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Review

Physical fitness level and the risk of severe COVID-19: A systematic review

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ABSTRACT

To verify systematically the association between the status of physical fitness and the risk of severe Coronavirus disease 2019 (COVID-19). This systematic review is in accordance with the Preferred Reporting Items for Systematic Review and Meta Analyses (PRISMA) statement and the eligibility criteria followed the Population, Intervention, Comparison, Outcomes and Study (PICOS) recommendation. PubMed, Embase, SciELO and Cochrane electronic databases were searched. All studies that explored the relationship between the pattern of physical fitness and COVID-19 adverse outcomes (hospitalization, intensive care unit admission, intubation, or mortality), were selected. The quality of the studies was assessed by the specific scale of the Newcastle–Ottawa Scale. A total of seven observational studies were identified in this systematic review; 13 468 patients were included in one case-control study, two cohort studies, and four cross-sectional studies. All studies reported an inverse association between high physical fitness and severe COVID-19 (hospitalization, intensive care admission, or mortality). Only some studies reported comorbidities, especially obesity and cardiovascular disorders, but the results remained unchanged after controlling for comorbidities. The quality of the seven studies included was moderate according to the Newcastle-Ottawa Quality Assessment Scale. The methodological heterogeneity of the studies included did not allow a meta-analysis of the findings. In conclusion, higher physical fitness levels were associated with lower risk of hospitalization, intensive care admissions, and mortality rates among patients with COVID-19.

Introduction

Coronavirus disease 2019 (COVID-19) has led to 683 million confirmed cases and 6.8 million deaths until March 28, 2023.[1] Many public health interventions have been tried to control this pandemic, including lockdowns, mask wear, and vaccinations.[2–4] However, lockdown intervention leads to a reduction of recommended levels of physical activity and an unhealthy lifestyle.[5,6] Besides, a reduction in physical activity and an unhealthy lifestyle are associated with obesity, diabetes, hypertension, and cardiovascular disease (CVD), all of which are risk factors for COVID-19 severity and mortality.[7,8]

The health benefits of physical activity and high physical fitness are acknowledged, and regular physical activity improves physical fitness.[9,10] However, low physical fitness and insufficient physical activity are separate concepts. There are associations between physical activity and physical fitness, but there is also evidence supporting their independence as health-related variables.[11] The correlation between physical activity and physical fitness is only modest, possibly because physical fitness is influenced by genetics in addition to physical activity patterns.[12]

Physical fitness has been considered a better predictor of morbidity and mortality than physical activity itself.[13,14] Cardiorespiratory fitness has been identified as a strong predictor of chronic disease mortality, and in 2016, the American Heart Association recommended that cardiorespiratory fitness be measured as a clinical vital sign and a vitally important opportunity to improve patient management and patient health.[15] Physical fitness is defined as the ability to complete daily activities without undue fatigue and with enough energy left over to pursue leisure activities.[16] A physical fitness assessment includes measures of

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Abbreviation list

COVID-19	Coronavirus disease 19
PICOs	participants, intervention, comparisons, outcomes, and study design
PRISMA	Preferred Reporting Items for Systematic Review and Meta Analyses statement
$\dot{V}O_{2max}$	Maximal oxygen consumption
$\dot{V}O_{2peak}$	Peak oxygen uptake
OR	odds ratio
CRF	cardiorespiratory fitness
METs	metabolic equivalents task
BMI	body mass index
CVD	cardiovascular disease
M	male
F	female
RT-PCR	reverse transcription-polymerase chain reaction
NR	not reported

cardiorespiratory endurance, body composition, muscular fitness, and musculoskeletal flexibility.[17] Physical fitness captures the health benefits of sustained physical activity, albeit with considerable inter-individual variability, and is an established predictor of cardiovascular disease, cancer, cardiometabolic disease, and all-cause mortality.[18,19] High physical fitness boosts the immune system's capacity and reduces inflammation.[20,21] High cardiorespiratory fitness attenuates the risk of pneumonia and may contribute to mitigating the severe inflammatory response mediated by SARS-CoV-2.[22,23] Therefore, high physical fitness may contribute to prevent severe forms of COVID-19.[24]

Recently, systematic reviews have pointed out that physical activity is associated with decreased COVID-19 hospitalizations, intensive care unit admissions, and mortality rates.[25–27] Nevertheless, it is not known if high physical fitness reduces the risk, severity, and mortality of COVID-19. This research question has important implications for the public health in the face of COVID-19. In this context, the study aims to systematically verify the association between physical fitness and the risk of severe COVID-19.

