13, 18–20, 28, 34–40, 42, 45, 48–52, 54, 55, 57, 60, 62, 66, 77, 81–83, 86, 87], body size [11, 15, 17, 18, 20, 27, 28, 34–41, 43, 45, 48–51, 54–56, 60–62, 67, 76, 81, 83, 84, 86], physical activity [11, 13, 15, 17–20, 26, 27, 34–38, 41–43, 45, 50, 52, 54, 55, 60–62, 65, 66, 76, 77, 81–84, 86], or cardiorespiratory fitness [17–20, 26–28, 34–43, 45, 48, 50–52, 54–57, 60–62, 65, 67, 76, 77, 81, 83, 84, 86, 87] were not considered by the studies, which may have contributed to an overestimation of significant results. When considering the results according to the study design, the body of evidence from longitudinal studies suggested a low (maximum muscular strength/power) or even no association (muscular endurance) of muscular fitness with these indicators (BMI and WC). Regarding the assessment of maximum muscular strength/power, lower limb tests (e.g., jumps), tests involving recruitment of upper limbs (e.g., handgrip strength) and results normalized for body mass, and/or a combination of tests that evaluate maximum strength/power and results obtained normalized for body mass have been shown to be more

sensitive tests/measurements to identify associations with obesity (although identifying an association is not always positive if the association is not causal). Although body mass (body-related index predominantly adopted by the included studies to consider body size) is a determinant for muscular fitness, this interrelation can be mediated by other body-related indexes, such as body fat [121]. Thus, the adoption of techniques that consider the effect of body fat/body size, such as the use of maximum muscular strength/power tests evaluated by jumps, or the normalization (or standard ratio) of results by body mass appear to be appropriate strategies to investigate the interrelationship between maximum muscular strength/power and obesity indicators. However, it is worth noting that in addition to impacting muscular fitness levels, body fat is directly related to adverse prognoses in relation to cardiometabolic variables [122], where the hypothesis that muscular fitness may be a mediator in the relationship between adiposity with these variables cannot be ruled out (especially in subgroups with high body fat) [77]. While considering body mass as a strategy for reducing differences in the mass of non-skeletal muscle tissues (such as fat, organ, and bone) can be a good strategy, it also introduces statistical problems since muscle mass is part of both the numerator and denominator (i.e., muscle mass is a fraction of body mass) [123, 124]. Additionally, when considering adding body mass in the expression of results, it must be understood that the level of body adiposity can negatively influence this interrelation, since the ratio of muscular fitness to body mass will decrease as the fat percentage increases [124]. Thus, considering the existing limitations when normalizing muscular fitness for body mass, the adoption of additional strategies such as the use of muscular fitness indexes not correlated with body mass, generated from the use of residuals derived from regression analysis (including absolute values of muscular fitness as outcome and body mass as exposure variable) [13, 32, 66, 80, 81], or adoption of allometric parameters [15, 25, 65], was described, suggesting other possibilities for considering body size when determining muscular fitness values in children and adolescents. Also, based on the premise that adolescence is a period of changes in body structures [125], and that muscle mass plays an important role in maintenance of growth development [126], it is speculated that the expression of the values of muscular fitness according to height allows inclusion of such development in the structure and body composition, and that the use of this technique can result in more reliable muscular fitness values. Such an assumption is based on the fact that an increase in fat-free mass throughout puberty occurs similarly to an increase in height—at least in the shape of the growth curve [126]. Finally, given that the magnitude of the relationship between muscular fitness and body size tends to grow concomitantly with the increase in body dimensions—possibly due to the

increase in muscular cross-sectional area (proportional to height and body mass) [23]— consideration of height and body mass simultaneously in the expression of muscular fitness values can contribute to the determination of muscular quality (rather than muscular quantity). Thus, in addition to the need for a greater body of evidence derived from longitudinal studies with rigorous control of confounding factors in order to confirm the results identified in this review, it is suggested that future studies should consider height, or height and body mass simultaneously, in the expression of muscular fitness values (especially when the goal is to investigate maximum muscular strength or muscular power), since it is possible that the identified associations and conclusions assumed by the studies vary depending on the inclusion or not of these parameters in the muscular fitness values.

