Independent Association of Muscular Strength and Carotid Intima-Media Thickness in Children

Authors

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Abstract

The aim of this cross-sectional study was to examine the influence of muscular strength on carotid intima-media thickness (cIMT) in children, controlling for the effect of cardiorespiratory fitness (CRF) and central adiposity and to examine if differences among muscular strength tertiles translate to physiological differences. We assessed cIMT of the common carotid artery in 366 children between 11–12 years of age (191 girls). Measures included cIMT assessed with high-resolution ultrasonography, a maximal handgrip strength test, body fat mass and lean mass from DXA and CRF determined using a maximal cycle ergometer test. Association between muscular strength and cIMT adjusted for CRF and central adiposity, as measured by trunk fat, was tested with multiple linear regression analysis. Differences in risk factors among muscular strength groups were tested with ANOVA. The Muscular Strength Index (MSI) was inversely associated with cIMT independently of CRF and central adiposity (p < 0.05). The low MSI group had the highest values of cIMT, waist circumference and systolic blood pressure and the lowest CRF (p < 0.05). There was an inverse and independent association between muscular strength and cIMT. Low muscular strength was associated with higher levels of cardiovascular disease risk factors in children.

Abbreviations

BMI body mass index
CRF cardiorespiratory fitness
CV cardiovascular
CVD cardiovascular disease
HMSI high muscular strength index group
cIMT intima-media thickness
LMSI low muscular strength index group
MMSI middle muscular strength index group

Introduction

High levels of cardiorespiratory fitness (CRF) are associated with reduced cardiovascular (CV) morbidity and mortality in adults [6,36]. Although muscular strength has received less attention than CRF, low muscular strength in adulthood also predicts all-cause mortality, as well as mortality due to cardiovascular disease (CVD) [9,18]. A large prospective study verified that high muscular strength in adolescence, as assessed by knee extension and handgrip tests, was associated with a 20–35% lower risk of premature mortality due to any cause or CVD independently of body mass index (BMI) or blood pressure later in life [33]. Thus, muscular strength appears to be an important marker of CV health throughout one’s lifespan.

Greater muscular strength in youth is also associated with lower levels of CVD risk factors [11], including fasting insulin, markers of insulin resistance and beta-cell function in young adulthood independently of CRF and adiposity [10]. These data suggest that muscular strength in youth is important for maintaining healthy insulin sensitivity and beta-cell function later in life. However, whether muscular strength is associated with more specific arterial risk factors with a focus on target-organ damage has not been tested to date. Alterations of the CV system can be identified at an early age and premature changes in carotid intima-media thickness (cIMT), an intermediate phenotype for early atherosclerosis, and an important predictor of future vascular events [24] have been increasingly examined. cIMT may be reduced with regular exercise in children [29].
and an improved fitness level, in particular CRF, is inversely associated with cIMT in children, although central adiposity appears to be more related with cIMT than CRF [28]. However it remains unknown whether other physical fitness dimensions such as muscular strength may also be related to cIMT in children, independently of CRF and central adiposity. If there are health benefits of muscular strength early in life, independent of engagement in other physical activities, increasing muscular strength could be recognized as an important target for intervention. Therefore, the purpose of this study was to analyze the independent association of muscular strength with cIMT in 11–12-year-old children controlling for the effect of CRF and central adiposity. Additionally we examined whether differences among muscular strength tertiles translate to physiological differences in CVD risk.

Methods

Study population
Participants were 366 children (191 girls) between 11–12 years of age, enrolled in 2012 from 6 different schools in Portugal. The study was approved by the ethics committee of the Faculty of Human Kinetics – University of Lisbon, Portugal and performed in accordance with the ethical standards of the International Journal of Sports Medicine [13]. Children provided assent for their participation, and informed consent was obtained from their parents or legal guardians. The study population was sequentially studied without specific exclusion criteria, hence the investigation did not specifically target children who were overweight/obese, or of any particular fitness level.