Methods

Study design

This systematic review was carried out in accordance with the methodological guidelines from the Cochrane Handbook for Systematic Reviews and reported in accordance with the Preferred Reporting Items for Systematic Review and Meta Analyses statement (PRISMA).[28,29] The protocol for this systematic review is registered at PROSPERO (CRD42023412015).

Search strategy

Studies were systematically searched in the following electronic databases: MEDLINE/PubMed, SciELO, Cochrane library, and Embase, from December 2019 to April 2023, i.e., during the COVID-19 pandemic. The search strategy was as follows: ("severe acute respiratory syndrome" or "SARS-CoV-2″ or "COVID" or "COVID-19″) and ("fatal outcome" or "mortality" or "death" or "hospitalization" or "intensive care" or "intubation") and ("fitness" or "physical fitness" or "cardiorespiratory fitness" or "endurance fitness"). The references of the included studies were also searched for any other eligible articles.

Eligibility criteria

The eligibility criteria followed the PICOs recommendation (participants, intervention, comparisons, outcomes, and study design).[29] Observational studies that explored the relationship between the previous or current pattern of fitness and severe COVID-19 were eligible. Any assessment of physical fitness was considered. Severe COVID was considered the primary outcome based on one of the following outcomes: hospitalization, intensive care unit admission, intubation, or death. There was no restriction on language. Letters, editorials, commentaries, and abstracts were not included; studies with only univariate analysis for statistics were excluded.

Data extraction

The data extraction was performed by two reviewers (JGBA and DRV) independently regarding the characteristics of the studies and participants, the assessment method of physical fitness levels, and the main outcome (inclusion phase). All the relevant full text studies selected were reviewed to check for inclusion criteria. Local, study design, fitness evaluation, COVID-19 diagnostic, outcome, and comorbidity data were extracted from eligible studies. Discrepancies were resolved through discussion between the two reviewers and eventual consensus.

Quality assessment

The quality of the non-randomized studies was assessed by two researchers independently according to the eight items of the specific scale of the Newcastle– Ottawa Scale (NOS).[30] The NOS includes quality of selection, comparability, and assessment of exposure or outcomes. The NOS scale is composed of three dimensions with a full score of nine points. Studies with scores of 0–3, 4–6, and 7–9 were considered to be of low, moderate, and high quality, respectively.

Analysis

Results were interpreted based on the association between physical fitness and severe COVID-19 outcomes (hospitalization, intensive care admission, intubation, or death). Meta-analysis was not possible because there were no studies that provided effect sizes for the same outcome. Separate narrative syntheses were used to analyze the data from the selected studies.

Results

Study characteristics

A total of 639 studies were found by searching the following databases: PubMed (n = 365), Embase (n = 136), Cochrane (n = 109), and SciELO (n = 29). After excluding duplicate manuscripts (n = 118) and studies not meeting the inclusion criteria based on titles and abstracts (n = 146), 11 studies showed potential relevance for full analysis. The full-texts of the remaining 11 articles were then screened for eligibility, and four were excluded; two articles did not include a measure of fitness and the other two did not present the main outcome. Accordingly, seven articles[31–37] were included in this systematic review (Fig. 1).