Considering the results described in the literature and included in this review, which reported mostly an inverse association between maximum muscular strength/power and muscular endurance with clustered cardiometabolic variables regardless of the variables investigated or number of clustered indicators analyzed, these muscular fitness phenotypes were associated with better results related to clustered cardiometabolic variables. The plausibility for the aforementioned relationship has been related to the potential effect of muscular fitness in reducing the harmful health impact of each of the cardiometabolic variables when grouped [6, 9, 88]. However, findings described in this present systematic review indicated that maximum muscular strength/power and muscular endurance was associated with lower values of some specific cardiometabolic variables and not for all of these variables, suggesting additional aspects are involved in this association. It is noteworthy that although the results for the inverse association between maximum muscular strength/power and clustered cardiometabolic variables are based on a large number of longitudinal and cross-sectional evidence, the same is not true for muscular endurance, which is based on cross-sectional studies [25, 43, 82, 109, 116, 117] and one single longitudinal study [13], of which the result differs from those summarized by cross-sectional evidence. With regard to this single longitudinal study [13], the hypothesis raised by the authors to justify the absence of association would be related to a minor role of muscular endurance in children and adolescents on clustered cardiometabolic variables, or the possible greater measurement error of tests for muscular endurance compared to tests for maximum muscular strength/power [22]. Thus, although the synthesis of evidence (regardless of design) points to an inverse association between muscular fitness and clustered cardiometabolic variables, longitudinal evidence for the interrelationship of muscular endurance/clustered cardiometabolic variables is needed to confirm the identified findings.

Due to the small amount of evidence ($\geq 50.0\%$) that identified that muscular fitness was associated with lower blood pressure, lipids, glucose homeostasis biomarkers, and inflammatory markers, the adoption of muscular fitness as a marker for these cardiometabolic indicators is still largely unknown. The aforementioned absence of an association occurred independently of the muscular fitness phenotypes or tests/measurements adopted. It is noteworthy that the direction of evidence derived from longitudinal and cross-sectional studies was similar with regard to the lack of association of muscular fitness (measured by maximum muscular strength/power or muscular endurance) with blood pressure and blood variables, although a very small amount of information regarding the relationship between muscular endurance with blood pressure, lipids, glucose homeostasis, biomarkers, and inflammatory markers has been derived from longitudinal studies [12, 80], or from studies in which multiple confounding factors likely to change the direction of associations have been considered (including age, sex, sexual maturation, body size, or physical activity) [80, 115, 118]. Greater muscular fitness and muscle mass are both associated with better vascular and endothelial function, lower central arterial stiffness [127, 128], prevention of abnormalities attributed to lipids [124], and glucose homeostasis control in children and adolescents [124]. Regarding the relationship between muscular fitness and inflammatory markers, it has been linked to improved insulin sensitivity by muscles and a reduction of the adverse impact attributed to body fat (seen in individuals with higher levels of muscular fitness), which contributes to the reduction/attenuation of inflammatory substances [75, 121, 129, 130]. However, it is hypothesized that the underlying hormonal effect in these interrelationships may moderate the magnitude of the associations [124, 131, 132]. Thus, it is possible that the lack of consideration of the effect of sexual maturation by a significant portion of the studies analyzed [10–16, 19, 25, 29, 31, 32, 65, 68, 72, 77, 80, 82, 115] may have contributed to the lack of common direction for the results reported. Another aspect that could justify the inconsistent results is related to the adoption of strategies to consider body size in the obtained muscular fitness values [11, 13, 14, 16, 25, 26, 30, 33, 75, 77, 79, 82, 84, 85, 102, 108, 110, 111, 113, 114, 119].

Results for the relationship between muscular fitness – investigated by the combination of maximum muscular strength/power/endurance phenotypes (evaluated by different tests, of which the resulting values were aggregated and used as a muscular fitness score) – and cardiometabolic variables in children and adolescents were also extracted from the identified studies [13, 79, 101, 105]. Evidence from these studies indicated that the combination of maximum muscular strength/power/endurance phenotypes was inversely related to obesity indicators, lipids, and inflammatory

markers. However, caveats must be considered for the reported results, including the fact that only one longitudinal study [13] was responsible for all the evidence for the association between maximum muscular strength/power/ endurance phenotypes with obesity, blood pressure, and lipids. Thus, considering the absence of longitudinal evidence for the interrelationship between maximum strength/ power/endurance phenotypes and inflammatory markers, and the small number of studies for which confounding factors have been adequately controlled, a larger body of evidence to confirm the direction of these associations is needed.

