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Mediation of obesity-related variables in the association between physical fitness and cardiometabolic risk in children and adolescents: a systematic review and meta-analysis

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ABSTRACT

Objective To examine the mediation of obesity-related variables in the association between physical fitness and cardiometabolic risk in children and adolescents.

Design Systematic review and meta-analysis.

Data sources Studies from electronic databases from inception to 31 December 2023.

Eligibility criteria for selecting studies Included were 123 observational studies (cross-sectional and longitudinal) that assessed risk by constructing a continuous score incorporating cardiometabolic parameters. Studies were considered if they evaluated at least one fitness component as an exposure in children and adolescents (5–19 years). Thirty-one were included in the main meta-analyses.

Results Cross-sectional findings indicate that cardiorespiratory fitness is modestly but beneficially associated with cardiometabolic risk, either indirectly via obesity-related variables (indirect standardized beta coefficient [$\beta_{Indirect}$]=−0.17; 95% confidence interval [CI] −0.23; −0.11; inconsistency index [I^2]=94.4%) or directly and independently from obesity-related variables (r=−0.11; 95% CI −0.15; −0.07; I^2=87.4%), whereas muscular fitness seems to be associated with risk only via obesity-related variables ($\beta_{Indirect}$=−0.34; 95% CI −0.47; −0.20; I^2=85.1%). There was no cross-sectional difference between biological sexes (p≥0.199). Longitudinal findings indicate no total (r=−0.12; 95% CI −0.24; 0.01; I^2=23.1%) and direct (r=−0.03; 95% CI −0.08; 0.03; I^2=0%) associations.

Conclusion The association between fitness and risk appears to take place either indirectly through the reduction of obesity-related levels or directly by influencing risk. The latter underscores that the inverse association extends beyond a mere reduction in obesity-related variables, encompassing specific enhancements linked to exercise training, including increased metabolic efficiency, and cardiovascular capacity.

PROSPERO registration number CRD42022354628.

WHAT IS ALREADY KNOWN

⇒ Continuous scores are useful in understanding the continuum of metabolic health in youth, aiding in early risk identification.

⇒ Cardiometabolic parameter clustering is believed to occur due to physiological processes related to higher body adiposity, especially in the abdominal region.

⇒ Physical fitness components, beyond cardiorespiratory and muscular fitness, may influence cardiometabolic health.

WHAT ARE THE NEW FINDINGS

⇒ Obesity-related variables may hypothetically mediate the association between physical fitness and cardiometabolic risk, but fitness importance should not be excluded, as improving fitness to maintain lower body fat may be a key to a healthier cardiometabolic profile.

INTRODUCTION

Non-communicable chronic diseases, such as cardiovascular diseases, cancer, type II diabetes mellitus and respiratory diseases, are the leading causes of worldwide mortality.[1] Among the risk factors for the development of chronic diseases are disorders and dysfunctions that constitute metabolic syndrome (eg, high adiposity, hypertension and dysregulated lipid and glucose parameters).[2] Metabolic syndrome has been studied in children and adolescents and recognised as a paediatric issue.[3] In fact, diagnosing the syndrome during this stage of life is a strong predictor of a later diagnosis of the syndrome in adulthood as well as chronic disease.[4]

Despite being widely adopted, there is no consensus on the diagnosis of metabolic syndrome in children and adolescents.[5] For this reason, in recent years, the literature has increasingly adopted a continuous score constructed using well-defined

cardiometabolic parameters to measure cardiometabolic risk, rather than relying on traditional dichotomised definitions for the diagnosis of metabolic syndrome.[6] This is because dichotomisation reduces information,[7] and children typically do not exhibit symptoms of illness. Therefore, their metabolic status is a continuum, which is better described using continuous scores. Regardless of the criterion used for computing a continuous score (eg, the sum or mean of z-scores, the sum of standardised residuals from regression models, dimensionality reduction techniques), attention is given to the clustering of cardiometabolic parameters at unfavourable levels simultaneously in the same subject,[8] which is known as cardiometabolic risk and should be a sign of poor cardiometabolic health.[6] A higher value obtained from the mean continuous score (eg, continuous score ≥0.85[6] or ≥1.00[9] represents three/four or more cardiometabolic parameters at 'risk'[6 9] and it confers a high degree of health risk, tending to remain unfavourable from childhood to adolescence[10] and from childhood and adolescence to adulthood,[11] potentially leading to an early onset of chronic diseases.[12] Therefore, identifying to what extent and which children and adolescents are at risk is crucial, as early prevention can be much more efficient than later treatment when a disease is already developing.[6]

It is believed that the clustering of cardiometabolic parameters and, consequently, high cardiometabolic risk occurs due to physiological processes related to higher levels of body adiposity,[13] especially in the abdominal region.[14] Meta-analysed longitudinal studies provide evidence that unfavourable measures of obesity-related variables during childhood and adolescence are associated with unfavourable cardiometabolic parameters in adulthood.[15] However, the ability to identify healthy cardiometabolic levels based on obesity-related variables seems to be possible using a cross-sectional design during childhood and adolescence.[16 17] There is also evidence summarised in systematic reviews and meta-analyses that components of physical fitness can identify cardiometabolic risk.[18–22] The literature has clearly shown that different components of physical fitness are associated with distinct healthier outcomes.[23 24] Among these benefits, there are healthier measurements of cardiometabolic parameters, especially obesity-related variables measured longitudinally.[18–21] Nevertheless, there are gaps in the extant literature that warrants further investigation.

First, most studies investigating associations between physical fitness components and cardiometabolic risk have focused mainly on cardiorespiratory fitness[19 21] and muscular fitness components (eg, muscle strength, power, endurance and isokinetic strength)[18 20 22] as exposures and have not focused on other physical fitness components, such as flexibility, agility or speed. Second, the aforementioned studies focused on what is known as total and direct associations, without considering the potential indirect mechanisms linking physical fitness and cardiometabolic risk through mediator variables. Conceptually, an association between a specific physical fitness component and cardiometabolic risk could be mediated by a third variable if physical fitness influences this variable, which in turn could carry the influence of the physical fitness component into cardiometabolic risk. This could be the case of obesity-related variables, since hypothetically being physically fit results in lower adiposity. In other words, comprehending conceptualised mediational frameworks could offer a better understanding of *how* physical fitness and cardiometabolic risk are associated.[25] From this perspective, the present systematic review and meta-analyses aim to examine the mediation of obesity-related variables in the association between physical fitness and cardiometabolic risk in children and adolescents.

METHODS

Protocol and registration

This systematic review was registered in the International Prospective Register of Systematic Reviews (PROSPERO; ID CRD42022354628) and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.[26] Checklist is available in Online supplemental file 1.

Eligibility criteria

Studies were included if they met the following eligibility criteria: (1) were observational studies (cross-sectional and longitudinal) published or accepted for publication; (2) evaluated cardiometabolic risk by constructing a continuous score with different cardiometabolic parameters for children and adolescents with no diseases or special clinical conditions (eg, diabetes, kidney disease, cancer, HIV/AIDS, etc) and (3) evaluated at least one physical fitness component as an exposure variable and cardiometabolic risk as the outcome variable. Grey literature, conference abstracts and studies evaluating individual cardiometabolic parameters as outcome variables were excluded.