Across the observational studies, a total of 13 468 people with COVID-19 were included, with sample sizes ranging from 246 to 6 674. In one study,[31] the sample of participants was only male. Swedish military service participants were included in each study at various times before the SARS-CoV-2 infection, with studies including participants eight years before infection onset (i.e., three months after the initial presentation of symptoms related to the infection). The age of

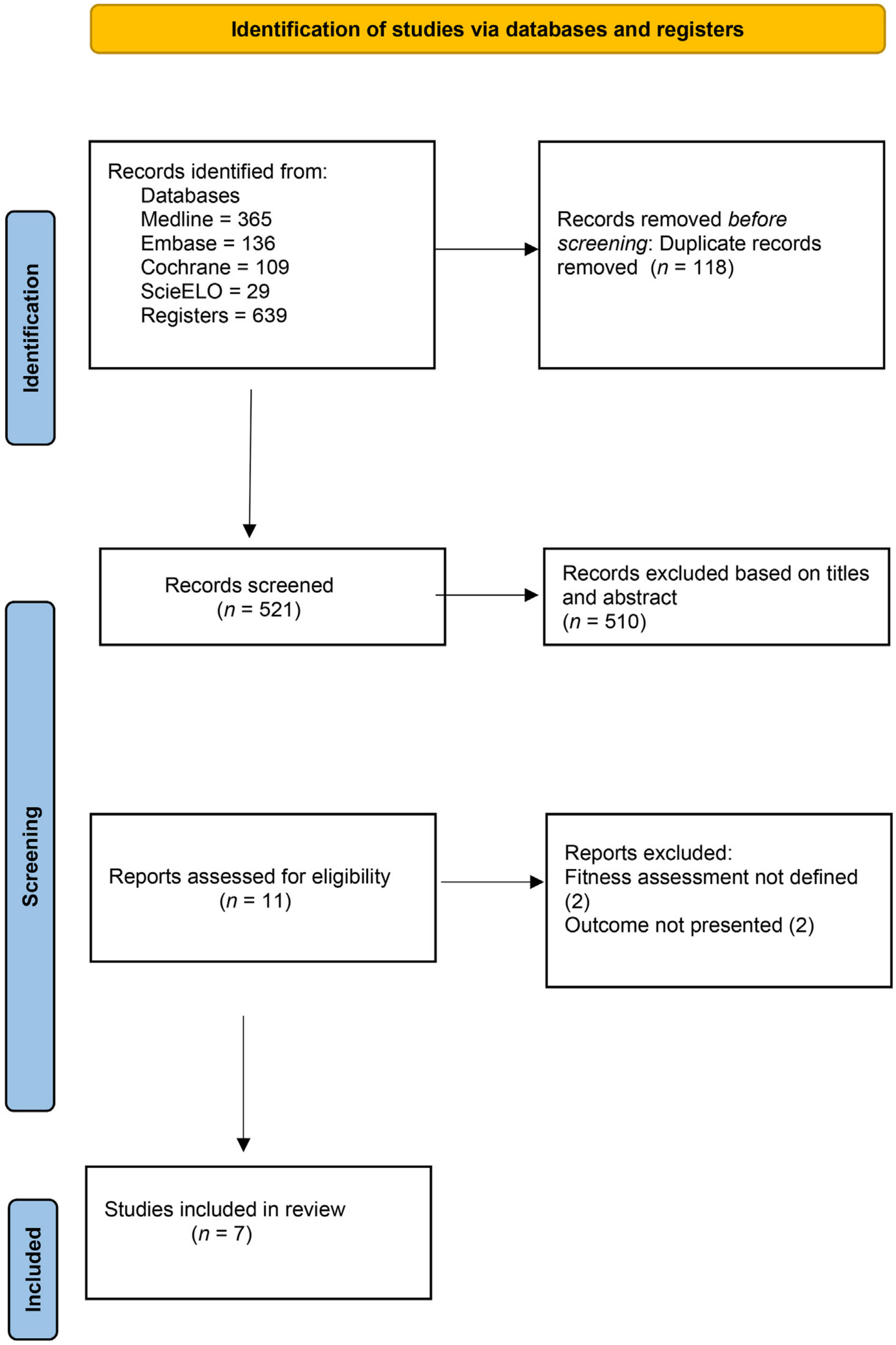

Fig. 1. Flow chart.

participants ranged between 40.9 and 70.0 years old. The assessment of physical fitness included self-reported evaluation (two studies), muscle strength (two studies), maximal oxygen consumption ($\dot{V}O_{2max}$) (two studies), and Metabolic Equivalents of Task (METs), one study. Few studies addressed comorbidities, with obesity and cardiovascular disorders being the most prevalent.