Although muscular fitness is determined to a large extent by genetic factors (30.0–95.0% of the variability, according to the type of contraction, contraction speed, or test/ predominant muscle group evaluated) [133, 134], the rest of the variability arises from behavioral factors, with physical activity being the main modifiable component associated with muscular fitness [92]. This issue is especially important to address, considering that in addition to directly impacting muscular fitness (especially vigorous physical activity or participation in sports) [98], physical activity has been directly associated with better prognosis regarding cardiometabolic variables in adolescents [135]. Another variable known to be associated with muscular fitness and inversely associated with cardiometabolic risk factors [10, 102] in children and adolescents, is cardiorespiratory fitness. The relationship between these health-related physical fitness components seems to be even more relevant considering that although the mechanisms responsible for the inverse association with cardiometabolic variables are different depending on the physical fitness component [121, 136], some improvements are partially mediated by similar pathways, including the reduction of visceral adipose tissue [67] and improved insulin sensitivity [10]. In this sense, although studies have identified an association of muscular fitness with cardiometabolic variables in young people regardless of physical activity [67] or cardiorespiratory fitness [10, 102], disregard for the possible effect attributed to these variables when investigating the association between muscular fitness and cardiometabolic variables may lead to different interpretations regarding obtained results. Thus, in addition to muscular fitness, it seems appropriate that studies measure physical activity and cardiorespiratory fitness, and consider adjusted models with and without the inclusion of these variables in order to remove the confounding, and thus provide a better interpretation of the results obtained. Additionally, it is suggested that when the inclusion/adjustment of associations for such variables is not possible, the authors of the studies must acknowledge the possible limitations that the absence of control for the analyses for physical activity and cardiorespiratory fitness may result, whether in the results obtained in their own studies, or when citing the results

identified in other studies or comparing their own results with others described in the literature.

In addition to a large number of databases and information analyzed/reviewed, the analysis of all available information according to the muscular fitness tests/measurements adopted by the studies and the presentation of results according to sex, design, and number of variables for the control of confounding are considered strengths of this review. Conversely, important limitations of this review should be reported, such as the small number of studies that aimed to investigate the association between muscular fitness and lipids, glucose markers and inflammatory markers, which reduces the possibility of conclusive establishment for these associations. Although rigorous methodological control was adopted in the search for information, publication bias cannot be disregarded. However, the global percentage for the inverse association of muscular fitness with cardiometabolic variables below 50.0% identified in most of the results indicates a reduced possibility of this bias in the summarized of evidence. Additionally, although evidence according to sex reported by the studies indicated a similar direction compared to those analyzed in general, information according to sex for most of the investigated associations is not available in the literature. Another aspect that must be stated concerns the quality of conduct of the analyzed longitudinal studies. Approximately three out of ten studies analyzed did not include outcome values measured at baseline as a covariate in the adjusted longitudinal analyses. The inclusion of measured outcome values at baseline can lead to different scenarios with regard to the direction of associations, which can be important for understanding the tested associations. Not adjusting analysis results to baseline outcome values will indicate the total longitudinal effect of exposure on the outcome, whereas adjusting the analyses for the baseline outcome values will essentially indicate the direct effect of exposure on the longitudinal outcome [137]. Finally, the evidence mainly derives from cross-sectional studies that preclude inferences about causality and directionality. Properly controlled longitudinal studies for confounding and mechanistic studies are needed to better understand the role of muscular fitness in the cardiometabolic health of children and adolescents and possible differences based on sex. In this same sense, Mendelian randomization studies could provide valuable contributions regarding the causality of these associations.

5 Conclusions

In view of the studies included in this systematic review regarding the relationship between muscular fitness and cardiometabolic variables in children and adolescents, it can be concluded that:

1. Muscular fitness assessed by maximum muscular strength/power or muscular endurance is potentially associated with lower obesity. When considering the assessment of maximum muscular strength/power, tests with lower limb demand (e.g., jumps), tests involving recruitment of upper limbs (e.g., handgrip strength) and results normalized for body mass, and/or a combination of tests that evaluate maximum muscular strength/power and results normalized for body mass have been shown to be more sensitive for this interrelationship.
2. Maximum muscular strength/power or muscular endurance are associated with a lower risk related to clustered cardiometabolic variables, with no differences attributed to the muscular fitness tests/measurements adopted.
3. The associations between muscular fitness and blood pressure, lipids, glucose homeostasis biomarkers, and inflammatory markers are inconsistent.

Declarations

Conflict of interest Tiago Rodrigues de Lima, Priscila Custódio Martins, Yara Maria Franco Moreno, Jean-Philippe Chaput, Mark Tremblay, Xuemei Sui and Diego Augusto Santos Silva declare that they have no conflicts of interest relevant to the content of this review.

Authorship contributions TRL conceived the review, wrote and edited significant sections of the manuscript, carried out the literature search, screened all identifed studies based on title and abstract, and assisted with the full text screening, the risk-of-bias assessment, and the data extraction process. PCM assisted with the title and abstract screening, the full text screening, and the risk-of-bias assessment. YMFM wrote and edited significant sections of the manuscript. JPC wrote and edited significant sections of the manuscript. MST wrote and edited significant sections of the manuscript. XS revised and edited significant sections of the manuscript and assisted with the risk-of-bias assessment. DASS revised and edited significant sections of the manuscript and assisted with the risk-of-bias assessment. All authors reviewed and approved the final manuscript.

Data availability statement The material analyzed in this study (including the strategies and descriptors used in each database, the detailed risk-of-bias assessment, and the totality of information analyzed) are available in the Electronic Supplementary Materials.

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