Baseline physical activity is associated with reduced mortality and disease outcomes in COVID-19: A systematic review and meta-analysis

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Abstract
Among coronavirus disease 2019 (COVID-19) patients, physically active individuals may be at lower risk of fatal outcomes. However, to date, no meta-analysis has been carried out to investigate the relationship between physical activity (PA) and fatal outcomes in patients with COVID-19. Therefore, this meta-analysis aims to explore the hospitalisation, intensive care unit (ICU) admissions, and mortality rates of COVID-19 patients with a history of PA participation before the onset of the pandemic, and to evaluate the reliability of the evidence. A systematic search of MEDLINE/PubMed, Cumulative Index to Nursing and Allied Health Literature, Scopus, and medRxiv was conducted for articles published up to January 2022. A random-effects meta-analysis was performed to compare disease severity and mortality rates of COVID-19 patients in physically active and inactive cases. Twelve studies involving 1,256,609 patients (991,268 physically active and 265,341 inactive cases) with COVID-19, were included in the pooled analysis. The overall meta-analysis compared with inactive controls showed significant associations between PA with reduction in COVID-19 hospitalisation (risk ratio (RR) = 0.58, 95% confidence intervals (CI) 0.46–0.73, \( P = 0.001 \)), ICU admissions (RR = 0.65, 95% CI 0.52–0.81, \( P = 0.001 \)) and mortality (RR = 0.47, 95% CI 0.38–0.59, \( P = 0.001 \)). The protective effect of PA on COVID-19 hospitalisation and mortality could be attributable to the types of exercise such as resistance exercise (RR = 0.27, 95% CI 0.15–0.49, \( P = 0.001 \)) and endurance exercise (RR = 0.41, 95% CI 0.23–0.74, \( P = 0.003 \)), respectively. Physical activity is associated with decreased hospitalisation, ICU admissions, and mortality rates of patients with COVID-19. Moreover, COVID-19 patients with a history of resistance and endurance exercises experience a lower rate of hospitalisation and mortality, respectively. Further studies are warranted to determine the biological mechanisms underlying these findings.

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; ICU, Intensive care unit; MET, Metabolic Equivalent of Task; PA, Physical activity; PRISMA, Preferred Reporting Items for Systematic Review and Meta-Analyses; RR, risk ratio; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
1 | INTRODUCTION

The rapid spread of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus two (SARS-CoV-2) has led to 282 million confirmed cases and 5.4 million deaths. A high rate of transmission of SARS-CoV-2 and mortality owing to COVID-19 is mainly due to emerging new variants, which make efforts less effective in the fight against the virus. However, a variety of public health interventions such as government policy, mask-wearing, and vaccination have been implemented worldwide to mitigate and control the spread of the outbreak of COVID-19 disease. Restrictive measures to prevent the spread have resulted in difficulties for the population to maintain healthy lifestyles such as the engagement in recommended levels of physical activity (PA). Meyer et al. reported 30% reduction in PA during COVID-19 quarantine independent of sex and age. Specific home-based PA recommendations have been recently published in an attempt to take advantage of both quarantine and staying physically active. Adherence to government PA guidelines during the COVID-19 pandemic has been strongly recommended. Studies have shown that potential outcomes from leading an unhealthy lifestyle, such as hypertension, diabetes, obesity, and cardiovascular disease (CVD) increase the risk of SARS-CoV-2 infection as well as the severity and mortality rate. Importantly, obesity and hypertension were the most prevalent disorders reported in hospitalised and deceased patients due to COVID-19.

Several studies have shown that a baseline sedentary lifestyle increases the mortality of hospitalised patients with COVID-19. Moreover, engaging in healthy lifestyle behaviours may protect against the most severe consequences of COVID-19 disease including systemic inflammation, and reduced quality of life. Importantly, an unhealthy lifestyle has been considered a risk factor for COVID-19 hospital admission. Different mechanisms may explain the protective effect of PA on COVID-19 outcomes and disease severity. Regular PA improves immune function, and regularly active individuals have a lower incidence, intensity of symptoms, and mortality from COVID-19 and other various viral infections. Moreover, regular PA reduces the risk of systemic inflammation, which is considered the primary contributor to lung damage in COVID-19 patients. Additionally, it has a protective impact on COVID-19 risk factors such as obesity and hypertension. Furthermore, we previously reported that a sedentary lifestyles increase the risk of COVID-19 severity and mortality. Further, high hospitalisation rates have been reported in patients with less cardiorespiratory fitness.