Synthesis observational studies

There was a case-control study,[37] two cohort studies,[31,35] and four cross-sectional studies.[32–34,36] The characteristics of the studies reviewed are shown in Table 1. The risk of severe COVID-19 was inversely associated with a high physical fitness evaluation in all studies included in this review (Table 2).

Yates et al.[33] reported that both body mass index (BMI) and walking pace were independently associated with the risk of severe COVID-19 and mortality. Compared to those with a brisk walking pace, the odds ratio (*OR*) of severe COVID-19 for steady and slow walkers was 1.13 (95%*CI*, 0.98–1.31) and 1.88 (95%*CI,* 1.53–2.31), respectively. For COVID-19 mortality, the *OR* were 1.44 (95%*CI,* 1.10–1.90) and 1.83 (95%*CI,* 1.26–2.65), respectively. Self-reported slow walkers were at high-risk for severe COVID-19 independent of obesity.

Brawner et al.[36] discovered that the maximal exercise capacity, as measured by Peak Metabolic Equivalents Task (METs), was significantly lower ($p = 0.001$) among hospitalized patients (6.7 ± 2.8) compared to those who were not hospitalized (8.0 ± 2.4). Peak METs were inversely

Table 1
Characteristics of studies included in this systematic review.

Authors and year of publication	Location of study	Design	Sample size/Gender	Age (years)	COVID-19 confirmation
Ekblom-Bak et al. 2021[37]	Sweden	Case-Control	4 283 F = 1 268 M = 3 015	49.9 ± 10.7	RT-PCR
Yates et al. 2021[33]	UK	Cross-sectional	1 337 F = 540 M = 797	66–69 (60–74; 25th 75th)	RT-PCR
Geijerstam et al. 2021[31]	Sweden	Cohort	6 674 Male	51.8 ± 9.9	RT-PCR
Cheval et al. 2021[34]	Sweden	Cross-sectional	3 600 F = 2 044 M = 1 556	68.8 ± 8.8	NR
Christensen et al. 2021[35]	Canada	Cohort	2 690 F = 1 376 M = 1 314	70 (61,75; IQR)	RT-PCR
Brawner et al. 2021[36]	USA	Retrospective observational study	246 F = 142 M = 104	59 ± 12	NR
Brandenburg et al. 2021[32]	Canada	Cross-sectional	263 F = 113 M = 150	227 (86%) < 65 years	NR

Legend: M = male; F = female; COVID-19: Coronavirus disease 2019; RT-PCR: reverse transcription-polymerase chain reaction; NR: not reported.

Table 2
Risk of severe COVID-19 according to the physical fitness evaluation.