Search strategy

The systematic search strategy was constructed by a professional librarian using the PECOT framework (**P**opulation: children and adolescents; **E**xposure: physical fitness components; **C**omparator(s)/control: physically inactive or poorer physical fitness participants at any physical fitness component were included as a control group whenever they were available; **O**utcome: cardiometabolic risk measured by a continuous score; **T**ype of studies: observational). The search strategy was applied to six different electronic databases in August 2022: LILACS, PubMed, Scielo, Scopus, SPORTDiscus and Web of Science. There were no publication date or language restrictions. A common search strategy was adopted. However, it was adapted for each database when necessary (see the full search strategy for each database in online supplemental material 2). Additionally, the reference lists of the included studies and previous

reviews—identified through the search strategy (online supplemental table 1 shows the revisions screened)—that evaluated the associations between physical fitness and cardiometabolic risk were manually reviewed to identify potential studies for inclusion. The searches were rerun just before the final analyses by including a publication date filter in the search strategy (from August 2022 to December 2023), resulting in the retrieval of additional studies for inclusion.

Selection and data collection process

Screening and evaluating titles, abstracts and full-text articles were independently conducted by two authors, with guidance from a senior author, who resolved disagreements. The same authors independently extracted the following data: authors, title, year of publication, study design, study location, sample size, percentage of males and females, mean±SD age, physical fitness exposures and assessment procedure, statistical treatment of exposure (categorised or continuous), cardiometabolic parameters included within the continuous score, method of computing the continuous score, statistical method used to define risk using the outcome (categorised or continuous), statistical model applied, adjusted variables within the model and main results.

Quality assessment of individual studies

The methodological quality of the studies was assessed using the *National Heart, Lung, and Blood Institute* tool (NHLBI)[27] for observational longitudinal and cross-sectional studies (online supplemental material 3). The tool involves 14 items to the internal validity of a study. For cross-sectional studies, items 7 and 13 were considered 'not applicable'. Item 8 was marked 'no' if the study dichotomised the physical fitness exposure variable for the main analyses (eg, cardiorespiratory fitness classified as fit or unfit (Independently from the way of dichotomisation: sample-specific medians or means, previous cutpoints based on the available literature, or ROC curve cutpoints generated within the study itself)). For item 9, field-based physical fitness tests were considered reliable and valid.[28–30] Item 12 was marked as 'not applicable' because assessors measuring the outcome (eg, blood samples or blood pressure) would not be influenced by the exposure results (physical fitness), even if the same assessor was used since laboratory measurements are usually taken before physical assessment (if they are conducted on the same day). Item 14 received a 'yes' response if, within the analysis, there were adjustments for at least three confounding variables relevant to the associations between physical fitness and cardiometabolic risk (eg, age, sex, sexual maturation, ethnicity, body size, other physical fitness components, obesity-related variables, sedentary behaviour and physical activity level). Additionally, it is worthwhile to note that there is no need to adjust for sex or age when the outcome continuous score variable was constructed using cardiometabolic scores, which were previously calculated based on sex-specific and age-specific references. A quality rating was calculated using the following equation: $\frac{Number\ of\ questions\ with\ "Yes"\ response}{Total\ number\ of\ applicable\ questions}$. Thus, the quality rating score for each included study ranged from 0 (low) to 1 (high). The quality rating score was descriptively presented using measures of range, medians and IQRs. Two authors independently assessed methodological quality, with guidance from a senior author, who resolved disagreements.

Statistical analysis

RStudio software was used for all meta-analyses, which were performed when at least three studies provided the same measures of effect size for a given association between a specific physical fitness component and cardiometabolic risk. Meta-analyses were first conducted for physical fitness as a global construct and within subgroups stratified by physical fitness component. Before the analyses, duplicated samples were screened within each meta-analysis. If a single study presented associations for two or more physical fitness components with cardiometabolic risk, the following hierarchy was used to choose one measure of association: (1) cardiorespiratory fitness; (2) muscular fitness score; (3) muscular endurance; (4) muscular strength/power or (5) any other physical fitness component. Additionally, the outcomes across studies within the meta-analyses should be similar (eg, the continuous score had to include at least one measure of each cardiometabolic parameter: obesity-related variables, glucose regulation, arterial blood pressure and lipid profile). This is because two different continuous scores that include two different measures of obesity-related variables (eg, waist circumference or sum of skinfolds), blood pressure (eg, systolic blood pressure or mean arterial pressure) or lipid profile (eg, total cholesterol or triglycerides) tend to provide highly correlated results.[6 31]

The meta-analyses for the indirect associations were conducted using the parameter-based meta-analytic structural equation modelling (MASEM) approach in the '*metaSEM*' package.[32] This approach employed a two-stage process: first, the *indirectEffect*() function was used to estimate the standardised indirect association coefficient of each study as a measure of effect size and to estimate their pooled covariance matrix from covariance matrices of each study. Covariances were obtained using the following equation: $covariance_{xy} = r * SD_x * SD_y$; where r represents the correlation coefficient between variables x and y and SD represents the SD of x or y[33]; second, a multivariate random-effects meta-analysis was conducted using the standardised indirect association coefficients with the *meta*() function. The standardised indirect effects were classified as small (β≅0.14), medium (β≅0.39) or large (β≅0.59).[34]

The considered effect sizes for the meta-analyses of total and direct associations were the Pearson correlation coefficient and ORs, depending on the measures reported by the original studies. If a study reported

unstandardised (B) or standardised (β) regression coefficients, these estimates were converted to correlation coefficients (r) using the following equations: (I) $r = 0.98 * (\beta) + 0,05 * \lambda$; where λ is an indicator variable equal to 1 when β≥0 and 0 when β<0[35] and (II) $\beta = \frac{SD_x}{SD_y} * B$; where SD represents the SD, x represents the predictor of interest (physical fitness component) and y represents the outcome of interest (continuous score).[36] The effect size r was classified as small ($r \leq 0.29$), medium ($0.3 \leq r \leq 0.49$) or large ($r \geq 0.5$).[37] If a study did not report the SE of the OR required for the meta-analyses, these estimates were obtained from the 95% CIs using the following equation: $SE = \frac{\ln(Upper\ limit) - \ln(Lower\ limit)}{3.92}$; as suggested by the Cochrane Handbook.[38] The meta-analyses for total and direct associations were performed using the '*meta*' package[39] within RStudio, employing the Hartung-Knapp-Sidik-Jonkman method for random effects to calculate the overall estimate of the effect size and its respective 95% CIs.[40] The inconsistency index (I^2) was used as a measure of inconsistency across studies[41] and classified as mild ($I^2 \leq 0.30$), moderate ($0.31 \leq I^2 \leq 0.55$) or severe ($I^2 \geq 0.56$).[42] Whenever possible, random effects meta-regression analyses were conducted to verify whether the effect sizes of indirect, total and direct associations varied by sex (coded as 0=females; 1=males), in addition to reporting a subgroup analysis.[43]

Sensitivity analyses were performed by removing one study at a time from the main meta-analyses to verify the robustness of the findings. The Luis Furuya-Kanamori (LFK) index was computed using the '*metasens*' package[44] to assess publication bias; the results are presented as Doi plots and classified as no asymmetry (−1≤LFK≤1), minor asymmetry (|2|≤LFK<|1|) or major asymmetry (LFK>|2|).[45]

Finally, considering the methodological heterogeneity of observational studies, an individual interpretation presenting the results of the analysis between physical fitness and cardiometabolic risk in each study, including those statistical models that could not be included in the meta-analyses, was constructed.