Given this mortality risk in physically inactive COVID-19 patients, this meta-analysis aims to explore the hospitalisation, intensive care unit (ICU) admissions, and mortality rates of COVID-19 patients with a history of PA participation before the onset of the pandemic.

2 | METHODS

The present study was carried out in accordance with methodological guidelines from the Cochrane Handbook for Systematic Reviews. The present study’s findings were reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analyses statement (Supplementary Material S1).

2.1 | Search strategy

Relevant studies were systematically searched in electronic databases including MEDLINE/PubMed, Cumulative Index to Nursing and Allied Health Literature, Scopus, and medRxiv by two researchers (MA and FM) up to January 2022. The search strategy was as follows: (“severe acute respiratory syndrome coronavirus 2” or “novel coronavirus” or “COVID-19” or “2019-nCoV” or “SARS-CoV-2”) and (“survival” or “fatal outcome” or “mortality” or “death” or “hospitalisation” or “intensive care”) and (“physical activity,” or “exercise activity”); Supplementary Material S1).

2.2 | Eligibility criteria

The Eligibility criteria followed the PICOs question. In prospective and cross-sectional studies, we included studies that examine the relationship between PA and COVID-19 clinical outcomes and have reported at least one of the following outcomes: COVID-19 related mortality, hospitalisation, and ICU admission. Furthermore, editorial, letters, commentaries, and abstracts with insufficient data were excluded from the present meta-analysis.

2.3 | Data extraction

First, titles and abstracts of all retrieved articles were screened by two investigators (MA, FM) for relevance. Second, the relevant full-text articles were reviewed for inclusion and the following data were extracted from eligible studies, where available: study design,
country, PA documentation, age and gender, relative outcomes, and comorbidity factors. In all stages, discrepancies were resolved through discussion before conducting meta-analysis.

2.4 | Quality assessment

The Newcastle–Ottawa Scale (NOS) was used to assess the quality of studies. The NOS for cohort studies includes 3 domains (quality of selection, comparability, quality of outcome, and adequacy of follow-up), with a maximum score of nine points. Studies with NOS scores of 0–3, 4–6, and 7–9 were considered low, moderate, and high quality, respectively.

2.5 | Subgroup analysis

We also performed a subgroup analysis to determine the effect of PA levels on our study outcomes based on Metabolic Equivalent of Task (MET) minutes per week. Low and moderate-vigorous PA levels were classed as achieving less than or equal to 500 and higher than 500 MET-min per week, respectively. Additionally, we performed another subgroup analysis to determine the effect of PA induced-adaptation on our study outcomes based on types of exercise related to endurance exercise, resistance exercise, and combined training adaptations.

2.6 | Statistical analyses

All meta-analyses were conducted using Review manager (Version 5.4, The Nordic Cochrane Centre, Copenhagen, The Cochrane Collaboration, 2014). Dichotomous outcomes were pooled and expressed as risk ratios (RRs) with 95% confidence intervals (CI). The pooled analysis results were classified based on study types into two categories, prospective cohorts and cross-sectional and the pooled RRs were estimated using the random-effect model. Heterogeneity was calculated using Cochran’s Q statistics and $I^2$. $I^2$ from zero to 24%, 25%–49%, 50%–74% and 75%–100% were interpreted as low, moderate, substantial and considerable heterogeneity. Funnel plots with Egger weighted regression test were used for assessing publication bias using STATA version 16. Finally, the overall pooled prevalence of the respective outcomes was re-estimated by the one study removed methods to perform sensitivity analysis.