Authors	Fitness evaluation	Fitness classification	Severe COVID - Hospitalization	Intensive Care	Mortality	*OR* (95% *CI*)
Ekblom-Bak et al.[37]	Sub-maximum Cycle test - Estimated $\dot{V}$ O2max (ml/min/Kg)	Very low (<25 ml min^{-1}·kg^{-1}) Low (25 ml min^{-1}·kg^{-1}-< 32 ml min^{-1}·kg^{-1}) Moderate (32 ml min^{-1}·kg^{-1} -< 46 ml min^{-1}·kg^{-1}) High (≥46 ml min^{-1}·kg^{-1}) Total	97 (21.3%) 166 (36.4%) 171 (37.5%) 22 (4.8%) 456	37 (27.2%) 45 (33%) 49 (36%) 5 (3.8%) 136	32 (33%) 40 (42%) 23 (24%) 1 (1.0%) 96	1.0 (0.6–1.6) 2.6 (1.1–4.1) 1.8 (1.1–2.8)
Yates et al.[33]	Walking pace (self reported)	Slow (< 3 mph)/Steady (3–4 mph): *n* = 248 684 Brisk (> 4 mph): *n* = 163 912	710 (0.28%) 291 (0.17%)	NR	264 (0.10%) 72 (0.04%)	1.6 (1.4–1.8) 1.0
Geijerstam et al.[31]	Cycle ergometric test and Muscle Strenght	Low, Medium, and High CRF: *n* = 1 143 670 Muscle Strength (Continuous Predictor) *n* = 1 161 827	2 006 (0.17%) 2 252 (0.19%)	445 (0.03%) 514 (0.0.04%)	149 (0.01%) 180 (0.01%)	0.5 (0.3–0.8) 0.6 (0.4–0.7) 0.7 (0.6–0.8)
Cheval et al.[34]	Muscle Strenght (Kg) Hand-grip	Muscle Strenght (Kg, mean ± *SD*) 34.5 ± 11.8 31.9 ± 11.4	83 (2.3%)	NR	NR	0.008 (0.003–0.016) 0.019 (0.01–0.03)
Christensen et al.[35]	Bicycle test $\dot{V}$ O2max	Low fitness: *n* = 77 (22%) Moderate fitness: *n* = 214 (63%) High fitness: *n* = 55 (15%)	NR	NR	59 (17%)	2.3 (1.3–4.0) 0.4 (0.2–0.7) 0.3 (0.1–0.8)
Brawner et al.[36]	Exercise stress test	Peak METs: 6.7 ± 2.8 8.0 ± 2.4	89 (36%)	28 (11%)	13 (5%)	3.8 (1.7–8.7)
Brandenburg et al.[32]	Self-reported (Pace to cover 4.8 km)	CRF min/km > 10 8.7–10 8.7–6.2 6.2–4.4	28 (11%)	NR	NR	0.3 (0.1–0.9) 0.2 (0.05–1.02)

Legend: $\dot{V}$ O2max = maximal oxygen consumption; *OR* = odds ratio; CRF = cardiorespiratory fitness; METs = metabolic equivalents task; NR = not reported. Data in fourth, fifth and sixth column mean number(percentage) of patients hospitalized, admitted to intensive care, and who died.

associated with the likelihood of hospitalization in unadjusted (odds ratio, 0.83; 95% *CI*, 0.74–0.92) and adjusted models (odds ratio, 0.87; 95% *CI*, 0.76–0.99). The covariates included in the logistic regression were age, gender, history of asthma, cancer, cardiovascular disorders, chronic kidney disease, chronic obstructive pulmonary disease, diabetes, obesity, and tobacco smoking.

Christensen et al.[35] showed that individuals with moderate (adjusted relative *risk-aRR* = 0.43, 95% *CI*: 0.25, 0.75) and high fitness (*aRR* = 0.37, 95% *CI*: 0.16, 0.85) had a significantly lower risk of dying from COVID-19 as compared with those with low fitness. Estimates were adjusted for age, gender, race, BMI category, and alcohol use frequency.

Geijerstam et al.[31] reported that a high cardiorespiratory fitness or muscle strength in late adolescence/early adulthood had a protective effect for severe COVID- 19 later in life; *OR* = 0.76 (95% *CI*:0.67, 0.85) for hospitalization (*n* = 2 006), *OR* = 0.61 (95% *CI:* 0.48, 0.78) for intensive care (*n* = 445) and *OR* = 0.56 (95% *CI:* 0.37, 0.85) for mortality (*n* = 149), compared with the lowest category of cardiorespiratory fitness. This association remains unchanged when controlled for comorbidities (overweight and obesity, hypertension, CVD, diabetes, kidney disease, and respiratory disease).

Cheval et al.[34] showed that higher muscle strength, measured by hand-grip strength (kg), was associated with a lower risk of COVID-19 hospitalization (adjusted odds ratio [*OR*] per increase of 1 standard deviation in grip strength = 0.64, 95% confidence interval [95% *CI*] = 0.45–0.87, *p* = 0.015). These results were controlled by comorbidities (BMI, cardiovascular diseases, respiratory diseases, diabetes, cancer, chronic kidney disease, rheumatoid disease). Sensitivity and robustness analyses were consistent with the main results.