Anthropometrics
Standing and sitting height were measured to the nearest 0.1 cm and body mass was measured to the nearest 0.1 kg on a scale with an attached stadiometer (model 770, Seca, Deutschland), wearing minimal clothing and no shoes. Leg length was calculated by subtracting sitting height from standing height. Body mass index (BMI) was calculated and categorized according to the established criteria [7]. Waist circumference was measured to the nearest millimeter with an inelastic flexible metallic tape (Lufkin, W606PM, Canada) midway between the lower rib margin and the iliac crest. Age- and gender-specific waist circumference percentiles for Portuguese youths [38] were used to dichotomize waist circumference as normal (<P85) and increased risk (≥P85).

Dual-energy X-ray absorptiometry
A total-body scan was performed by dual-energy radiographic absorptiometry (DXA) and analyzed using an extended analysis program for body composition (Hologic Explorer-W, fan-beam densitometer, software QDR for windows version 12.4, USA) to determine total, trunk and upper limb body fat and lean soft tissue. Trunk fat was used as an estimate of a central pattern of fat (visceral + subcutaneous) distribution. The same technician positioned the subjects, performed the scans and completed the scan analysis according to the operator’s manual using the standard analysis protocol. All scans were made in the morning after an overnight 12-h fast. The coefficients of variation for repeated measurements in our laboratory for total and regional DXA measurements have been reported elsewhere [37].

Maturity
Maturity offset, that is, time before or after peak height velocity (PHV), was predicted with the equation of Mirwald et al. [30] using the following variables: leg length, sitting height, age, weight, and height.

Muscular strength
Maximal isometric forearm grip strength was determined on the dominant arm using a handgrip dynamometer (Lafayette, Model 78010, Lafayette Instrument Company, USA). The test was performed in the standing position with the arms alongside the body, without contact with the trunk and with the elbow of the dominant arm slightly flexed (~20°). A standard instruction of ‘push as hard as you can’ and visual feedback of the recorded strength were provided to each participant for each trial. The maximum trial of 2 attempts (10s of contraction with a rest period of at least 60s) was used as peak absolute force (kg). The 20th percentile of the derived sex- and age-specific normative values for physical fitness [32] was used to define a “Very Poor Level” of muscular strength. Absolute muscle strength may be the simplest way to express muscle strength, especially when measured with weight-bearing tests, since it does not require other measurements. However, handgrip strength is positively associated with weight status [2] and, as a result, relative muscle strength may be more relevant in understanding health-related fitness, especially when measured with a non-weight-bearing tests as in this study. The DXA method provides lean soft tissue estimates of the extremities, and a large proportion of total-body skeletal muscle is within the fat-free appendicular compartment [14]. We calculated a muscular strength index (MSI) dividing peak absolute force (kg) by the lean soft tissue of the upper limbs (kg) [25].

Cardiorespiratory fitness
CRF was indirectly determined by a cycle test with progressively increasing workload using an electronically braked cycle ergometer (Monark 828 E Ergomedic; Monark, Sweden). Initial and incremental workloads were 20 W for children weighing < 30 kg and 25 W for children ≥ 30 kg [19]. The workload was increased every 3-min until the maximal effort of the participants was reached. Heart rate was recorded continuously (Polar Electro Oy, Finland) throughout the test. Criteria for maximal effort were heart rate > 185 beats.min⁻¹ and a subjective judgment by the observer that the participant could no longer continue, even after encouragement. Maximal power output and maximal oxygen consumption (ml.min⁻¹) were calculated according to the formulas by Hansen et al. [12]. Maximal oxygen consumption was normalized for body weight (ml.min⁻¹ kg⁻¹) and termed CRF from here on. The test has been previously validated against direct measurement of maximal oxygen consumption [19].

Hemodynamics
Heart rate at rest, brachial systolic blood pressure and diastolic blood pressure were measured after 10 min with the participants in supine position using an automated oscillometric cuff (HEM-907-E, Omron, Tokyo, Japan). 2 measurements were taken and if these values deviated by > 5 mmHg, a third measurement was performed. The average of the closest 2 values was used. The pressure difference between the systolic and diastolic blood pressure (pulse pressure) was calculated for adjustment purposes, as both were positively correlated with the mean IMT of
both the common and internal carotid arteries in a total of 128 children and adolescents between 10 and 19 years of age [40].