![PRISMA flow diagram of study selection](image)
| Study                          | Design                        | Country     | Physical activity documentation | Age (year) | Gender | COVID-19 diagnosis                  | Outcome                              | Hospitalisation, n (%) | ICU admissions, n (%) | Mortality, n (%) |
|-------------------------------|-------------------------------|-------------|---------------------------------|------------|--------|-------------------------------------|---------------------------------------|------------------------|----------------------|---------------------|
| Ahmadi et al. 2021\(^{12}\)   | Community-based cohort        | UK          | International physical activity questionnaire | 56.5 ± 8.1 | F = 255,838 M = 212,731 | RT-PCR                             | Inactive (92,221)         | NR                    | NR                  | 112 (12%)          |
|                               |                               |             |                                 |            |         |                                     | Insufficient (140,609)  |                       |                     | 115 (0.08%)        |
|                               |                               |             |                                 |            |         |                                     | Sufficient (232,603)   |                       |                     | 160 (0.06%)        |
| Cho et al. 2021\(^{13}\)     | Nationwide case-control       | Korea       | Self-reported questionnaire      | 50.7 ± 14.3| F = 3832 M = 2456                 | RT-PCR                             | Physically inactive (1313) | NR                    | NR                  | 31 (33.7%)          |
|                               |                               |             |                                 |            |         |                                     | Light (1752)            |                       |                     | 27 (29.3%)          |
|                               |                               |             |                                 |            |         |                                     | Moderate (861)          |                       |                     | 4 (4.3%)           |
|                               |                               |             |                                 |            |         |                                     | Vigorous (2362)         |                       |                     | 13 (14.1%)         |
|                               |                               |             |                                 |            |         |                                     | Moderate to vigorous (3223)|                       |                     |                     | 17 (18.5%)         |
| de Souza et al. 2021\(^{36}\) | Cross-sectional               | Brazil      | International physical activity questionnaire | 18–80      | F = 658 M = 371                    | RT-PCR                             | None (485)              | 36 (13.8%)            | NR                  | NR                  |
|                               |                               |             |                                 |            |         |                                     | 1 times/week (192)      | 19 (9.9%)              |                     |                     |                     |
|                               |                               |             |                                 |            |         |                                     | ≥ 2 times/week (261)    | 36 (7.4%)              |                     |                     |                     |
| Ekblom-Bak et al. 2021\(^{14}\) | Case-control                  | Sweden      | Self-reported questionnaire      | 49.9 ± 10.7| F = 254 M = 603                    | RT-PCR                             | Never/irregular (293)    | 181 (36%)             | 67 (43%)            | 45 (36%)           |
|                               |                               |             |                                 |            |         |                                     | 1–2 times/week (254)    | 157 (32%)             | 49 (31%)            | 48 (38%)           |
|                               |                               |             |                                 |            |         |                                     | ≥ 3 times/week (232)    | 159 (32%)             | 41 (26%)            | 32 (26%)           |
| Halabchi et al. 2021\(^{8}\)  | Cross-sectional               | Iran        | Electronic health record        | 492.3 ± 119| F = 2629 M = 2065                  | RT-PCR                             | Inactive (4445)          | 820 (18.4)            | 58 (1.3)            | 79 (1.8)           |
|                               |                               |             |                                 |            |         |                                     | Active (249)            | 28 (11.2)             | 2 (0.8)             | 0 (0)               |
| Hamer et al. 2020\(^{15}\)    | Community-based cohort        | UK          | International physical activity questionnaire | 57.1 ± 9.0| F = 173,038 M = 214,071          | RT-PCR                             | None (68,913)            | 186 (27%)             | NR                  | NR                  |
