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Effect modification by cardiorespiratory fitness on the association between physical activity and cardiometabolic health in youth: A systematic review

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Abstract

Introduction: Physical activity and cardiorespiratory fitness are inversely associated with markers of cardiometabolic risk in children and adolescents, but the interplay between these variables in relation to the cardiometabolic risk profile is unclear. We systematically reviewed the literature to examine whether the association between physical activity and cardiometabolic health differs by levels of cardiorespiratory fitness in youth.

Methods: A literature search was conducted in PubMed and EMBASE, filtered from 2001 up until July 2019. We obtained 8980 citations, with 6915 remaining after removal of duplicates. Estimates were retrieved from 18 studies. All included articles went through a risk of bias assessment.

Results: We found that 14 out of 20 (70 %) effect-estimates supported stronger associations between physical activity and cardiometabolic health markers among low-fit youth as compared to their high-fit peers. The most consistent findings were observed with biochemical markers and blood pressure as outcomes. However, substantial uncertainty is associated with these findings as most of the included studies (~72 %) had a high risk of bias.

Conclusion: More than two thirds of the findings supported greatest benefits of physical activity on cardiometabolic risk markers in youth with low cardiorespiratory fitness, although the clinical importance of this difference is unclear.

Keywords: Physical activity, cardiorespiratory fitness, cardiometabolic health, effect modification, youth

Introduction

The prevalence of overweight and obese children has increased dramatically in the western world the last fifty years, and excessive body weight among 6- to 9-year-old's poses a serious multinational health concern (1,2). The development of adult type 2 diabetes and subclinical atherosclerosis can be predicted from children's body mass index (BMI) already from 8 years of age, indicating a high degree of tracking of cardiometabolic risk from childhood to early adulthood (3). Moreover, obesity often clusters with other risk factors for developing cardiovascular disease (CVD) such as hypertension, dyslipidemia and insulin resistance (4). A clustering of these abnormalities, often referred to as the metabolic syndrome, is particularly associated with increased incidence of CVD (5).

An inverse relationship between physical activity of sufficient amount and intensity and cardiovascular disease risk factors has previously been shown in children and adolescents (6), independent of the amount of time spent sedentary (7). Likewise, low cardiorespiratory fitness (CRF) is a strong predictor for clustering of cardiometabolic risk factors in youth (8). High CRF, on the other hand, has been associated with a favorable cardiometabolic risk score in children (9). Accordingly, both physical activity and CRF seem vital for a favorable cardiometabolic health profile among youth.

The interplay between physical activity and CRF with cardiometabolic health is less clear. While especially vigorous physical activity has the potential to substantially increase CRF over time (10), more than 50% of CRF may be genetically determined (11). Furthermore, there is a lack of consensus regarding the combined impact of physical activity and CRF on cardiometabolic health in youth. Some have concluded that both variables have separate and independent associations that work through different pathways (12), whereas others have suggested that CRF and physical activity work together (13).

The term effect modification refers to whether the relationship between exposure and outcome differs between levels or strata of a third variable. Although related, this differs slightly from the term interaction which requires the effect of two exposures together to be different from the combination of the two effects considered separately (14). We systematically reviewed the current literature to examine effect modification between physical activity and CRF, that is; whether the associations between physical activity and cardiometabolic health differ by levels of CRF in youth. We hypothesized that the association between physical activity and cardiometabolic health is strongest in youth with low levels of CRF.

Methods

The reporting of this systematic review follows the principles outlined in the PRISMA statement (15). A literature search was conducted for studies examining the modifying role of CRF between physical activity and cardiometabolic health markers in youth (PROSPERO ref: CRD42019126887).

Information sources and study selection

We performed a literature search in two databases – PubMed and EMBASE – filtered from 2001 up to July 2019. The search strategy focused on the combination of the following four topics; 1) participants AND 2) physical activity AND 3) cardiorespiratory fitness, AND 4) cardiometabolic risk factors. The full search strategy can be found in Supplementary file 2.

The study selection involved a three-step process – first screening titles and abstracts by two independent authors (AH, JT). These authors then independently reviewed the articles in full-text. Any disagreements between the two authors were settled by discussion with a third author (UE). Reference lists of all included articles were checked and went through a backward and forward tracking procedure in Web of Science.

Inclusion criteria

Eligibility criteria included journal articles investigating the association between physical activity and cardiometabolic risk markers across levels of cardiorespiratory fitness in ostensibly healthy youth (under 18 years of age) from the general population. We only included observational studies assessing physical activity by device-based methods (e.g. accelerometry), and experimental studies implementing a physical activity intervention with a control condition. Several publications originating from the same study could be included if the outcomes or analysis of effect modification differed. No restrictions on the level of detail provided for the modification analysis were enforced. Thus, studies could be included that only stated in-text whether an effect modification had occurred.

In addition to being a modifier, CRF could also be an outcome in intervention studies examining whether the effect of physical activity on CRF differed by baseline CRF levels. The cardiometabolic outcomes considered comprised body composition and adiposity, blood pressure, blood lipids, glucose, insulin, CRF, or any kind of clustered cardiometabolic risk score (e.g. a composite score of measures of adiposity, blood pressure, dyslipidemia and insulin resistance). Studies combining a fitness score of CRF and muscular fitness, and studies investigating effect modification of CRF as part of a clustered risk score, were also eligible for inclusion. The full inclusion and exclusion criteria used are shown in table 1.

Data extraction

Data were extracted through pre-piloted forms, collecting information on study setting and design, participants eligible for study and analysis, length of follow-up, physical activity and cardiorespiratory fitness assessment methods, intervention characteristics (if relevant), outcomes, statistical adjustments, and findings.