RESULTS

Study selection

After 6260 studies were retrieved from the systematic search strategy, 312 studies were assessed for eligibility after excluding duplicated studies and screening titles and abstracts; 118 of these studies met the inclusion criteria and were included in the present review. Additionally, the reference lists of the included studies and previous systematic reviews—identified by the search strategy—were screened manually to identify potential studies for inclusion: 1007 studies were identified, and after excluding duplicated studies and screening titles and abstracts, 102 studies were assessed for eligibility, of which only five studies met the inclusion criteria. In total, 123 studies were read in full and were used for potential further analyses (figure 1). The reasons for exclusion from revision of studies assessed for eligibility are listed in online supplemental table 2.

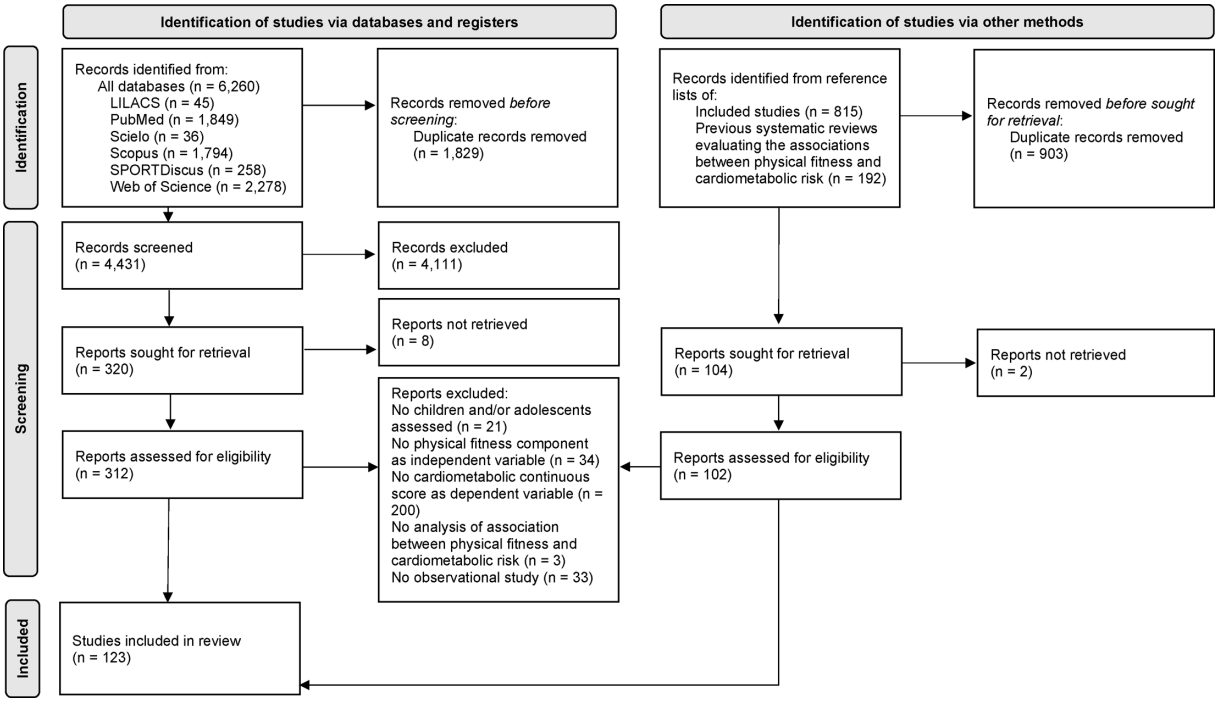

Figure 1 Flow diagram of systematic searches and studies selection process.

Study characteristics

The main characteristics of the 123 studies included in this systematic review are found in online supplemental table 3. The studies summarised associations between physical fitness components and cardiometabolic risk in children and adolescents from 35 countries, with sample sizes ranging from 28 to 15 794 participants per study. The age of the participants ranged from 5 to 19 years. Most of the studies had a cross-sectional design (N=112; 91.1%), while only three studies (2.4%) presented an observational longitudinal design. Eight studies (6.5%) reported both observational cross-sectional and longitudinal analyses.

Physical fitness component measurements

The analyses that sought to investigate associations between physical fitness components and cardiometabolic risk are described in online supplemental tables 4–17. The methods for assessing cardiorespiratory fitness included laboratory tests (eg, maximal or submaximal tests on treadmills or cycle ergometers with spirometry devices or measurements of physical work performance), indirect field-based tests (eg, the Andersen test, the 20 m Shuttle run test, the 1-mile and 6 or 9 min walking and running tests and the Yo–Yo test), and composite scores calculated from different assessment methods. Cardiorespiratory fitness was expressed in terms of (1) maximum or peak oxygen consumption (VO_{2max} and VO_{2peak}, respectively) reported as absolute values (litres or millilitres per minute) or scaled by fat-free mass or total body mass (raised to the power of 1 mL/kg/min or an allometric mass exponent); (2) number of stages or metres needed to complete a field-based test or number of seconds needed to cover a specific distance or (3) maximal power output scaled to total body mass or fat-free mass (W/kg).

Muscular fitness was assessed using a variety of methods for different components: handgrip strength was measured using dynamometers (normalised by body weight or not); lower limb power was measured using the standing long jump or the counter movement jump tests; abdominal endurance was measured using sit-up or curl-up tests; upper limbs endurance and power were measured using push-up and medicine ball throw tests, respectively; trunk endurance was measured using the modified Biering-Sørensen test; and, last, the sum of sex-specific and age-specific muscular components z-scores were used to create a single muscular fitness composite score. Flexibility was measured using sit-and-reach tests. Agility and speed were assessed using sprint tests with or without a change in direction. Balance was measured using the Flamingo test. Global physical fitness was also evaluated using composite scores of sex-specific and age-specific z-scores for different physical fitness components.

Cardiometabolic risk score measurements

Continuous scores were calculated using five different approaches (online supplemental table 3). The most used method was to sum z-scores using different cardiometabolic parameters (n=67), followed by the mean measure of z-scores (n=33). Only a few studies used the sum or mean of each cardiometabolic parameter regressed onto independent variables (eg, sex, age, sexual maturation, ethnicity) to construct a continuous score (n=12), whereas two studies used both the residuals and the sum of z-scores. Dimensionality reduction techniques, such as exploratory and confirmatory factor analyses and principal component analysis, were also employed (n=6). Three studies did not report methods for computing continuous scores.

Methodological quality of the individual studies

The methodological quality of the studies evaluated using the NHLBI tool for each of the included studies is exhibited in online supplemental table 18. Overall, the quality score ranged from 0.54 to 0.85 (median quality score=0.77 (IQR: 0.69–0.77]) within studies reporting longitudinal associations and from 0.50 to 0.82 (median quality score=0.64 (IQR: 0.64–0.70)) within studies reporting cross-sectional associations.