Bradenburg et al.[32] verified the association between self-reported cardiorespiratory fitness, determined as the pace to cover 4.8 km without becoming overly fatigued, and COVID-19 infection characteristics in 264 individuals. Multivariate logistic regression, controlling for BMI, age, and comorbidities, revealed a significant association between cardiorespiratory fitness and hospitalization due to COVID-19. Compared with the lowest level of cardiorespiratory fitness, the odds of hospitalization significantly decreased by 64% (*OR* = 0.36; 95% *CI*, 0.13–0.98; *p* = 0.04) in individuals reporting the ability to maintain a brisk walk. The additional reduction in hospitalization was not significant in individuals who reported the ability to maintain a jogging pace (*OR* = 0.22; 95% *CI*, 0.05–1.04; *p* = 0.05).

Patients with more severe COVID-19 had significantly lower cardiorespiratory fitness, according to Ekblom-Bat et al.[37]; matched analyses revealed a graded decrease in odds for severe COVID-19 with each milliliter in cardiorespiratory fitness (*OR* = 0.98, 95% *CI,* 0.970–0.998), and a two-fold increase in odds between the lowest and highest (32 mL $min^{-1}·kg^{-1}$ vs. 46 mL $min^{-1}·kg^{-1}$) cardiorespiratory group. A higher cardiorespiratory fitness level attenuated the risk associated with obesity and high blood pressure, and mediated the risk associated with various socioeconomic factors.

The quality of the seven studies included, classified based on the Newcastle-Ottawa Quality Assessment Scale, was moderate; 4 [32,36], 5,[31,33–35] and 6[37] (Table 3).

Discussion

This study, to the best of our knowledge, this is the first systematic review to verify the association between the risk for severe COVID-19 and according to previous physical fitness levels. The evidence shown in this systematic review highlights the protective effect of high physical fitness on severe COVID-19. A small number of studies found that patients with better physical fitness have a lower risk of being hospitalized, being admitted to the intensive care unit, or dying before acquiring the SARS-CoV-2 infection. An *OR* demonstrating an inverse relationship between a high level of physical fitness and the severity of COVID-19 was seen in all seven of the studies evaluated. However, due to the moderate quality of the studies reviewed, further evidence is required to determine the effectiveness of physical fitness in promoting defenses against severe COVID-19.

It has been hypothesized that high fitness, partly heritable and also resulting from regular physical activity, confers innate immune protection, attenuating the risk of infectious diseases.[38] The mechanisms underlying physical fitness's ability to protect against severe COVID-19 infection are most likely multifactorial. It is reasonable to assume that high fitness results in physio-molecular adaptations in all tissues affected by physical activity, which may be protective following SARS-CoV-2 infection.[39] Patients with severe COVID-19 may experience significant decreases in lung function and since fitness represents the ability of the organism to supply oxygen to skeletal muscles during sustained activity, fitness may be a key to identify individuals at the greatest risk for severe COVID-19 outcomes. Some studies have reported that a high fitness level may protect the organism against multiple organ dysfunction syndrome, which is frequently observed in severe COVID-19.[37,40] A low level of physical fitness is associated with increased plasma levels of proinflammatory cytokines such as C-reactive protein, IL-1β, IL-6, IL-7, and TNF.[41] In contrast, physical activity induces the production of myokines such as myostatin, IL-8, IL-10, IL-15, and leukemia inhibitory factor, improving cell-mediated and humoral immunity.[42] In line with this assumption, all studies found in this systematic review observed an inverse association of high physical fitness with COVID-19 hospitalization, intensive care admission, and mortality risk.