Risk of bias assessment

The risk of bias assessment tools are described in detail in Supplementary file 3. Briefly, the risk of bias assessment of the observational studies was based on the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (QATOC) (16). The tool focuses on four domains – selection bias, information bias, confounding bias and temporality bias. In accordance with the QATOC guidelines, the overall risk-of-bias cannot be lower than the highest risk of bias within each domain. Accordingly, cross-sectional studies are always rated as high-risk of bias. The risk of bias assessment of the intervention studies were performed using a modified version of the RoB 2 tool, a framework for considering the risk of bias in any type of randomized trial (17). This tool includes five domains – randomization bias, performance bias, missing outcome bias, measurement bias, and selection bias. For comparison purposes, non-randomized controlled studies were also rated using the RoB 2 tool, automatically receiving a high risk of bias. To specifically address the quality of the effect modification analyses, we added one extra domain to both tools using the ICEMAN instrument (18). Two authors (AH, JT) independently rated the risk of bias within each included study with a third author (UE) consulted in case of any discrepancies.

Data synthesis

As we expected original study data to be highly heterogeneous in exposure measurements, outcome measurements and statistical approach, we only considered a qualitative synthesis of results. The included studies were subdivided into observational studies and intervention studies, and the results synthesized separately by study designs. To avoid dichotomization of statistical significance (19), the direction of the results was also considered, if reported, by categorizing the results into either;

1) Significant effect modification
    - A statistically significant formal test of effect modification OR an explicit statement from the authors that associations were modified by CRF
2) Non-significant effect modification
    - A non-significant formal test of effect modification providing a direction of the results OR the authors implying a possible effect modification by CRF
3) No effect modification
    - A non-significant formal test of effect modification without any direction of the results OR the authors explicitly stating that no effect modification by CRF was observed

Additionally, a summary of whether the associations between physical activity and cardiometabolic health were modified by CRF was done separately for these groups of outcomes; a) biochemical cardiometabolic risk factors and blood pressure (lipids, blood pressure, carbohydrate metabolism, clustered risk score), b) body composition (adiposity, fat mass, lean mass), and c) CRF (intervention studies only).

Results

A total of 8980 citations were obtained through the study identification process, with 6915 remaining for screening after removal of duplicates. Of these, 6399 citations were excluded after screening of titles and a further 467 excluded after screening of abstracts. This left 49 articles for full text review, from which 18 studies were included – 9 observational and 9 intervention studies. The study selection flow is visualized in figure 1.

Observational studies

Of the nine included studies, eight were deemed to have a high risk of bias and one to have some risk of bias (Supplementary file 1). The domains predominantly causing a high risk of bias were the absence of temporal data and risk of confounding bias.

Study characteristics and results from the observational studies are summarized in table 2. The mean baseline age of participants included in the observational studies were 11.7 years (range 8.1-15.5 years). One study had a prospective design (20), with a follow-up length of 7 months. Four studies reported a significant effect modification with effect-sizes suggesting physical activity were associated with more pronounced cardiometabolic benefits among youth with low CRF as compared to those with high CRF (20–23). Three studies found a non-significant effect modification in direction of greater benefits from physical activity in low-fit youth (24–26), while two studies did not report on any effect modification (12,27). The studies reporting no effect modification generally presented this in-text and did not give any direction of the estimates obtained from the analysis. None of the observational studies reported a stronger association between physical activity and cardiometabolic risk markers among children and adolescents with the highest CRF levels.

Intervention studies

Overall, the included intervention studies were rated as having a lower risk of bias than the observational studies, but none was found to have an overall low risk of bias (Supplementary file 1). Four were deemed to have some risk of bias (28–31), whilst the remaining five studies were scored as having a high risk of bias. The factors causing a high risk of bias were inadequate randomization procedures and performance bias, referring to whether the intervention was carried out the way it was intended.

Results from the intervention studies are shown in table 3, with eleven effect-sizes reported from nine articles. The participants had a mean baseline age across studies of 8.1 years (range 5.2-9.2 years). All nine studies attempted to increase physical activity during school hours, with the length of follow-up ranging from 22 weeks (30) to 6.5 years (32). The intended additional amount of physical activity delivered varied between 90 min/wk (30) and 300 min/wk (33,34). A significant effect modification by CRF was reported in four articles, with estimates showing a stronger association between physical activity and cardiometabolic health among the low-fit youth as compared to those with higher CRF levels (29,31,33,35). Three studies observed a non-significant effect modification in favor of initially low-fit children and adolescents (28,32,34). No effect modification was observed for four outcomes from three studies (29,30,36). Similar to the results from observational studies, a lack of effect modification was usually presented in-text without a direction of the estimate. No intervention studies suggested that the effect of the physical activity intervention on and cardiometabolic health markers were more pronounced among youth with the highest levels of CRF.

Results by type of outcome

The findings from all included studies, grouped by type of outcome, are visualized in figure 2. Overall, a total of 20 effect-sizes were retrieved from the 18 included articles, covering 15 unique study samples. One of the five intervention studies modelling CRF as outcome observed a statistically significant effect modification of baseline CRF on the intervention effect of physical activity (33), whereas three of five studies did not report on any such effect modification (29,30,36). For biochemical markers and/or blood pressure, five of eleven studies observed that CRF significantly modified the association with physical activity (20–22,31,35), whereas four indicated a non-significant effect modification (24,26,32,34). When body composition and adiposity outcomes were modelled in association with physical activity, significant effect modification of CRF was observed in two of four studies (23,29), while a non-significant effect modification was reported in one study (25). All articles reporting either a significant effect modification or a non-significant effect modification (70 % of the findings) found that the beneficial associations of physical activity on cardiometabolic health markers were more pronounced among youth with the lowest levels of CRF.

Discussion

We found that 14 out of 20 (70 %) reported associations were either significantly or non-significantly modified by CRF, all implying a stronger association between physical activity and cardiometabolic health among low-fit youth as compared to their high-fit peers. The most consistent results were found with biochemical markers and blood pressure as outcomes. Results were less clear in studies that modelled body composition/adiposity and especially CRF as outcomes. However, substantial uncertainty is associated with these findings as more than two thirds of the included studies (~72 %) had a high risk of bias.