Indirect association meta-analyses

A total of seven cross-sectional studies[46–52] and one longitudinal study[53] proposed and tested indirect associations via measures of obesity-related variables. However, two studies included obesity-related variables in the cardiometabolic risk score,[49 52] and they were not used for meta-analyses. The main characteristics of the eight mediational studies are found in online supplemental table 19. There were no other conceptualised mediators other than obesity-related variables. Cardiorespiratory fitness was used as the exposure variable in four studies,[46–48 50] whereas a muscular fitness score was used in three studies.[47 51] Finally, four studies[54–57] provided enough data to derive a covariance matrix between cardiorespiratory fitness, obesity-related variables and cardiometabolic risk, and they were included in the meta-analytic structural equation model. Online supplemental table 20 presents the effect sizes between all three variables, sample sizes and SD in the four additional studies.

Five parameter-based meta-analytic structural equation models, including those from seven cross-sectional studies,[46–48 50 54 55 57] were constructed for the association between cardiorespiratory fitness and cardiometabolic risk because two studies presented different mediational models through different measures of obesity-related variables: body fat percentage, body mass index, fat-mass index, waist circumference and/or waist-to-height ratio.[46 54] Each meta-analysis was run separately considering the covariance matrices between cardiorespiratory fitness, cardiometabolic risk and an individual obesity-related variable at a time. Other studies used body fat percentage,[47] body mass index,[48 50] fat-mass index[55] and waist circumference[57] as mediating variables.

Cardiorespiratory fitness was indirectly associated with cardiometabolic risk through obesity-related

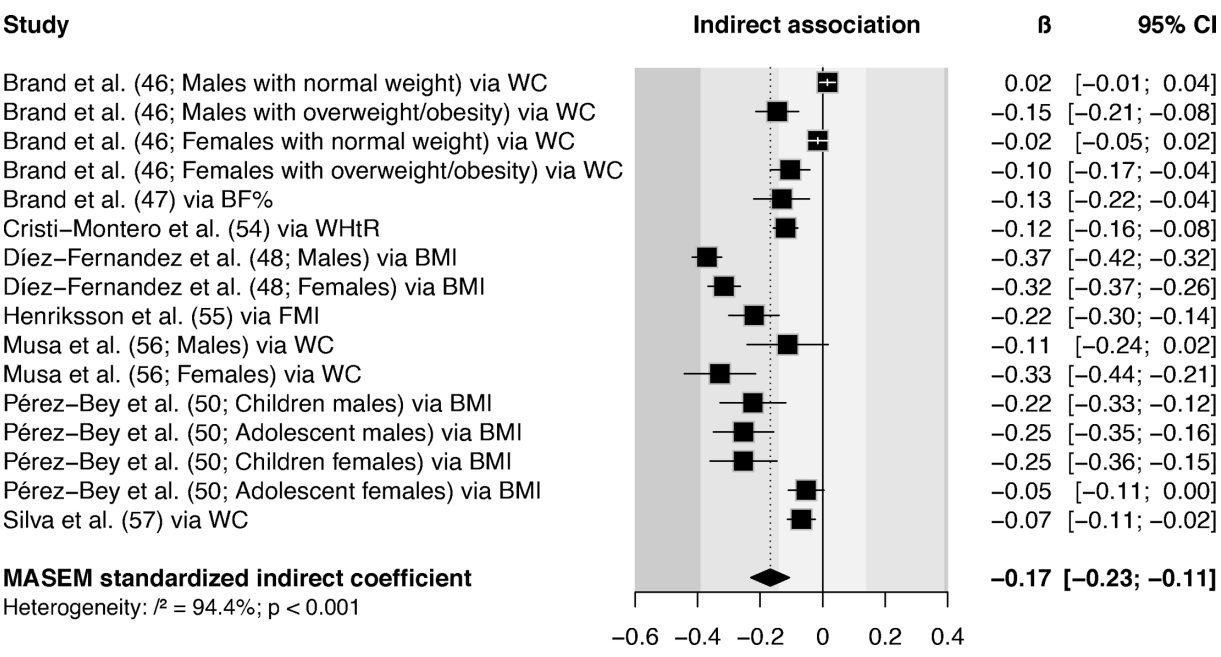

Figure 2 Forest plot for the indirect cross-sectional association between cardiorespiratory fitness and cardiometabolic risk via obesity-related variables. The size of squares is not determined by weight. BF%, body fat percentage; BMI, body mass index; FMI, fat mass index; MASEM, meta-analytic structural equation modelling; WC, waist circumference; WHtR, waist-to-height ratio; β, standardised indirect coefficient.

variables with a small to medium effect size (MASEM standardised indirect coefficient=−0.17; 95% CI −0.23; −0.11; I^2=94.4%). The indirect association did not change between males and females (p=0.924; online supplemental table 21). Figure 2 presents the forest plot for the indirect associations of cardiorespiratory fitness and cardiometabolic risk via obesity-related variables (waist indices were given preference for the main model; see online supplemental figures 1–4 for models using different measures of obesity-related variables from Brand *et al*[46] and Cristi-Montero *et al*.[54] Additionally, the sensitivity analysis indicated no modification in the results after removing one effect size at a time (online supplemental figure 5). However, the LFK index showed major asymmetry, indicating potential publication bias (LFK=−3.26; online supplemental figure 6). Longitudinal mediation was not meta-analysed because there was only one study.

A second meta-analysis revealed that the muscular fitness score was indirectly associated with cardiometabolic risk through obesity-related variables. Specifically, the parameter-based MASEM including two cross-sectional studies[47 51] revealed that the muscular fitness score was indirectly associated with cardiometabolic risk via obesity-related variables (MASEM standardised indirect association=−0.34 (95% CI −0.47; −0.20] I^2=85.1%), with a small to medium effect size. Figure 3 presents the forest plot for the indirect association between muscular fitness score and cardiometabolic risk via obesity-related variables.

A parameter-based MASEM for global physical fitness would be the same as the aforementioned results for cardiorespiratory fitness because effect sizes for cardiorespiratory fitness would be chosen

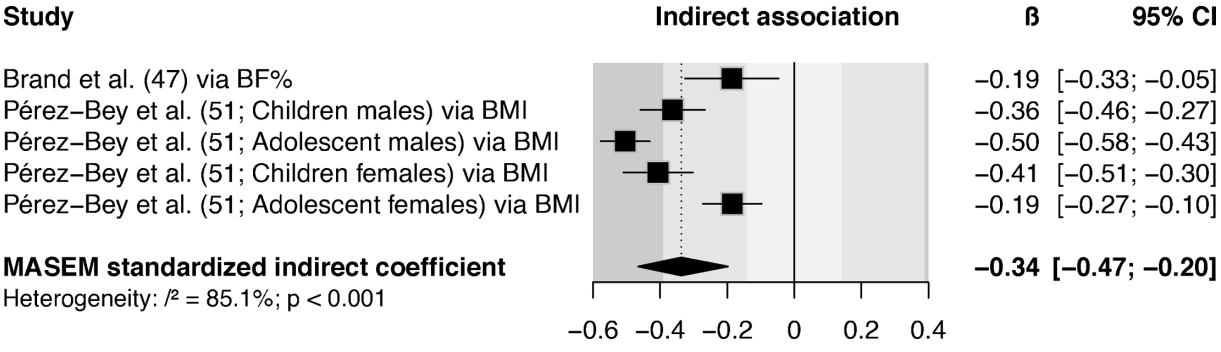

Figure 3 Forest plot for the indirect cross-sectional association between muscular fitness score and cardiometabolic risk via obesity-related variables. The size of squares is not determined by weight. BF%, body fat percentage; BMI, body mass index; MASEM, meta-analytic structural equation modelling; β, standardised indirect coefficient.