**Intima-media thickness**

cIMT was defined as the distance between the leading edge of the lumen-intima interface to the leading edge of the media-adventitia interface of the far wall of the carotid artery (Fig. 1). The far wall was imaged, and cIMT and carotid diameter were measured in a common carotid artery segment ~1 cm before the bifurcation. The coefficients of variation for repeated measurements in our laboratory for carotid IMT and diameter are reported elsewhere [27].

**Cardiovascular risk score**

In 2010 the American Heart Association released a set of 7 cardiovascular (CV) health metrics for children and adults to describe ideal cardiovascular health [23]. The metrics used to indicate CV health included 4 health behaviors and 3 health factors. The behavioral criteria were being a nonsmoker, being physically active, having normal body mass index (BMI) and eating a healthy diet. Normal blood pressure, total cholesterol and plasma glucose levels indicated ideal health factors. Ideal CV health was defined as having all 7 metrics of the behaviors and factors. In this study, using adapted metrics and criteria of individual CV health, we calculated an optimal CV health score mainly for behavioral criteria and health factors (Table 1), where a value of 0 was assigned for each metric in the presence of risk and a value of 1 if the optimal criterion was met. The range of scores was thus 0–5, with a higher score indicating a higher CV health profile.

**Statistical analyses**

All values were expressed as mean and SD. Multiple linear regression analysis was used to estimate the association between cIMT with physical fitness and body composition phenotypes. We tested the association between cIMT and MSI and then adjusted the model for CRF (2nd model), and central adiposity (3rd model). R², Beta (standardized) and 95% CI were calculated for all models which were adjusted for sex, maturity offset and pulse pressure.

Subjects were categorized according to the number of optimal CV health metrics [Low Score (≤2); Middle Score (3–4) and High Score (≥5)] and MSI level [low MSI (LMSI): ≤7.23, middle MSI (MMSI): >7.23 and ≤8.23, and high MSI (HMSI): ≥8.23]. Physiological differences between groups and MSI level were assessed with one-way ANOVA and ANCOVA. LSD post hoc test was used for unadjusted and adjusted (diameter of the artery, sex, maturity, CRF, and trunk fat) comparisons. Linear trends between groups were calculated using polynomial coefficients. Statistical significance level was set at p<0.05 for all tests. The statistical analyses were computed and analysed by a certified researcher using the SPSS Statistics 19.0.

**Results**

Prevalence of overweightness and obesity in this study was 28.7%, and 12% of the children had increased waist circumference (Table 2). 72% of the children were above the 20th percentile of muscular strength. Mean values of absolute and indexed muscular strength were similar between boys (23.36; 7.70) and girls (22.61; 7.80) (p>0.05). The recommended CRF level for metabolic health was attained by 61.7% of the children. Mean cIMT was 0.50 mm. Approximately 27% of children had all the optimal health behaviors and health factors after dichotomization according to Table 1. The criterion for optimal blood pressure was the least often met criterion (61.5%). The Low Score group had the highest cIMT (0.53 mm; p<0.05) and cIMT decreased linearly as children scored higher on the optimal CV health metrics (p<0.05) (Fig. 2).

The determinants of cIMT were examined in multivariate regression analyses in the entire cohort (Table 3). cIMT was inversely associated with MSI independently of sex, maturity offset and pulse pressure (1st model). This association was also independent of CRF (2nd model) and trunk fat (3rd model). Physiological differences in CVD risk were examined following categorization of participants into MSI tertiles. The 3 MSI groups were similar in age, fat and lean soft tissue, maturity offset,
chronotropic responses and diastolic blood pressure (p > 0.05; Table 2). The highest relative prevalence of overweightness and obesity, high waist circumference and children failing the recommended CRF cut-off values were found in the LMSI group (32.0%, 13.1%, 44.3%, respectively). The lowest prevalence was found in the HMSI group (26.7%; 9.0%, 34.4%, respectively). Children in the LMSI group had the highest cIMT (0.52 mm; p < 0.05; Fig. 3), while children in the MMSI had the lowest cIMT mean values (0.48 mm), although this was not significantly different from that of the HMSI group (0.49 mm; p > 0.05). Increased cIMT in the LMSI does not merely reflect a larger vessel. Indeed, there were no differences in diameter among MSI groups once adjusted for sex and maturity (p = 0.10). Furthermore, differences in cIMT between LMSI and MMSI and between LMSI and HMSI remained following adjustments for the diameter of the artery (p = 0.001, p = 0.04, respectively) and other confounders such as sex, CRF, trunk fat and maturity (p = 0.02, p = 0.04, respectively).