If CRF does modify the association between physical activity and cardiometabolic health in youth, the collective inference of the evidence suggests that the association is strongest among children and adolescents with the lowest levels of CRF. This would mean that interventions aimed at increasing physical activity for improving cardiometabolic health may have the greatest effects in, and may specifically target, young people with low CRF levels. This is encouraging as low CRF in adolescence is associated with increased risk of incident type 2 diabetes and cardiovascular disease in adulthood (37,38). Since cardiometabolic risk factors tend to track from childhood into adulthood (3,39), promotion of physical activity already at an early age seems vital for primordial prevention of non-communicable diseases in adult life (40).

We were unable to synthesize these results in a formal meta-analysis due to heterogeneity across studies, with known challenges in study comparability due to both different epoch lengths and intensity cut-offs in accelerometer analyses (41–43), different measures of cardiorespiratory fitness (44), different categories used to define “high- and low-risk” groups (45), and different combinations of cardiometabolic risk factors as outcome in youth (46,47). For example, one study where data were published in two different papers (33,34) examined whether the effect of a physical activity intervention on CRF differed by baseline fitness levels. The results suggested a significant effect modification when the sample was grouped by quartiles of CRF (33) and a non-significant effect modification when the grouping was based on a median split (34). These methodological inconsistencies set aside, standardized differences in associations between low- and high-fit youth – from the studies reporting a significant effect modification – ranged from 0.05 to 0.55 standard deviations which conforms to what Cohen described as very small to medium large effect-sizes (48).

A problem in evaluating whether CRF modifies the associations between physical activity and cardiometabolic health in youth is that the exact biological mechanisms in which physical activity affects health remains to be fully understood (49). While ~40-60 % of the risk reduction of CVD achieved through exercise can be attributed to how physical activity is beneficial for traditional risk factors, almost half of the protective effect by physical activity and exercise remains unexplained (50). CRF may also act as a mediator between PA and cardiovascular risk factors as previously suggested (26,51). However, exercise leads to an acute upregulation of GLUT4 translocation in muscle cells which in turn leads to improved muscle glucose uptake (52) – an association that has been observed regardless of exercise intensity levels (53). This supports the hypothesis of an independent pathway between physical activity and carbohydrate metabolism in humans, which may imply a non-fitness related exercise-induced adaptation in the cardiovascular system and peripheral musculature (54). Boreham & Riddoch reviewed the associations between physical activity, CRF and cardiometabolic health in children 19 years ago and concluded that these relationships are complex and more prospective studies covering the transition from adolescence into early adulthood are needed (55). Despite the tremendous progress in assessing free-living physical activity by device-based methods, the findings from this review corroborate their conclusion. Indeed, we only identified one short-term prospective study (20) examining the potential modifying effect of CRF on the association between physical activity and cardiometabolic health markers in youth.

In an attempt to create a more nuanced picture of the findings, we decided to not only consider statistical significance but to take the direction of the estimates into account. The dichotomization of statistical significance, i.e. interpreting a p-value as either statistically significant or not, has been heavily criticized on several occasions (56–60). This either-or approach would often lead to an unreasonable singling out of one particular value (null) from a range of values (confidence interval) all compatible with the data at hand (19). Although a more nuanced picture indeed is provided by including the direction of non-significant results, the rate of type I errors would certainly increase with the current approach as compared to a more conservative method. Thus, we urge readers to interpret these findings in light of the considerable uncertainty underlined by the risk of bias evaluation.

To avoid biased results from effect modification analyses one generally cannot use effect modifiers that condition on the exposure itself (14). While aerobic exercise of vigorous intensity over time can increase cardiorespiratory fitness in youth (61), numerous observational studies have demonstrated non-significant or low correlation (≤ 0.3) between objectively measured habitual physical activity and cardiorespiratory fitness in this age group (62–68). We therefore considered it unlikely to have been any causal relationship between these two variables in the data included.

A strength of this systematic review is the comprehensive literature search, with almost 9000 articles involved in the screening process, and backward and forward tracking performed on all articles read in full text. We have also followed a systematic process in line with the PRISMA statement and focused on a high degree of transparency and reproducibility of our results. A limitation of this review is the quality of evidence provided by the included studies, which is weak for several reasons. Except for one study, all included observational studies were cross-sectional. Furthermore, a general limitation of the evidence was a lack of statistical adjustment, especially for putative confounders such as sexual maturity, diet quantity/quality, and socioeconomic status. The intervention studies generally lacked an appropriate randomization procedure, or were non-randomized, which increases the likelihood of selection bias and confounding (69). Other limitations include missing outcome data and, for intervention studies, limited information on intervention fidelity. Moreover, more than one hundred citations discovered in the screening process had measured the variables necessary for a modification analysis of interest to this article. While this theoretically means that a more harmonized analysis would be possible if all data were obtained and re-analyzed, it also implies that selective reporting (i.e. not sharing information on a non-significant test of effect modification) may have occurred. Several of the included studies also had a small sample size. Tests of effect modification are often prone to low power if not accounted for in the power calculations, perhaps leading to failure to detect a difference in the studies not planning for these analyses a priori.

In conclusion, the result of our systematic review – including data from 15 unique study samples – suggests that CRF modifies the association between physical activity and cardiometabolic health markers in youth. More than two thirds of the findings (70 %) supported greater benefits of physical activity on cardiometabolic risk markers in children and adolescents with low cardiorespiratory fitness, compared to their more fit peers, although the clinical importance of this difference is unclear. The quality of evidence was weak due to risk of selective reporting in the literature and high risk of bias in most of the included studies. Hence, the current results need to be replicated in prospective studies and well-designed randomized controlled trials.

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Declaration of interest

The authors declare no conflict of interest.