in the studies testing associations of both cardiorespiratory and muscular fitness with cardiometabolic risk.[47 50 51]

Total and direct associations meta-analyses

All the mediational studies conceptualised their statistical models for the association between physical fitness and cardiometabolic risk using obesity-related variables as the mediating variable. Therefore, the following meta-analyses of total and direct associations were constructed considering whether there was (direct association) or was not (total association) an adjustment for obesity-related variables in the original measures of effect size included in the meta-analyses. Additionally, the main text meta-analyses were conducted only for physical fitness and cardiometabolic continuous scores not including measures of obesity-related variables in addition to measures of glucose regulation, arterial blood pressure or lipid profile; to avoid spurious association between the mediator obesity-related variables and the continuous score (online supplemental figures 7–10 present the total association of global physical fitness and its subgroup analyses by components with the cardiometabolic risk continuous score including obesity-related variables; and the LFK=−0.54).

Global physical fitness

Global physical fitness was cross-sectionally and inversely associated with cardiometabolic risk (r=−0.22 95% CI −0.27; −0.17); p<0.001; I^2=85.2%) with small to medium effect sizes.[46 47 50 55–71] This total association did not change between males and females (p=0.199; online supplemental figure 11 and table 21). Figure 4 presents the forest plot for the total cross-sectional association between global physical fitness and cardiometabolic risk. The LFK index showed no asymmetry, indicating no publication bias (LFK=−0.95; online supplemental figure 12). Additionally, the sensitivity analysis indicated no modification in the results after removing one effect size at a time (online supplemental figure 13).

The statistically significant inverse association between global physical fitness and cardiometabolic risk remained significant when the associations were meta-analysed after adjustment for obesity-related variables (r=−0.11 95% CI −0.15; −0.07); p<0.001; I^2=87.4%) with small effect sizes.[46–48 50 54–57 63 65 67 69 71–75] This direct association did not change between males and females (p=0.653; online

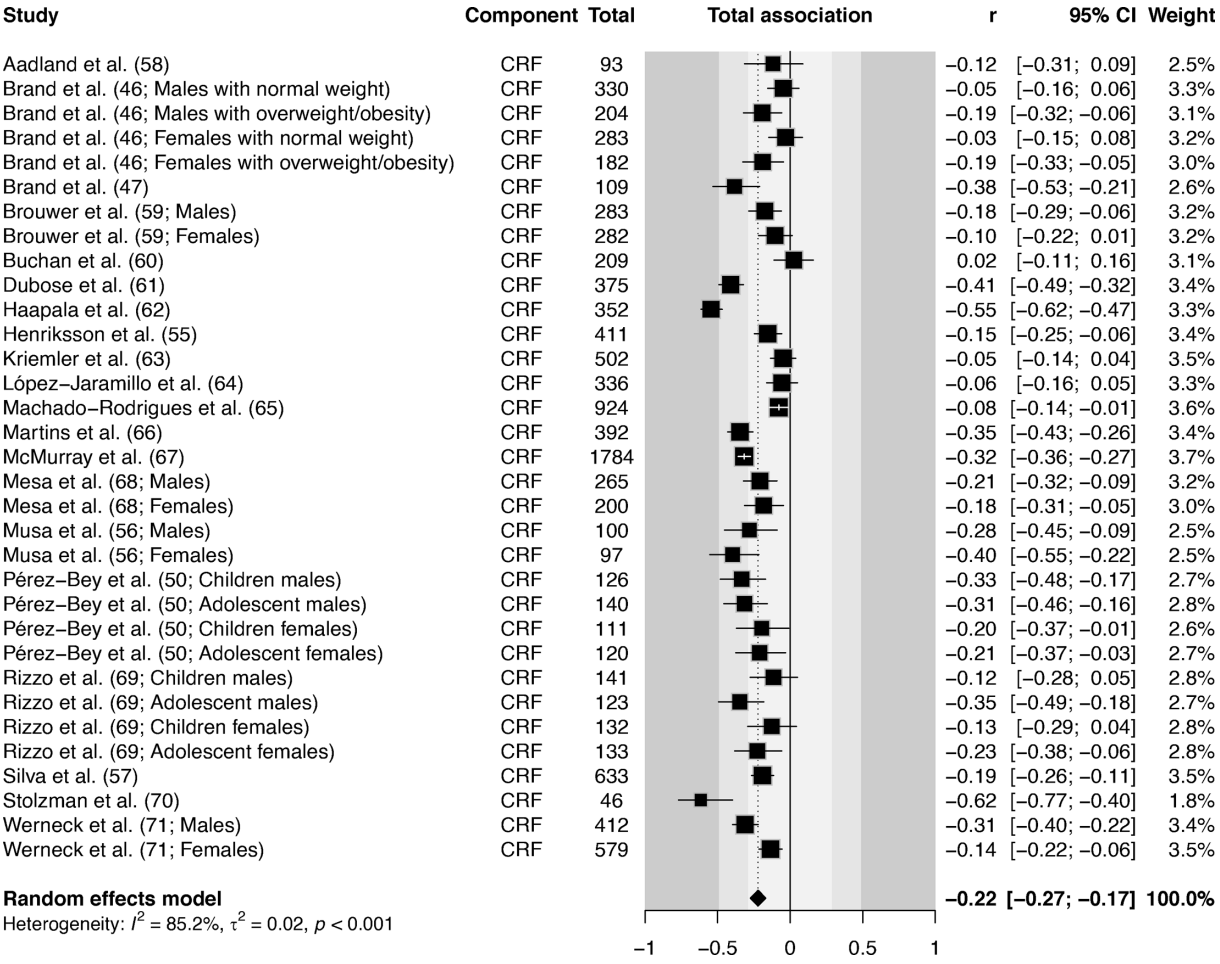

Figure 4 Forest plot for the total cross-sectional association between global physical fitness and cardiometabolic risk. CRF, cardiorespiratory fitness; r, correlation coefficient.