|                               |                               |             |                                 |            |         |                                     | Insufficient (108,707)  | 192 (17%)             |                     |                     |                     |
|                               |                               |             |                                 |            |         |                                     | Sufficient (209,489)    | 382 (18%)             |                     |                     |                     |
| Hamrouni et al. 2021\(^{28}\) | Prospective cohort            | UK          | International physical activity questionnaire | 37–73      | F = 135,884 M = 123,603          | RT-PCR                             | Low (47,827)            | NR                    | NR                  | 109 (27%)          |
|                               |                               |             |                                 |            |         |                                     | Moderate (105,564)      |                       |                     | 150 (38%)          |
|                               |                               |             |                                 |            |         |                                     | High (106,006)          |                       |                     | 138 (34%)          |
| Study            | Design              | Country                  | Physical activity documentation                      | Age (year) | Gender | COVID-19 diagnosis       | Group (n)                      | Hospitalisation, n (%) | ICU admissions, n (%) | Mortality, n (%) |
|------------------|---------------------|--------------------------|------------------------------------------------------|-------------|--------|--------------------------|--------------------------|------------------------|----------------------|------------------|
| Lee et al. 2021  | Nationwide cohort   | Korea                    | Personal medical interview                           | 20-60       | F = 37,272 M = 39,123 | RT-PCR                   | Insufficient training (41,293) | NR                     | 273 (21.1)           | 32 (2.5)           |
|                  |                     |                          |                                                      |             |         | Resistance training (18,994) | 25 (16.7)               | 0 (0.0)                |                      |                    |
|                  |                     |                          |                                                      |             |         | Endurance training (5036)   | 109/561 (19.4)          | 11 (2.0)               |                      |                    |
|                  |                     |                          |                                                      |             |         | Combined training (1,072)   | 39/291 (13.4)           | 2 (0.7)                |                      |                    |
| Maltagliati et al. 2021 | Cross-sectional 27 European countries Self-reported questionnaire | 69.3 ± 8.5 | F = 1763 M = 1376 | RT-PCR | Hardly ever or never (1167) | 36 (54%) | NR | NR |                    |
|                  |                     |                          |                                                      |             |         | 1 times/week (541)          | 10 (15%)                |                       |                      |                    |
|                  |                     |                          |                                                      |             |         | >1 times/week (1161)        | 15 (23%)                |                       |                      |                    |
|                  |                     |                          |                                                      |             |         | 1–3 times/month (270)       | 5 (%)                   |                       |                      |                    |
| Salgado-Aranda et al. 2021 | Retrospective cohort Spain Rapid physical activity questionnaire | 54.3 ± 10.7 | F = 236 M = 284 | RT-PCR | Inactive (297) | NR | 26 (8.8%) | 41 (13.8%) |
|                  |                     |                          |                                                      |             |         | Active (223)                | 14 (6.3%)               | 4 (1.8%)               |                      |                    |
| Sallis et al. 2021 | Retrospective observational cohort US Electronic health record | 47.5 ± 16.9 | F = 29,992 M = 18,447 | RT-PCR | Consistently inactive (6984) | 732 (10.5%) | 195 (2.8%) | 170 (2.4%) |
|                  |                     |                          |                                                      |             |         | Some activity (38,338)      | 3405 (8.9%)             | 972 (2.5%)               | 590 (1.5%)            |
|                  |                     |                          |                                                      |             |         | Consistently meeting PA guidelines (3118) | 99 (3.2%) | 32 (1%) | 11 (0.4%) |
| Yuan et al. 2021  | Cross-sectional China Personal medical interview | 61.8±13.6 | F = 80; M = 84 | RT-PCR | Inactive (103) | NR | 26 (25.2) | 6 (5.8) |
|                  |                     |                          |                                                      |             |         | Active (61)                  | 3 (4.9)                 | 0 (0.0)                |                      |                    |