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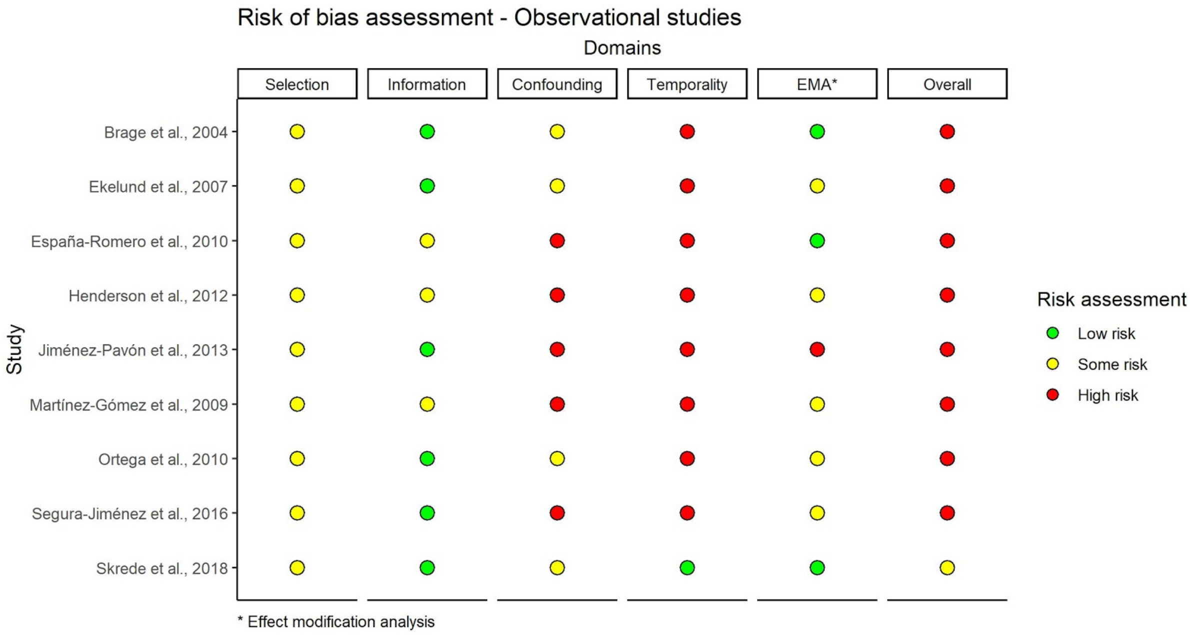
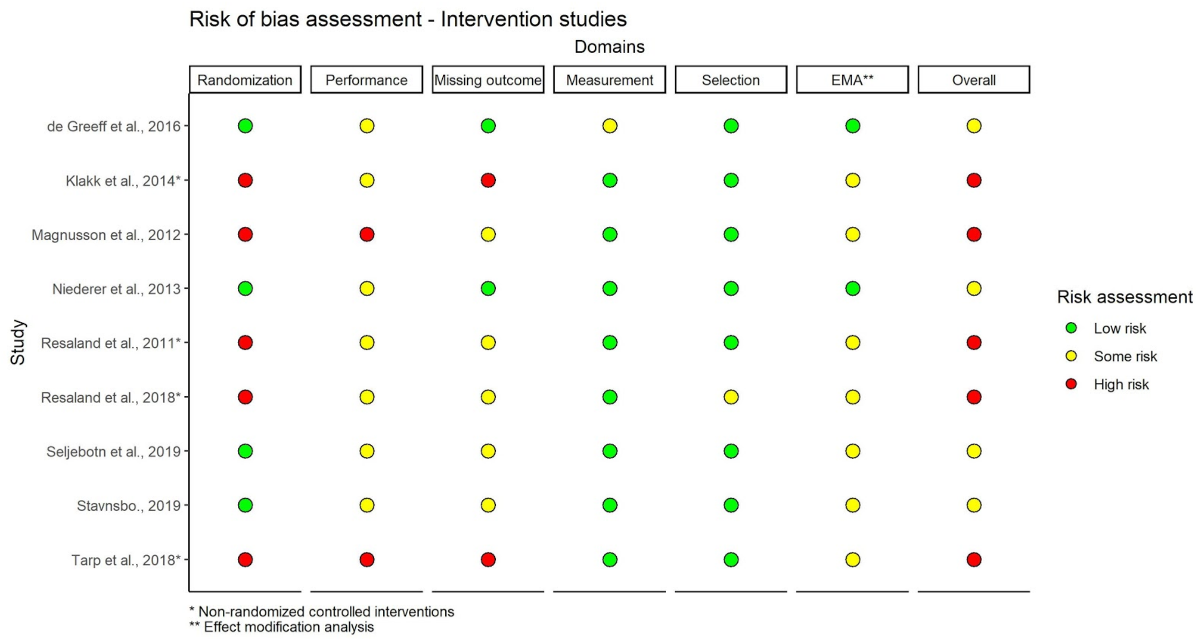
Supplementary data

1. Risk of bias assessment





2. Full search strategy in PubMed

#1 child[Title/Abstract] OR childhood[Title/Abstract] OR children[Title/Abstract] OR children's[Title/Abstract] OR youth[Title/Abstract] OR youths[Title/Abstract] OR adolescen*[Title/Abstract] OR young[Title/Abstract] OR school[Title/Abstract] OR school-aged[Title/Abstract] OR "school aged"[Title/Abstract] OR child[MeSH] OR Adolescent[MeSH] OR pupils[Title/Abstract] OR "early life"[Title/Abstract] OR teen[Title/Abstract] OR teens[Title/Abstract] OR teenage[Title/Abstract] OR teenagers[Title/Abstract] OR puberty[Title/Abstract] OR prepubertal[Title/Abstract] OR prepubescence[Title/Abstract] OR pubertal[Title/Abstract] OR pubescence[Title/Abstract] OR pediatric[Title/Abstract]