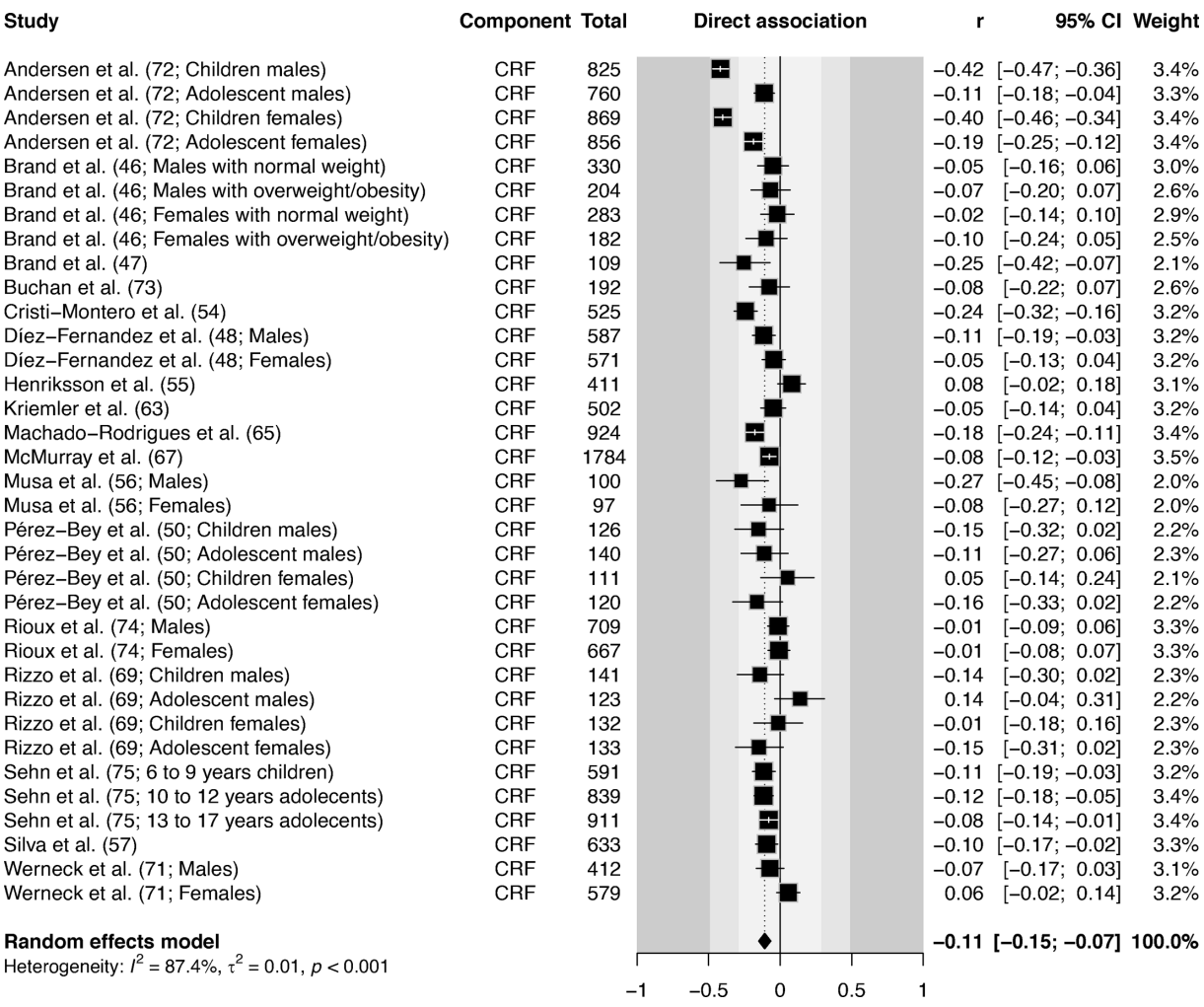

Figure 5 Forest plot for the direct cross-sectional association between global physical fitness and cardiometabolic risk. CRF cardiorespiratory fitness; r, correlation coefficient.

supplemental figure 14 and table 21). Figure 5 presents the forest plot for the direct association between global physical fitness and cardiometabolic risk. The LFK index showed no asymmetry, indicating no publication bias (LFK=0.06; online supplemental figure 15). Additionally, the sensitivity analysis indicated no modification in the results after removing one effect size at a time (online supplemental figure 16).

Subgroup analyses for physical fitness components

Subgroup analyses indicated that cardiorespiratory fitness was the only physical fitness component that presented statistically significant total (r=−0.22 95% CI −0.27; −0.17); p<0.001; I^2=85.2%) and direct (r=−0.11 95% CI −0.15; −0.06); p<0.001; I^2=87.4%) cross-sectional associations with cardiometabolic risk with small to medium effect sizes. The muscular fitness score (r=−0.23 95% CI −0.40; −0.03); p=0.033; I^2=66.5%) exhibited a total cross-sectional statistically significant association with cardiometabolic risk with small to medium effect sizes, whereas handgrip strength (r=−0.11 95% CI −0.26; 0.03); p=0.094; I^2=59.8%) and lower limb power (r=−0.08 95% CI −0.18; 0.02); p=0.088; I^2=45.3%) did not associate with cardiometabolic risk. However, the statistically significant inverse association of muscular fitness score with cardiometabolic risk disappeared after adjustment for obesity-related variables (online supplemental figures 17 and 18).

Categorised physical fitness exposures

Secondary meta-analyses reported ORs for the cross-sectional association between categorised cardiorespiratory fitness and cardiometabolic risk. Online supplemental figure 19 presents the forest plot demonstrating that when cardiorespiratory fitness was dichotomised, participants within the less favourable classifications exhibited 3.73 (95% CI 1.72; 8.06; p=0.012; I^2=41.7%) higher odds of having cardiometabolic risk 1 SD above the mean than participants within the more favourable cardiorespiratory fitness classification. However, the statistically significant inverse association disappeared after adjustment for obesity-related variables, independently of whether cardiorespiratory fitness was classified into quartiles (OR=2.00 (95% CI 0.49; 8.12); p=0.101; online supplemental figure 20) or dichotomised (OR=1.94 (95% CI 0.32; 11.59); p=0.133; online