Abbreviations: NR, not reported; RT-PCR, reverse transcription polymerase chain reaction.
results

3.1 Study identification and characteristics

A total of 1956 potentially relevant articles were identified in our literature search. Four hundred and 60 studies remained after removing duplicates. After screening titles and abstracts, 1397 research articles were excluded. Of 33 obtained research articles, another 21 articles were excluded (no sufficient data (n = 8); editorial or news (n = 2) and reviews (n = 11); Supplementary Table S2). Finally, 12 articles met the eligibility criteria and were included in the meta-analysis (Figure 1). The characteristics of the included studies are listed in Table 1. Twelve studies involving 1,256,609 cases (991,268 physically active cases and 265,341 physically inactive cases) reported COVID-19 hospitalisation, but it did not reach a statistically significant difference (RR = 0.90, 95% CI 0.35–2.34; P = 0.83). Resistance exercise was significantly associated with reduction in COVID-19 hospitalisation (RR = 0.27, 95% CI 0.15–0.49; P = 0.0001; Figure 2b).

3.2 Physical activity and the risk of coronavirus disease 2019 hospitalisation

Six studies involving 441,651 cases (360,605 physically active cases and 81,046 control cases) reported COVID-19 hospitalisation. Overall, PA was significantly associated with a reduction in COVID-19 hospitalisation compared with control (RR = 0.58, 95% CI 0.46–0.73, P = 0.00001). Significant heterogeneity was observed among the included studies (I² = 92%, P = 0.00001; Figure 2a). According to the study types, the pooled main effect of PA on COVID-19 hospitalisation in cohort and cross-sectional studies were RR, 0.58 (95% CI: 0.38, 0.89; P = 0.01) and RR, 0.57 (95% CI: 0.43, 0.77; P = 0.0003), respectively. Subgroup analysis of PA-induced adaptation according to the type of exercise showed that endurance exercise positively affected COVID-19 hospitalisation, but it did not reach a statistically significant difference (RR = 0.90, 95% CI 0.35–2.34, P = 0.83). Resistance exercise was significantly associated with reduction in COVID-19 hospitalisation (RR = 0.27, 95% CI 0.15–0.49, P = 0.0001; Figure 2b).

3.3 Physical activity and risk of coronavirus disease 2019 intensive care unit admissions

Six studies involving 130,774 cases (77,435 physically active cases and 53,339 control cases) were included. The random-effect model showed that PA was associated with reduction in COVID-19 ICU admissions compared with control (RR = 0.65, 95% CI 0.52–0.81, P = 0.0001). The value of I² = 73% indicated that significant heterogeneity exists in the included studies (P = 0.0001; Figure 3a). The pooled main effects were comparable for the different study designs: RR = 0.67, 95% CI: 0.51, 0.89; P = 0.005 (cohort studies) and RR = 0.60, 95% CI: 0.43, 0.86; P = 0.004 (cross-sectional studies). Subgroup analyses that stratified studies based on different PA-induced adaptation showed that the positive effects of endurance and resistance exercises on COVID-19 ICU admissions did not reach a statistically significant difference.

Table 2. Characteristics of comorbidity for different groups among the included studies

| Study                  | Group (n)          | BMI, mean (SD) | Diabetes, n (%) | CVD, n (%) | Hypertension, n (%) | COPD, n (%) | Smoker, n (%) |
|------------------------|--------------------|----------------|-----------------|------------|---------------------|-------------|---------------|
| Lee et al. 2021 16     | Insufficient training (41,293) | 23.8 (3.9) | 3738 (9.1) | 1372 (3.3) | 8245 (20.0) | NR          | 7130 (17.3)   |
|                        | Strength training (18,994)       | 23.7 (3.3) | 355 (7.1) | 151 (3.0) | 832 (16.5) | 934 (18.6)  |               |
|                        | Aerobic training (5036)         | 24.1 (3.8) | 1745 (9.2) | 601 (3.2) | 3866 (20.4) | 3382 (17.8) |               |
|                        | Combined training (11,072)      | 24.1 (3.5) | 680 (6.1) | 233 (2.1) | 1585 (14.3) | 2230 (20.1) |               |
| Salgado-Aranda et al. 2021 17 | Inactive (297) | 25 (11.2) | 2 (3.7) | 1585 (14.3) | 2230 (20.1) |               |               |
|                        | Active (223)                | 26 (11.2) | 2 (3.7) | 1585 (14.3) | 2230 (20.1) |               |               |
| Sallis et al. 2021 18  | Consistently inactive (6984)    | 32.2 (7.39) | 2665 (14.9) | 689 (16.5) | 1682 (15.6) | 788 (14.5)  | 1558 (15.5)   |
|                        | Some activity (38,338)       | 31.3 (7.06) | 15,133 (81.1) | 3410 (81.6) | 8827 (81.7) | 4449 (81.7) | 8008 (79.6)   |
|                        | Consistently meeting PA guidelines (3118) | 28.2 (5.45) | 851 (3.4) | 82 (2) | 297 (2.7) | 210 (3.9) | 492 (4.9) |
| Yuan et al. 2021 19    | Inactive (103)               | 19 (18.4) | 14 (13.6) | 37 (35.9) | 10 (9.7) | 9 (8.7)     |               |
|                        | Active (61)                 | 12 (19.7) | 4 (6.6) | 15 (24.6) | 2 (3.3) | 8 (13.1)    |               |