AND

#2 "physical activity"[Title/Abstract] OR "physical activities"[Title/Abstract] OR "physically active"[Title/Abstract] OR "physical exercise"[Title/Abstract] OR exercise*[Title/Abstract] OR walk*[Title/Abstract] OR PA[Title/Abstract] OR "moderate physical activity"[Title/Abstract] OR "moderate-to-vigorous physical"[Title/Abstract] OR "moderate to vigorous physical activity"[Title/Abstract] OR MVPA[Title/Abstract] OR "vigorous physical activity"[Title/Abstract] OR VPA[Title/Abstract] OR activity[Title/Abstract] OR intensity[Title/Abstract] OR "energy expenditure"[Title/Abstract] OR PAEE[Title/Abstract] OR accelerometer[Title/Abstract] OR accelerometry[Title/Abstract] OR objectively[Title/Abstract] OR "objectively measured"[Title/Abstract] OR "activity monitor"[Title/Abstract] OR device[Title/Abstract] OR "device-based"[Title/Abstract] OR "device-measured"[Title/Abstract] OR monitors[Title/Abstract] OR Actigraph[Title/Abstract] OR MTI[Title/Abstract] OR csa[Title/Abstract] OR "computer science"[Title/Abstract] OR application[Title/Abstract] OR ActivPAL[Title/Abstract] OR GENEActiv[Title/Abstract] OR Actiheart[Title/Abstract] OR Axivity[Title/Abstract]

AND

#3 "cardiorespiratory fitness"[Title/Abstract] OR "cardiopulmonary fitness"[Title/Abstract] OR "cardiovascular fitness"[Title/Abstract] OR fitness[Title/Abstract] OR "aerobic fitness"[Title/Abstract] OR "physical fitness"[Title/Abstract] OR "maximal oxygen uptake"[Title/Abstract] OR "maximal oxygen consumption"[Title/Abstract] OR "maximum oxygen uptake"[Title/Abstract] OR "maximum oxygen consumption"[Title/Abstract] OR VO2*[Title/Abstract] OR "aerobic capacity"[Title/Abstract] OR "peak oxygen uptake"[Title/Abstract] OR "peak oxygen consumption"[Title/Abstract] OR "power output"[Title/Abstract]

AND

#4 obesity[Title/Abstract] OR overweight[Title/Abstract] OR fat[Title/Abstract] OR fatness[Title/Abstract] OR BMI[Title/Abstract] OR "body mass index"[Title/Abstract] OR "waist circumference"[Title/Abstract] OR "hip circumference"[Title/Abstract] OR "waist-hip ratio"[Title/Abstract] OR WHR[Title/Abstract] OR "abdominal fat"[Title/Abstract] OR "visceral fat"[Title/Abstract] OR adiposity[Title/Abstract] OR "central obesity"[Title/Abstract] OR "fat mass"[Title/Abstract] OR skinfold[Title/Abstract] OR "sum of skinfold"[Title/Abstract] OR "blood pressure"[Title/Abstract] OR hypertension[Title/Abstract] OR hypertensive[Title/Abstract] OR dyslipidemia[Title/Abstract] OR dyslipidaemia[Title/Abstract] OR lipids[Title/Abstract] OR lipoproteins[Title/Abstract] OR cholesterol[Title/Abstract] OR HDL[Title/Abstract] OR "high-density lipoprotein"[Title/Abstract] OR LDL[Title/Abstract] OR "low-density lipoprotein"[Title/Abstract] OR triglycerides[Title/Abstract] OR hypertriglyceridemia[Title/Abstract] OR "bone health"[Title/Abstract] OR osteoporosis[Title/Abstract] OR osteopenia[Title/Abstract] OR "peak bone mass"[Title/Abstract] OR diabetes[Title/Abstract] OR pre-diabetes[Title/Abstract] OR "metabolic syndrome"[Title/Abstract] OR "carbohydrate metabolism"[Title/Abstract] OR "glucose intolerance"[Title/Abstract] OR hyperinsulinemia[Title/Abstract] OR hyperinsulinaemia[Title/Abstract] OR "insulin resistance"[Title/Abstract] OR cardiometabolic[Title/Abstract] OR cardiovascular[Title/Abstract] OR coronary[Title/Abstract] OR atherosclero*[Title/Abstract] OR morbidity[Title/Abstract] OR "cardiovascular disease risk factor"[Title/Abstract] OR "cardio-metabolic risk factor"[Title/Abstract] OR "metabolic risk factor"[Title/Abstract] OR "CVD risk factor"[Title/Abstract] OR "clustered cardio-metabolic risk"[Title/Abstract] OR "cardiovascular disease risk factors"[Title/Abstract] OR "cardio-metabolic risk factors"[Title/Abstract] OR "metabolic risk factors"[Title/Abstract] OR "CVD risk factors"[Title/Abstract] OR "clustered cardio-metabolic risk"[Title/Abstract] OR cluster[Title/Abstract] OR clustering[Title/Abstract] OR "composite score"[Title/Abstract] OR "composite risk score"[Title/Abstract] OR "z score"[Title/Abstract] OR z-score[Title/Abstract] OR "z scores"[Title/Abstract] OR z-scores[Title/Abstract]

3. Risk of bias tools

Risk of bias tool – Observational studies

Selection bias;

1) Were all subjects recruited from the same or similar populations, and inclusion and exclusion criteria pre-specified and applied uniformly to all participants? Y / PY / PN / N / NI
2) Was the participation rate of eligible persons at least 50%? Y / PY / PN / N / NI
3) Was loss to follow-up after baseline 20% or less? Y / PY / PN / N / NI

- Highest bias risk possible in the domain: some risk of bias

Information bias;

4) For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)? Y / PY / PN / N / NI – maximal rating on this item; some risk of bias
5) Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants? Y / PY / PN / N / NI
6) Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants? Y / PY / PN / N / NI
7) Was a sample size justification, power description, or variance and effect estimates provided? Y / PY / PN / N / NI - maximal rating on this item; some risk of bias