Table 2 Characteristics of the study group and differences between muscular strength index groups.

<table>
<thead>
<tr>
<th></th>
<th>LMSI</th>
<th>MMSI</th>
<th>HMSI</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>122</td>
<td>122</td>
<td>122</td>
<td>366</td>
</tr>
<tr>
<td>age (years)</td>
<td>11.35 ± 0.48</td>
<td>11.33 ± 0.47</td>
<td>11.37 ± 0.48</td>
<td>11.35 ± 0.48</td>
</tr>
<tr>
<td>girls/boys (n)</td>
<td>58/64</td>
<td>63/59</td>
<td>70/52</td>
<td>191/175</td>
</tr>
<tr>
<td>BMI (kg.m⁻²)</td>
<td>19.89 ± 3.74</td>
<td>19.45 ± 3.07</td>
<td>19.05 ± 3.39</td>
<td>19.46 ± 3.42</td>
</tr>
<tr>
<td>waist circumference (cm)</td>
<td>68.31 ± 8.17</td>
<td>66.58 ± 6.30</td>
<td>65.15 ± 6.80</td>
<td>66.68 ± 7.23</td>
</tr>
<tr>
<td>total body fat (%)</td>
<td>27.05 ± 7.35</td>
<td>27.25 ± 7.19</td>
<td>27.97 ± 7.96</td>
<td>26.82 ± 6.05</td>
</tr>
<tr>
<td>trunk fat (%)</td>
<td>23.37 ± 8.47</td>
<td>23.04 ± 8.23</td>
<td>23.90 ± 8.86</td>
<td>23.44 ± 8.51</td>
</tr>
<tr>
<td>upper limb body fat (%)</td>
<td>26.98 ± 10.34</td>
<td>27.49 ± 10.18</td>
<td>28.83 ± 11.09</td>
<td>27.77 ± 10.54</td>
</tr>
<tr>
<td>total body lean soft tissue (%)</td>
<td>69.91 ± 7.05</td>
<td>69.67 ± 6.90</td>
<td>68.95 ± 7.65</td>
<td>69.51 ± 7.20</td>
</tr>
<tr>
<td>trunk lean soft tissue (%)</td>
<td>74.80 ± 8.28</td>
<td>75.12 ± 8.04</td>
<td>74.27 ± 8.67</td>
<td>74.73 ± 8.32</td>
</tr>
<tr>
<td>upper lean soft tissue (%)</td>
<td>69.74 ± 10.12</td>
<td>69.16 ± 9.94</td>
<td>67.89 ± 10.90</td>
<td>68.93 ± 10.33</td>
</tr>
<tr>
<td>maturity offset (years)</td>
<td>-0.85 ± 1.08</td>
<td>-0.89 ± 1.02</td>
<td>-0.92 ± 1.11</td>
<td>-0.89 ± 1.07</td>
</tr>
<tr>
<td>muscular strength (kg)</td>
<td>20.84 ± 4.08</td>
<td>23.20 ± 4.36*</td>
<td>24.86 ± 3.91*</td>
<td>22.96 ± 4.43</td>
</tr>
<tr>
<td>heart rate at rest (bpm)</td>
<td>89.63 ± 14.98</td>
<td>89.56 ± 13.20</td>
<td>89.51 ± 15.25</td>
<td>89.57 ± 14.47</td>
</tr>
<tr>
<td>heart rate at maximal effort (bpm)</td>
<td>193.55 ± 12.14</td>
<td>195.22 ± 10.67</td>
<td>196.09 ± 9.88</td>
<td>194.95 ± 10.95</td>
</tr>
<tr>
<td>CRF (ml.kg⁻¹.min⁻¹)</td>
<td>40.86 ± 7.86</td>
<td>42.55 ± 7.88</td>
<td>43.21 ± 8.90*</td>
<td>42.21 ± 8.27</td>
</tr>
<tr>
<td>systolic blood pressure (mmHg)</td>
<td>112.50 ± 11.36</td>
<td>110.94 ± 9.97</td>
<td>110.54 ± 10.13*</td>
<td>110.99 ± 10.55</td>
</tr>
<tr>
<td>diastolic blood pressure (mmHg)</td>
<td>62.05 ± 8.36</td>
<td>61.40 ± 8.52</td>
<td>61.61 ± 7.79</td>
<td>61.69 ± 8.21</td>
</tr>
<tr>
<td>diameter of carotid artery (mm)</td>
<td>6.33 ± 0.49</td>
<td>6.29 ± 0.50</td>
<td>6.16 ± 0.46*</td>
<td>6.26 ± 0.49</td>
</tr>
</tbody>
</table>