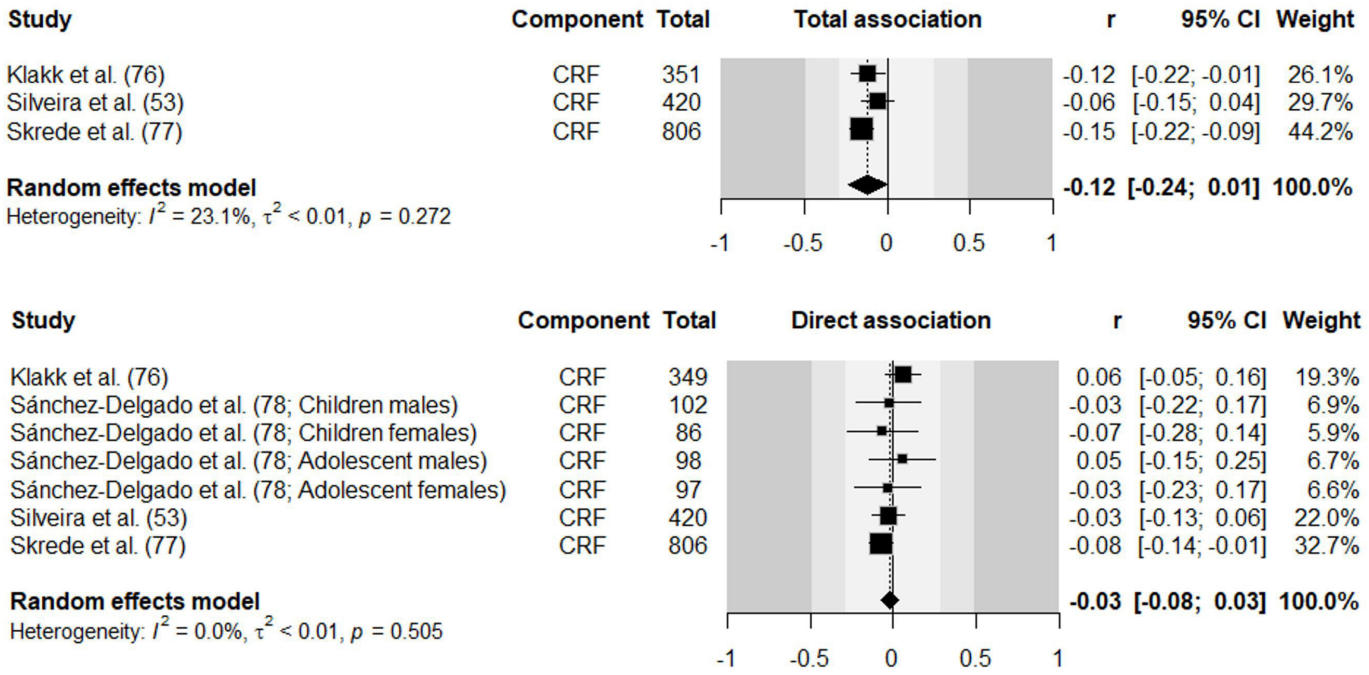

Figure 6 Forest plot for the total and direct longitudinal association between cardiorespiratory fitness and cardiometabolic risk. CRF, cardiorespiratory fitness; r, correlation coefficient.

supplemental figure 21). There were not enough studies to perform a meta-analysis of the cross-sectional total associations between categorised into quartiles cardiorespiratory fitness and cardiometabolic risk. Finally, global physical fitness was not meta-analysed because there were no studies with other physical fitness components other than cardiorespiratory fitness.

Longitudinal analyses

Cardiorespiratory fitness did not show total (r=−0.12 95% CI −0.24; 0.01); p=0.056; I^2=23.1%)[53 76 77] and direct (r=−0.03 95% CI −0.08; 0.03); p=0.285; I^2=0%)[53 76–78] longitudinal associations with cardiometabolic risk. Figure 6 presents the forest plots for the total and direct longitudinal associations between cardiorespiratory fitness and cardiometabolic risk. With respect to the direct longitudinal association, the LFK index showed minor asymmetry, indicating potential publication bias (LFK=1.39; online supplemental figure 24). Additionally, the sensitivity analysis indicated modification in the results after removing the effect size from Klakk *et al*,[76] turning it into a statistically inverse direct association (r=−0.05 (95% CI −0.09; −0.01); p=0.029; I^2=0%; online supplemental figure 25).

Other physical fitness components

There were no or insufficient studies to perform a meta-analysis of the subgroup indirect cross-sectional associations between handgrip strength, lower limbs power, abdominal endurance, upper limbs endurance and power, trunk endurance, strength, flexibility, agility, speed, balance, nor physical fitness score with cardiometabolic risk. Also, there were no or insufficient studies to perform a meta-analysis of the total and direct subgroup cross-sectional associations between abdominal endurance, upper limb endurance and power, trunk endurance, strength, flexibility, agility, speed, balance, nor balance with cardiometabolic risk. Finally, there were no or insufficient studies to perform longitudinal meta-analyses for physical fitness components other than cardiorespiratory fitness.

Studies not included in the meta-analyses

An individual interpretation for each study that implemented Analysis of Variance (ANOVA), Analysis of Covariance (ANCOVA), Multivariate Analysis of Covariance (MANCOVA), t-tests, non-parametric tests or Poisson regression models, in addition to studies that implemented partial correlations, correlations and linear or logistic regression models that were not included in the meta-analyses, is provided within online supplemental tables 4–17. Finally, the reasons for exclusion from the main meta-analyses are listed in online supplemental table 22.

DISCUSSION

This systematic review with meta-analyses presents cross-sectional evidence that cardiorespiratory fitness is modestly but beneficially associated with cardiometabolic risk measured by a continuous score in children and adolescents, either indirectly via obesity-related variables or directly and independently from obesity-related variables, whereas muscular fitness seems to be associated with cardiometabolic risk only via obesity-related variables, suggesting that muscular fitness influences

adiposity, which in turn carries muscular fitness influence on cardiometabolic risk. There was no difference of cross-sectional effect sizes between males and females, indicating that the following discussion may apply for both sexes. Longitudinal findings indicate no association between cardiorespiratory fitness and cardiometabolic risk. Both small to moderate effect sizes and study designs suggest that the obtained results should be interpreted with caution. Importantly, the main text meta-analyses were conducted using a continuous score not including measures of obesity-related variables in the score to avoid spurious association between the mediator and outcome variables[79] since obesity-related variables are often included in the continuous score as a traditional cardiometabolic parameter to measure cardiometabolic risk.

All the proposed mediation models conceptualised obesity-related variables as the link between physical fitness and cardiometabolic risk, and the parameter-based MASEM approach suggests that this proposed mechanism fits the observed data well across studies, providing evidence of its validity.[80] However, it is important to note that all studies included in the analyses had an observational design, implying that obesity-related variables may either serve as a mediator or act as a partial confounder in the association between physical fitness and cardiometabolic risk. The difference is that if obesity-related variables are mediating the association, physical fitness is still the cause of poorer cardiometabolic risk via adiposity; on the other hand, if adiposity is confounding the association, adiposity is the cause and physical fitness is not of importance to cardiometabolic risk.

The literature has highlighted the possible cause-and-effect association between obesity-related variables and cardiometabolic risk.[13] Indeed, the key for a healthier cardiometabolic profile appears to lie in maintaining lower levels of body fat, particularly fat deposits in the trunk and abdominal regions.[14] However, the fact that adiposity hypothetically serves as a mediator linking physical fitness to cardiometabolic risk should not exclude the importance of fitness, even though some components (eg, muscular fitness components) are not directly associated with cardiometabolic risk. It is essential to recognise that mediation analyses establish a link between exposure and outcome, and even if it was possible to control for every single confounder to eliminate their influence on the paths, causation of one or another could not be firmly established.[25]

Nevertheless, the present systematic review and meta-analyses pool data from different studies suggesting a mechanism from physical fitness to cardiometabolic risk via obesity-related variables that should still be properly evaluated using a randomised controlled trial approach to assert the causality between the observed variables. The dilemma of '*chicken-and-egg*' lies in the fact that it is not possible to know which comes first because even when physical fitness is modified, obesity-related variables will not be kept constant and will be modified as well.[81] The present findings suggest that physical fitness and adiposity are complex biological traits associated with cardiometabolic risk via different pathways, but it is very difficult to quantify which of these traits is more important for cardiometabolic health. From this perspective, achieving and/or maintaining a more favourable body composition may potentially have a protective effect on cardiometabolic health. However, being physically fit may exert its own role by first influencing a healthier body composition, which, in turn, will affect cardiometabolic risk. This pathway could explain the non-significant total longitudinal association and support the presence of adiposity as a mediator in the longitudinal relationship between physical fitness and cardiometabolic risk.