- Highest bias risk possible in the domain: high risk of bias

Bias due to confounding;

8) Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)? Y / PY / PN / N / NI

- Highest bias risk possible in the domain: high risk of bias

Bias due to temporality;

9) For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured? Y / PY / PN / N / NI
10) Was the exposure(s) assessed more than once over time? Y / PY / PN / N / NI
11) Was the timeframe sufficient so that one could reasonably expect to see an association

- Highest bias risk possible in the domain: high risk of bias

Bias in the effect modification analysis (ICEMAN tool);

12) Was the direction of effect modification correctly hypothesized a priori? Y / PY / PN / N / NI
13) Was the effect modification supported by prior evidence? Y / PY / PN / N / NI
14) Does a test for interaction suggest that chance is an unlikely explanation of the apparent effect modification? Y / PY / PN / N / NI
15) Did the authors test only a small number of effect modifiers or consider the number in their statistical analysis? Y / PY / PN / N / NI
16) If the effect modifier is a continuous variable, were arbitrary cut points avoided? Y / PY / PN / N / NI

- Highest bias risk possible in the domain: high risk of bias

Risk of bias tool – Intervention studies

Bias arising from the randomization process;

1. Was group allocation done by random sequence generation? Y / PY / PN / N / NI
2. Were the allocations concealed? Y / PY / PN / N / NI

Bias due to deviations from intended interventions;

3. Were there any unexpected deviances from the intervention, likely to affect the results (i.e. comparators wanting to be in the intervention group, and therefore seeking experimental conditions)? Y / PY / PN / N / NI

Bias due to missing outcome data;

4. Was incomplete outcome data reported and addressed appropriately? Y / PY / PN / N / NI
5. Was the dropout rate identical between groups? Y / PY / PN / N / NI
6. Is it likely that missing data of the outcome depended on its true value? Y / PY / PN / N / NI

Bias in measurements of the outcome;

7. Is it likely that outcome assessment was influenced by knowledge of intervention received? Y / PY / PN / N / NI
8. Were measurements of CRF and outcomes identical between groups? Y / PY / PN / N / NI
9. Was the intervention and/or follow-up period sufficient for changes in outcome to occur? Y / PY / PN / N / NI

Bias in selection of the reported results;

10. Was the sub-group or interaction analysis pre-specified in a published protocol? Y / PY / PN / N / NI
11. Were sub-groups defined identically (and with identical baseline CRF)? Y / PY / PN / N / NI

Bias in the effect modification analysis (ICEMAN tool);

12. Was the direction of effect modification correctly hypothesized a priori? Y / PY / PN / N / NI
13. Was the effect modification supported by prior evidence? Y / PY / PN / N / NI
14. Does a test for interaction suggest that chance is an unlikely explanation of the apparent effect modification? Y / PY / PN / N / NI
15. Did the authors test only a small number of effect modifiers or consider the number in their statistical analysis? Y / PY / PN / N / NI
16. If the effect modifier is a continuous variable, were arbitrary cut points avoided? Y / PY / PN / N / NI

Every domain can induce high risk of bias – depending on each setting.

Response options – all questions, both risk of bias tools:

1. Y (Yes)
2. PY (Probably yes)
3. PN (Probably no)
4. N (No)
5. NI (No information)

Algorithm for RoB classification – both risk of bias tools:

Overall rating based on 'highest' risk of bias classification across domains

Rated as (domain-based + overall);

Low risk of bias
Some risk of bias
High risk of bias

Tables

Table 1. Inclusion criteria.

	Inclusion criteria	Exclusion criteria
Setting	All countries	None
Participants	Ostensibly healthy children under 18 years of age If measurements are repeated, mean age must be < 18 years at all time-points	Mean age at or above 18 years Studies specifically on elite athletes or participants with known pre-existing conditions (including obesity)
Exposures	Physical activity and cardiorespiratory fitness Association between physical activity and cardiometabolic outcome across levels of cardiorespiratory fitness Subgroups by cardiorespiratory fitness defined on baseline values in the intervention studies	Other exposures No analyses of effect modification by cardiorespiratory fitness between physical activity and cardiometabolic outcome
Outcomes	At least one measure of cardiometabolic risk (body composition, blood pressure, blood lipids, glucose, insulin, fitness, clustered risk score)	Studies without any relevant outcomes
Study type	Observational studies with objective measure of physical activity, or experimental studies with a physical activity intervention and a control condition	Qualitative studies
Publication type	Journal article	Conference abstract, study protocol, review, report, book
Publication year	2001 onwards	Before 2001
Language	English, Scandinavian languages	Any other language

Table 2. Summary of the included observational studies.

Study and design	Number of participants	Baseline age Mean (SD)	Assessment of physical activity	Assessment of CRF	Outcome	Finding
Brage et al., 2004 (22) *EYHS Denmark* Cross-sectional	301	9.6 (0.4)	MTI Actigraph	Maximal cycle-ergometer test	Clustered CMR score	↑
Ekelund et al., 2007 (12) *EYHS Denmark, Portugal, Estonia* Cross-sectional	1709	9.7 (0.4) 15.5 (0.5)[a]	MTI Actigraph	Maximal cycle-ergometer test	Clustered CMR score	→
España-Romero et al., 2010 (25) *HELENA study, Zaragoza* Cross-sectional	254	Range: 12.5-17.5[b]	ActiGraph GT1M	20 m shuttle-run	Abdominal fat content	↗
Henderson et al., 2012 (27) *QUALITY study* Cross-sectional	424	9.7 (0.9)	ActiGraph LS7164	Maximal cycle-ergometer test	Insulin sensitivity	→
Jiménez-Pavón et al., 2013 (21) *HELENA study* Cross-sectional	711	Range: 12.5-17.5[b]	ActiGraph GT1M	20 m shuttle-run	Insulin sensitivity	↑[c]
Martínez-Gómez et al., 2009 (24) *AFINOS study* Cross-sectional	202	14.8 (1.3)	ActiGraph GT1M	20 m shuttle-run	Clustered CMR score	↗[d]
Ortega et al., 2010 (23) *EYHS Sweden* Cross-sectional	763	9.5 (0.4) 15.5 (0.4)[a]	MTI Actigraph	Maximal cycle-ergometer test	Abdominal adiposity	↑
Segura-Jiménez et al., 2016 (26) *UP&DOWN study* Cross-sectional	482	8.1 (1.5) 14 (1.6)[a]	ActiGraph GT1M, GT3X, GT3X+	20 m shuttle-run	Clustered CMR score	↗
Skrede et al., 2018 (20) *ASK study** Prospective (± 7 months)	718	10.2 (0.3)	ActiGraph GT3X, GT3X+	Andersen shuttle-run test	Clustered CMR score	↑