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; NR, not reported.
### Table 3: Summary of the Newcastle-Ottawa scale for bias assessment of included studies

| Cohort study | Selection (4) | Comparability (2) | Outcome (3) | Total |
|--------------|---------------|-------------------|-------------|-------|
| **Author**   | **Representativeness of exposed cohort** | **Selection of non-exposed cohort** | **Ascertainment of exposure** | **Demonstration that outcome of interest was not present at the start of study** | **Study control for age and sex** | **Additional factors; controlled for ≥2 variables including comorbidities** | **Assessment of outcome** | **Was follow-up long enough for outcomes to occur** | **Adequacy of follow up of cohorts** | **Score** |
| Ahmadi et al. 2021 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 8 |
| Hamer et al. 2020 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 8 |
| Hamrouni et al. 2021 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 8 |
| Lee et al. 2021 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 9 |
| Salgado-Aranda et al. 2021 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 9 |
| Sallis et al. 2021 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 9 |

| Cross-sectional study | Selection (5) | Comparability (2) | Outcome (3) | Total |
|------------------------|---------------|-------------------|-------------|-------|
| **Author**             | **Representativeness of the sample** | **Sample size** | **Non-respondents** | **Ascertainment of exposure** | **The subjects in different outcome groups are comparable, based on the study design or analysis. Confounding factors are controlled.** | **Assessment of the outcome** | **Statistical test** | **Score** |
| de Souza et al. 2021    | 1 | 0 | 1 | 2 | 1 | 1 | 1 | 7 |
| Maltagliati et al. 2021 | 1 | 1 | 1 | 2 | 1 | 1 | 1 | 8 |
| Yuan et al. 2021       | 1 | 0 | 1 | 2 | 2 | 1 | 1 | 8 |
| Cho et al. 2021        | 1 | 1 | 1 | 2 | 1 | 1 | 1 | 8 |
| Ekblom-Bak et al. 2021 | 1 | 0 | 1 | 2 | 1 | 1 | 1 | 7 |
| Halabchi et al. 2021   | 1 | 1 | 1 | 2 | 1 | 1 | 1 | 8 |
(RR = 0.78, 95% CI 0.45–1.35, P = 0.38 and RR = 0.75, 95% CI 0.50–1.13, P = 0.17; respectively). Whereas aerobic plus muscle strength training was significantly associated with a reduction in COVID-19 ICU admissions (RR = 0.53, 95% CI 0.38–0.74, P = 0.0002; Figure 3b). Subgroup analyses that stratified studies based on different PA levels, showed no difference between low and moderate-vigorous levels on the decreased risk of COVID-19 ICU admissions (RR = 0.66, 95% CI 0.49–0.89, P = 0.006 and RR = 0.62, 95% CI 0.48–0.80, P = 0.0003, respectively). Although, stratifying studies based on different PA levels decreased heterogeneity to $I^2 = 0\%$ (P = 0.80, Figure 3c).