LMSI: low muscular strength index group; MMSI: middle muscular strength index group; HMSI: high muscular strength index group; BMI: body mass index; CRF: cardiorespiratory fitness. * Significant differences from LMSI (p < 0.05).

All models were adjusted for sex, maturity offset and pulse pressure.

Table 3 Multiple regression analysis with cIMT as dependent variable and physical fitness and abdominal adiposity as determinants.

<table>
<thead>
<tr>
<th>cIMT Variables</th>
<th>R²</th>
<th>Beta</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>model 1</td>
<td>MSI 0.05</td>
<td>-0.11</td>
<td>-0.22</td>
</tr>
<tr>
<td>model 2</td>
<td>MSI 0.05</td>
<td>-0.11</td>
<td>-0.21</td>
</tr>
<tr>
<td>model 3</td>
<td>MSI 0.06</td>
<td>0.12</td>
<td>-0.22</td>
</tr>
<tr>
<td></td>
<td>CRF 0.01</td>
<td>-0.15</td>
<td>0.17</td>
</tr>
<tr>
<td></td>
<td>trunk fat 0.09</td>
<td>-0.06</td>
<td>0.23</td>
</tr>
</tbody>
</table>

All models were adjusted for sex, maturity offset and pulse pressure.

95% CI: 95.0% Confidence Interval for Beta; MSI: muscular strength index; CRF: cardiorespiratory fitness; cIMT: intima-media thickness of the common carotid artery.
Discussion

The novel finding from this study was that muscular strength is inversely associated with cIMT independently of sex, maturity offset, pulse pressure, central adiposity and CRF. Children with low muscular strength have the highest cIMT values, waist circumference and systolic blood pressure coupled with the low CRF, apparently setting the stage for increased risk of cardiovascular complications in adulthood.

The results of the present study extend those of Artero et al. [3] and Steene-Johannessen et al. [42], the latter demonstrating that muscular strength was independently and inversely associated with clustered metabolic risk in a cohort of 9- and 15-year-old Norwegian children (N=2,818). Others [10,11] have also shown that greater muscular strength (N/kg) in youth is associated with lowers levels of CVD risk factors, coupled with better insulin sensitivity and beta-cell function in young adulthood. Because initiation of muscle-strengthening activities can lead to gains in muscular strength [5], these observations indicate that it also has the potential to offer observable vascular value beyond that of CRF [28] and other traditional CVD risk factors [21]. This suggests that low muscular strength is causally related to development of unfavorable levels of CVD risk factors [11], in particular increased cIMT. In fact, we ran a supplementary multiple linear regression analysis (data not shown) to estimate the R² change from a model with cIMT as the dependent variable and BMI and cardiorespiratory fitness as independent variables to a second model where MSI was entered as an additional independent variable, both models being fully adjusted for sex, maturity offset and pulse pressure. A significant R² change (p<0.05) was observed when MSI was added. Thus, handgrip strength may be a useful tool in clinical settings and for preventive services in schools, offering good reliability without additional costly equipment [33].

Only 27% of the children in this study had optimal CV health scores. Others have found similar low prevalence of ideal CV health in youth [34]. Previous studies in adults have also reported a very low or non-existing prevalence of ideal CV health [47]. Based on our findings, vascular health benefits are gained by the avoiding a low CV health score. Consequently, we share the view of Pahkala et al. [35] that not all of the ideal metrics are needed to gain CV health benefits in childhood. The fact that the cIMT increased by 0.04 mm in children with 2 or less optimal metrics is disconcerting considering how difficult it is to reduce cIMT through interventions [46].