↑, Significant effect modification in favor of low-fit; ↗, Non-significant effect modification in favor of low-fit; →, No effect modification; ↘ , Non-significant effect modification in favor of high-fit; ↓, Significant effect modification in favor of high-fit; CRF, Cardiorespiratory fitness; CMR, Cardiometabolic risk; [a]Included both children and adolescents; [b]No mean or sd reported; [c]Only significant among females; [d]Use of three different risk scores – one yielded significant results, one yielded borderline significant results, and one yielded non-significant results; *The same study sample and outcome as (31), but different study design

Table 3. Summary of the included intervention studies.

Study and design	Number of participants	Baseline age Mean (SD)	Intervention characteristics	Assessment of CRF	Outcome	Finding
de Greeff et al., 2016 (30) *F&V study* Cluster-randomized controlled trial	376	8.1 (0.8)	22 weeks school intervention – 30 min PA 3 times/wk	Shuttle-run test	Cardiorespiratory fitness	→
Klakk et al., 2014 (35) *CHAMPS DK study* Non-randomized controlled intervention	712	8.5 (1.4)	2 years trebling of curricular PE – 270 min/wk	Andersen shuttle-run test	Clustered CMR score	↑[b]
Magnusson et al., 2012 (36) *Reykjavik, Iceland* Cluster-randomized controlled trial	166	7.4 (0.4)	2-year teacher-led school intervention focusing on increased PA	Maximal cycle-ergometer test	BC & cardiorespiratory fitness	→
Niederer et al., 2013 (29) *Ballabeina study* Cluster-randomized controlled trial	616	5.2 (0.6)	1-year school intervention – 45 min PA 4 times/wk	20 m shuttle-run	Adiposity[1], Cardiorespiratory fitness[2]	↑[1], →[2]
Resaland et al., 2011 (33) *Sogndal study* Non-randomized controlled intervention	188	9.2 (0.3)	2-year school intervention – 60 min daily PA	Direct VO_{2peak} on treadmill	Cardiorespiratory fitness	↑
Resaland et al., 2018 (34) *Sogndal study* Non-randomized controlled intervention	171	9.2 (0.3)	2-year school intervention – 60 min daily PA	Direct VO_{2peak} on treadmill	Clustered CMR score	↗[b]
Seljebotn et al., 2019 (28) *Active School study* Cluster-randomized controlled trial	364	Range: 8-10[a]	10-month school intervention – increase PA by 190 min/wk	Andersen shuttle-run test	Cardiorespiratory fitness	↗
Stavnsbo et al., 2019 (31) *ASK study** Cluster-randomized controlled trial	769	10.2 (0.3)	7-month school intervention – increase PA by 165 min/wk	Andersen shuttle-run test	Clustered CMR score	↑[c]
Tarp et al., 2018 (32) *CHAMPS DK study* Non-randomized controlled intervention	312	7.8 (1.3)	2 to 6.5 years trebling of curricular PE – 270 min/wk	Andersen shuttle-run test	Clustered CMR score	↗[b]

↑, Significant effect modification in favor of low-fit; ↗, Non-significant effect modification in favor of low-fit; →, No effect modification; ↘ , Non-significant effect modification in favor of high-fit; ↓, Significant effect modification in favor of high-fit; PA, Physical activity; CRF, Cardiorespiratory fitness; BC, Body composition; PE, Physical education; CMR, Cardiometabolic risk; [a]No mean or sd reported; [b]Low and high CRF groups defined as part of a standardized clustered risk score; [c]Significant interactions also for systolic blood pressure and Total:HDL cholesterol ratio; *The same study sample and outcome as (20), but different study design