Physical fitness may be evaluated in different ways: cardiorespiratory endurance, body composition, muscular fitness, and musculoskeletal flexibility.[43] Evaluation of cardiorespiratory fitness can be made directly, based on the assessment of $\dot{V}O_{2max}$, or indirectly.[44] Peak oxygen uptake ($\dot{V}O_{2peak}$) is the gold standard in the assessment of cardiorespiratory fitness. Only two studies[33,34] had fitness evaluated by estimating $\dot{V}O_{2max}$ using open circuit spirometry. The other studies performed indirect assessments of $\dot{V}O_{2max}$ using standardized protocols or assessments of muscular fitness. Such protocols are based on the linear relationship between exercise heart rate and oxygen consumption. These indirect tests are reliable and have been validated.[45] Walking and step tests, cycle ergometers, and muscular strength tests were used. Two studies[29,31] used this method, and this method has been shown to be associated with cardiorespiratory fitness.[46] Muscular strength is a main component of physical fitness and has also been indicated as an important marker of mortality as well as adverse health outcomes.[47,48] Reduced muscle strength has been reported as being associated with acute respiratory distress syndrome and death.[49] Muscle strength was used in two studies.[30,33] Thus, the studies used reliable and validated methods of assessing physical fitness, despite the fact that different aspects of physical fitness have been evaluated.

This systematic review has some limitations. Physical fitness was evaluated by different methods. Self-reported walking pace has been shown to be associated with cardiorespiratory fitness within the UK Biobank.[50] However, it is subject to possible reporting bias. Some risk factors, including physical fitness and comorbidities, were measured at different times before the pandemic. Although physical fitness may be stable over time, values may be less stable, especially at older ages.[51,52] Another limitation was that most of the studies included in this review did not report all comorbidities associated with severe COVID-19 outcomes. Furthermore, due to the small number and heterogeneity of the

Table 3
Quality assessments of reviewed studies (NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE).

Studies (*n* = 7)	Representativeness of the sample	Sample size	Non respondents	Risk Factor	Individual in different outcome groups are comparable	Assessment of outcome	Statistical test	Total score
Ekblom-Bak et al.[37]	–	☆	–	☆☆	☆	☆	☆	6
Yates et al.[33]	–	☆	–	☆	☆	☆	☆	5
Geijerstam et al.[31]	–	☆	–	☆	☆	☆	☆	5
Cheval et al.[34]	–	☆	–	☆	☆	☆	☆	5
Christensen et al.[35]	–	☆	–	☆	☆	☆	☆	5
Brawner et al.[36]	–	–	–	☆	☆	☆	☆	4
Brandenburg et al.[32]	–	–	–	☆	☆	☆	☆	4

included studies and the variability of study design, it was not possible to perform a meta-analysis.

In conclusion, this data further supports the important relationship between physical fitness and adverse health outcomes. Higher fitness levels were associated with lower risk of hospitalization, intensive care admissions, and mortality rates among adults and the elderly with COVID-19. Significant increases in the physical fitness of people already with high physical fitness were not significant enough to reduce hospitalization. Based on the fact that the quality of the studies reviewed was only moderate, further evidence is required to determine the effectiveness of physical fitness in promoting defenses against severe COVID-19.

In addition, this research query has significant public health implications, given the high COVID-19 mortality rates and the absence of a specific treatment for SARS-CoV-2 at present. In the current pandemic scenario, public strategies to maintain a high level of physical fitness must be devised as physical exercise protocols and other strategies to enhance endurance, mobility, strength, and flexibility.

Submission statement

All authors have read and agree with manuscript content. While this manuscript is being reviewed for this journal, the manuscript will not be submitted elsewhere for review and publication.

Authors' contribution

Concept/idea/research design: J. G. Alves, Writing: M.R. Taveira, A. C. Guimarães, C.A. Leal, J.R, Silva, F.J. Cardoso, J. G. Alves, and D. R. Victor, Data collection: M.R. Taveira, A. C. Guimarães, C.A. Leal, J.R, Silva, F.J. Cardoso, J. G. Alves, and D. R. Victor, Data analysis: M.R. Taveira, A. C. Guimarães, C.A. Leal, J.R, Silva, F.J. Cardoso, J. G. Alves, and D. R. Victor, Review: M.R. Taveira, A. C. Guimarães, C.A. Leal, J.R, Silva, F.J. Cardoso, J. G. Alves, and D. R. Victor.

Conflict of interest

All the authors declare no direct or indirect interests that are in direct conflict with the conduction of the study.

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