The aforementioned causal chains from physical fitness to obesity-related variables are supported by evidence demonstrating observational longitudinal associations between baseline fitness components and future adiposity parameters[18 19] as well as experimental manipulation involving concurrent aerobic plus resistance exercise and its beneficial effects on adiposity and fat-free mass.[82] A possible mechanism explaining this difference is that higher physical fitness performance could lead to more opportunities to be physically active and engage in moderate-to-vigorous activities,[83] which are intensities of activity positively associated with fitness itself and inversely with adiposity.[84 85]

Furthermore, there is a physiological explanation indicating that physical inactivity may be associated with mitochondrial density and dysfunction, leading to increased lactate accumulation and decreased tolerance to continue exercising.[86] This, in turn, could lead to greater adiposity due to an imbalance in energy intake and expenditure. Another conceptual mechanism suggests that increasing moderate-to-vigorous physical activity during youth longitudinally promotes the differentiation of stem cells into bone and muscle masses rather than into fat masses.[87] However, the relationships between physical fitness and obesity-related variables in the present proposed models lack a clear directionality, and it is plausible that an accumulation of excess adiposity could synergistically contribute to reduced physical fitness.[53 88] Notably, this bidirectional relationship explains why physical fitness is strongly associated with cardiometabolic risk measured by a continuous score, including obesity-related variables in the score rather than excluding it, in the present meta-analyses.

Another relevant mechanism evidenced by the present cross-sectional findings highlights the direct path from physical fitness to cardiometabolic risk, independent from obesity-related variables. These findings are once again supported by longitudinal evidence demonstrating beneficial inverse associations between physical fitness and cardiometabolic health.[18 19] Muscular fitness and cardiorespiratory fitness are both physiologically important. First, lipid oxidation is largely influenced by mitochondrial density and biogenesis, which can be increased through regular participation in resistance and

strengthening exercises,[89] the types of training associated with increased muscular fitness.[83] Second, with respect to cardiorespiratory fitness, a beneficial association between aerobic exercise (especially at higher intensities combined or not combined with resistance and strengthening training) and insulin sensitivity is often reported,[90–92] and insulin sensitivity is likely the key driver of changes in cardiometabolic parameters interconnected with the previously mentioned higher metabolic efficiency of muscle tissues.[6]

In fact, one-legged endurance training protocols have been shown to increase glucose uptake in the trained leg compared with the untrained leg, which is attributable to an increase in muscular blood flow[93 94] and an increase in the number of activated "glucose transporter protein type-4 (GLUT4) transporter proteins.[95] These protocols are interesting for providing insights into the association between physical fitness and cardiometabolic risk, independent of adiposity because both legs share participant body fat and individual biological responses.

Furthermore, two of the main adaptations of exercise and endurance training are the progressive increase in energy derived from lipid oxidation and the progressive decrease in the need for carbohydrates,[96] which are driven by greater blood flow within trained muscles and enhanced mitochondrial respiratory capacity.[97] However, more observational studies are needed to strengthen the present meta-analysis, which includes only four studies,[53 76–78] on direct longitudinal associations between physical fitness and cardiometabolic risk to infer whether an independent association exists beyond obesity-related variables or if it remains consistently non-existent across time.

Given the present discussion, it is also possible that physical activity plays a pivotal role somewhere in between the relationships between physical fitness, obesity-related variables and cardiometabolic risk. However, the proposed models did not account for the influence of physical activity as a possible antecedent and/or mediator variable. Future investigations could test this, as there is evidence of a relationship between physical activity intensity and physical fitness, obesity-related variables and cardiometabolic risk.[84] It is also suggested that physical fitness is associated with cardiometabolic risk, independent of physical activity.[65 69 71 72]

This is the first meta-analysis providing quantitative testing of direct and indirect mechanisms linking physical fitness to cardiometabolic risk in children and adolescents. However, caution should be taken, and some limitations should be considered before the findings can be interpreted. First, as deeply addressed in the discussion, the nature of an observational design makes it difficult to infer the direction between variables. Hence, the proposed conceptualised models should be properly evaluated using a randomised controlled trial approach to establish causality. However, observational designs are useful for providing insights into conceptualised mediational frameworks for understanding how physiological variables relate to each other. From this perspective, additional studies testing the mediating mechanisms from physical fitness to cardiometabolic risk, directly or indirectly via adiposity, physical activity or other variables should be conducted, given two reasons raised by the present findings: (1) publication bias (LFK=−3.26) identified in the indirect association meta-analyses and (2) the small number of studies investigating other physical fitness components (eg, muscular fitness components, speed, agility, etc).

Second, interaction terms between physical fitness exposures and moderator variables are usually not included in the analyses to explore under what circumstances or for which types of people an association exists. Briefly, an association between physical fitness and cardiometabolic risk may be inverse among certain types of people and proportional or non-existent for others. It could also be small for a certain level of the moderator variable and larger for another level, which may explain the high heterogeneity observed in the meta-analyses. Including such analyses will provide better insights into *when* physical fitness and cardiometabolic risk are associated.[25] Meta-regressions were initially planned for the direct association between physical fitness and cardiometabolic risk to explore modifications of the effect size at different levels of obesity-related variables. However, these analyses were not advanced because raw measurements of these variables do not accurately tell the real story within a sample of individuals of different sexes and ranging from 5 to 18 years of age, as obesity-related variables can be largely influenced by growth and sexual maturation.[98]

Third, despite the use of different methods for assessing cardiorespiratory fitness, most studies expressing oxygen consumption using ratio scaling have employed total body mass raised to the power of one or utilised field-based tests, in which participants have to move their own weight, making it similar to measures per total body weight. A future approach worth exploring further is to express oxygen consumption relative to fat-free mass to measure the quality of the muscles and avoid multicollinearity issues with adiposity,[67 99] as ratio scaling to total body mass does not eliminate the association between cardiorespiratory fitness and obesity-related variables.[100] Only a few studies applied this technique, and subgroup meta-analyses by cardiorespiratory fitness assessment methods are found in online supplemental figures 26 and 27. Briefly, no total cross-sectional association between cardiorespiratory fitness and cardiometabolic risk was observed, and there were insufficient studies to perform a meta-analysis of the direct cross-sectional association. However, there was a trend towards inverse associations.

CONCLUSION

The present systematic review and meta-analysis indicate that enhancing physical fitness in childhood and adolescence could be crucial for fostering a healthier cardiometabolic profile. This enhancement appears to take place either indirectly through the reduction of

obesity-related levels or directly by influencing risk. The latter underscores that the inverse association between physical fitness and cardiometabolic risk extends beyond a mere reduction in obesity-related variables, encompassing specific enhancements linked to exercise training, including increased metabolic efficiency and cardiovascular capacity. Future research should consider that observational studies cannot definitively conclude mediation or the direction of causality. In these studies, changes in the association between exposure and outcome may reflect confounding. True mediation analysis is more feasible in randomised controlled trials, where confounding is not just minimised but can be eliminated if randomisation is perfect and groups are sufficiently large. If baseline groups are identical, any changes in the effect size after statistical adjustment for a variable indicate mediation rather than confounding. Therefore, more accurate insights can be obtained into the mechanisms linking fitness and adiposity to cardiometabolic risk.

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