Figures

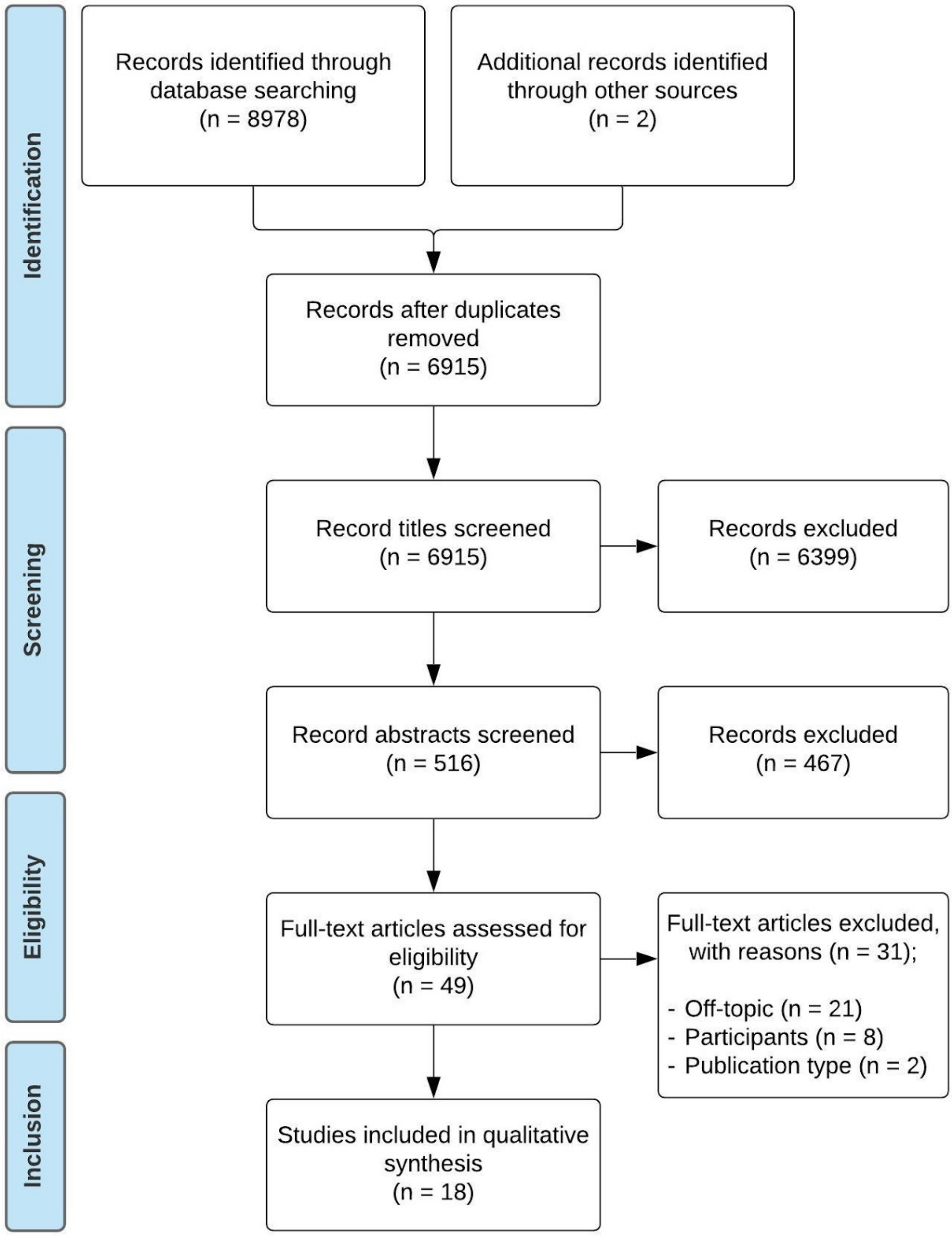


Figure 1. Flow diagram of the study inclusion process.

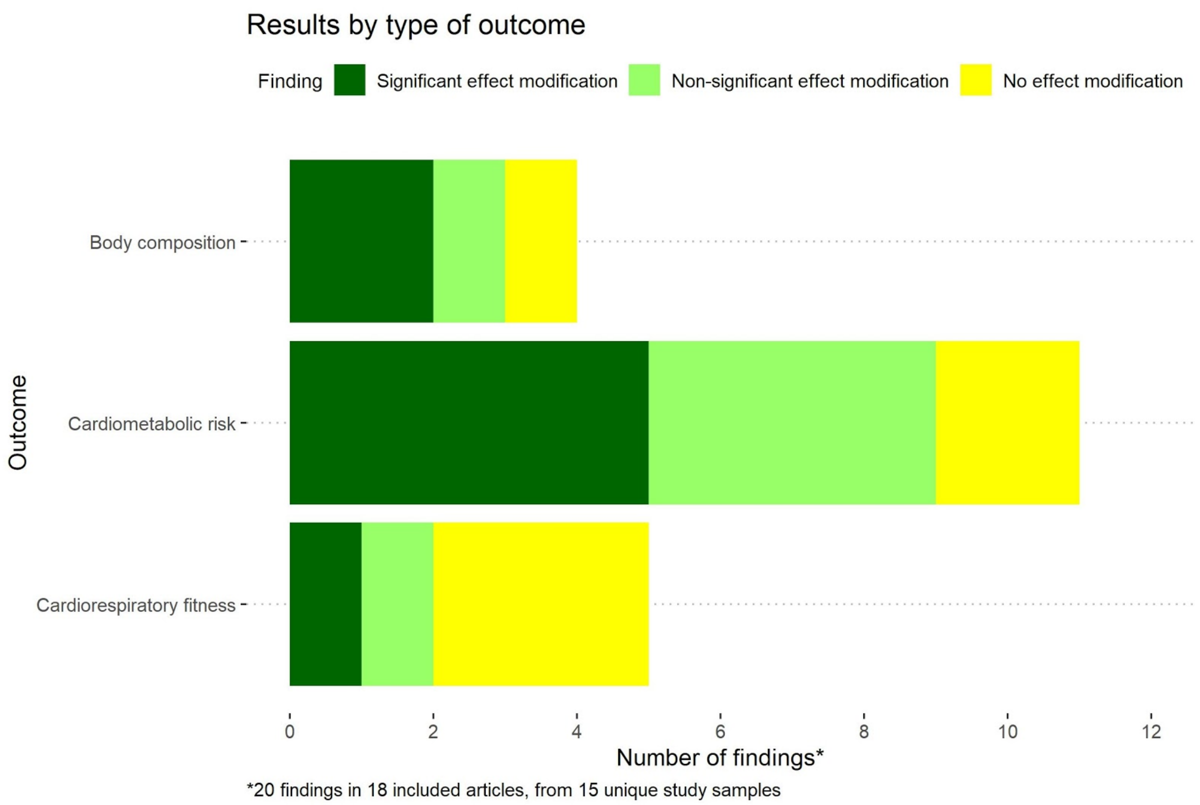


Figure 2. Summary of all findings reported in the included articles, grouped by type of outcome.

Figure captions

List Of Images