3.4 Physical activity and risk of coronavirus disease 2019 mortality

In total, nine studies involving 867,978 cases (670,357 physically active cases and 197,621 control cases) were included within this
There was a statistically significant association between PA with reduction in COVID-19 mortality compared with control (RR = 0.47, 95% CI 0.38–0.59, P = 0.00001). The heterogeneity between studies was high, $I^2 = 78\%$ (P = 0.00001; Figure 4a). The RRs observed in the cohort and cross-sectional studies were 0.50 (95% CI: 0.39, 0.64,
P = 0.00001), and 0.41 (95% CI: 0.23, 0.72, P = 0.002), respectively (Figure 4b). Subgroup analyses of PA-induced adaptation demonstrated a positive association between endurance exercise with reduction in COVID-19 mortality (RR = 0.41, 95% CI 0.23–0.74, P = 0.003). In addition, resistance exercise did not have a significant effect on reducing COVID-19 mortality (RR = 0.13, 95% CI 0.01–0.26, P = 0.15). The positive effect of combined training in reducing COVID-19 mortality, did not reach a statistically significant level (RR = 0.23, 95% CI 0.06–0.97, P = 0.05), (Figure 4c). Subgroup analyses that stratified studies based on different PA levels in cohort and cross-sectional studies showed no difference between low and moderate-vigorous levels on the risk of COVID-19 mortality (in cohort studies: RR = 0.67, 95% CI 0.54–0.84, P = 0.0004 and RR = 0.56, 95% CI 0.49–0.64, P = 0.00001, respectively; in cross-sectional studies: RR = 0.42, 95% CI 0.24–0.75, P = 0.003 and RR = 0.34, 95% CI 0.21–0.54, P = 0.00001, respectively). By stratifying studies based on different PA levels, heterogeneity decreased to I² = 0% in both cohort (P = 0.43) and cross-sectional studies (P = 0.95, Figure 4d).

### 3.5 | Sensitivity analysis and publication bias

In sensitivity analyses, the overall pooled estimates of the respective outcomes obtained in each analysis closely resembled the preliminary associations. Further, funnel plots were checked for the included studies, which suggested no noticeable bias in the present meta-analysis (Figure 5). Additionally, Begg’s correlation rank and Egger’s regression did not show significant publication bias (Table 4).

### 4 | DISCUSSION

In this study, we performed pooled analyses to estimate the hospitalisation, ICU admissions, and mortality rates of COVID-19 patients based on prior PA engagement. This study is the first meta-analysis to comprehensively compare disease severity in COVID-19 patients according to previous PA levels. The present meta-analysis indicates that PA decreases the risk of hospitalisation, ICU admissions, and mortality rates of patients with COVID-19. Moreover, patients with low PA intensity had comparable outcomes with those who had moderate to vigorous activities, suggesting any amount of PA may be beneficial. Furthermore, subgroup analysis showed that the protective effect of PA on COVID-19 hospitalisation and mortality is strongest for resistance exercise and endurance exercise, respectively.

Previous studies have demonstrated that PA reduces the incidence of non-communicable and chronic diseases and the mortality in infectious diseases. The beneficial effects of regular PA on the immune system have been considered one of the main underlying mechanisms in reducing severe outcomes in both chronic and infectious diseases and their subsequent hospitalisation. Additionally, regular PA has been shown to boost innate immune system responses, including the production of macrophages, natural killer cells, and neutrophils. More importantly, there is an improvement in acquired immune system function including T cells and antibody responses following regular PA. In addition to the direct effects of PA on the immune system, the metabolic regulation as a result of participating in regular PA can also improve the innate immune system’s response to pathogens. Taken together, these mechanisms partly explain the relationship between PA and COVID-19 severe outcomes in the present meta-analysis.
In addition to the beneficial effects on the immune system, PA also brings cardiorespiratory and musculoskeletal adaptations. According to the present results, increased muscle strength was associated with a reduced risk of COVID-19 hospitalisation. Considering the effects of age on increasing hospitalisation and the observed anti-sarcopenia effects of PA, participating in regular PA...
can promote muscle strength while maintaining muscle mass, which effectively prevents the occurrence of severe cases of disease.\textsuperscript{50,51} Interaction between exercised skeletal muscle and the immune system may be owing to the production of anti-inflammatory cytokines such as IL-6.\textsuperscript{52} Moreover, in some progressive diseases such as some types of cancer, the maintenance of muscle mass has been associated with more effective immune responses to fight against the severe outcomes of the disease.\textsuperscript{53,54} Taken together, the present findings and discussed mechanisms indicate that improved muscle strength may be protective from hospitalisation in COVID-19 disease. However, more studies are needed to investigate this issue.