The differences in the LMSI group in cIMT, CRF, waist circumference and blood pressure translate to physiological differences increasing CVD risk. The apparent protective effect in the higher MSI groups may be a function of insulin. Several cross-sectional studies among youth uncovered an inverse association between muscular strength and insulin resistance independent of CRF [10,42]. In addition, small-scale trials have been conducted among youth comparing the effect of resistance training on insulin resistance or glycemic control with a control group indicating that not only does this type of training increase strength and lean mass, but also enhances insulin sensitivity and slightly reduces glucose production [22,44]. Hyperinsulinemia driven by insulin resistance promotes cardiovascular pathology, stimulating mitogen-activated protein kinase, mitogenesis, and PAI-1 within vascular smooth muscle cells [4], endothelin-1 production with subsequent vascular smooth muscle growth [31], and ras-p21 in vascular smooth muscle, which promotes a cascade of other growth factors such as platelet-derived growth factor. Thus, interventions designed to prevent hyperinsulinemia and related metabolic disorders should focus not only on reducing fat but also improving muscular strength [3]. Although this study cannot evaluate causal pathways, children with increased cIMT should be encouraged to engage in exercise programs and other forms of physical activity that complement aerobic endurance training with muscle performance.

Strengths and Limitations

This study has several strengths and limitations:

An important strength of the current study was that we were able to examine the independent associations of muscular strength and cIMT, as well as control for important confounding factors such as CRF and body composition which were measured objectively. Automated edge-detection on the basis of RF signal processing of B + M mode US imaging is probably the most accurate method to measure cIMT [26]. The large number of participants in this study suggests that results are representative of the population tested.

The gold-standard measure of CRF in humans involves direct assessment of maximal oxygen consumption in response to an exercise test. In this study CRF was indirectly determined by a cycle test with progressively increasing workload using an electronically braked cycle ergometer. Although our concept of CV health score did not meet all of the criteria used in defining ideal CV health by the American Heart Association [23], we took into consideration similar concepts in health promotion and disease prevention: (1) The power of primordial prevention and (2) the evidence that CVD and risk factors for it often develop early in life. While these concepts informed our definition of optimal CV health as well as the metrics that would be needed to monitor it, this was only a scientific exercise. We calculated MSI dividing peak absolute force by an objective measure of body composition. However, we should consider that imaging techniques like DXA are not available for large scale use. Validated sex-specific anthropometric formulas to calculate lean body mass may aid in accounting for lean body mass in future studies. Because this was a cross-sectional study, and we did not measure insulin resistance or beta-cell function, the biological plausibility presented in this study can only be inferred. There are no data per se indicating an increased risk of mortality in children with higher than normal cIMT, probably as a function of extremely low mortality rates due to atherosclerosis in children. Additionally, there is currently no longitudinal evidence tracking cIMT from childhood to adulthood, evaluating whether high cIMT in childhood confers increased risk in adulthood. Still, there is evidence that atherosclerosis may start at an early age [41]. To evaluate early, subclinical disease, assessment of cIMT has been used extensively in children and young adults with known risk factors for cardiovascular disease. Increased cIMT relative to normal children has been demonstrated in pediatric patients with CVD risk factors [43]. In randomized clinical trials assessing statin therapy in children [20,45], diet, and exercise [8], cIMT decreased in accordance with changes in other cardiovascular risk factors, whereas cIMT in the placebo groups increased, suggesting that cIMT is indeed a surrogate marker of atherosclerotic burden in children. The developmental changes of cIMT during the developmental years have not been clearly elucidated [16,39]. If cIMT changes throughout childhood, these changes are very small [8].
and we understand that their clinical or functional relevance are truly questionable. We are also aware that these changes in the IMT are accompanied by increases in arterial size, including luminal diameter [17, 39]. Therefore, it is uncertain whether some of the changes in cIMT that occur with age represent normal vascular adaptation or a pathological change [43].

Conclusion

There is an inverse and independent association between muscular strength and cIMT. Low muscular strength is also associated with higher levels of CVD risk factors in children. From a public health perspective, a handgrip strength test may be a useful tool for designing preventive services in clinical and school settings.

Conflict of interest: The author have no conflict of interest to declare.

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