In the present meta-analysis, PA was associated with reducing the risk of ICU admission and mortality in COVID-19 patients. Moreover, the risk of mortality was associated with a lower baseline physical fitness. It has been suggested that preexisting health conditions are a major cause of mortality in COVID-19.\textsuperscript{55} Christensen et al. (2021) have also suggested that although cardiorespiratory fitness may not predict COVID-19 infection, it was a predictor of disease progression and mortality.\textsuperscript{56} The current study results also support the relationship between the rate of mortality and aerobic fitness. Also, based on the present meta-analysis results, combined exercises may reduce ICU admission rate, which may effectively
reduce mortality risk. It seems that cardiorespiratory and muscular adaptations following regular combined exercise training can effectively prevent severe cases and mortality from COVID-19 disease.

Based on the present meta-analysis results, there is no significant difference between low and high levels of PA in ICU admission and mortality rates in COVID-19 patients. Although some studies suggested a link between higher levels of PA and a reduction in COVID-19 mortality, according to the European CVD Prevention Guidelines, 500-100 MET per week is enough to reduce the risk of cardiovascular diseases. Moreover, according to the J-shaped theory of the immune system, long-term high-intensity exercise training can also effectively suppress immune system responses and develop upper respiratory infections. Taken together, even moderate to low levels of PA can reduce the risk of severe COVID-19 and mortality. Although, more studies in this field can be helpful.

An important issue raised just after the outbreak of COVID-19 is the decline in PA levels. A population-based study has shown that PA decreased by up to about 27.3% just 30 days after the onset of the COVID-19 pandemic. The potential risks of decreased PA in communities and new variants of the virus (e.g. delta and omicron) requires attention, as the present meta-analysis results indicate that PA is associated with the risk of COVID-19 severe outcomes. General recommendations should continue to seek to improve the level of PA to counteract with possible new strains.

Findings from the present meta-analysis must be interpreted in light of its limitations. First, because most of the studies included in our analysis did not report comorbidities associated with severe COVID-19 outcomes, the association of PA with adverse COVID-19 outcomes may be more exaggerated than indicated by the estimates. More prospective and well-organised studies are warranted to determine the leading cause of hospitalisation and mortality in COVID-19 patients and evaluate the impact of different aetiologies and clinical factors on prognosis. Second, most of the included studies used the International PA Questionnaire to measure PA behaviour and have not provided enough information about the types of PA and the possibility to reduce COVID-19 outcomes. Third, overall pooled analyses indicated a relationship between PA and COVID-19 severe outcomes. However, our results did not reach statistically significant levels in some analyses likely owing to the paucity of included studies.
in relation to PA type and COVID-19 severe outcomes. Therefore, further studies should consider evaluating the impact of specific types of PA on COVID-19 outcomes. Finally, definitions used for the intensity of PA varied between studies and should be consistent in future studies.

5 | CONCLUSION

In this meta-analysis, we showed that PA decreases the hospitalization, ICU admission, and mortality rates of COVID-19 patients. Additionally, COVID-19 patients with a history of resistance and endurance exercises experience a lower rate of hospitalization and mortality, respectively. The findings of this meta-analysis suggest that public health authorities should continue to encourage people to participate in recommended levels of PA during the COVID-19 pandemic while following public health safety guidelines.

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CONFLICT OF INTEREST
The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS
Masoud Rahmati and Jae Il Shin developed the idea and designed the study and had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Masoud Rahmati and Fatemeh Malakoutinia ran the search strategy; Masoud Rahmati, Fatemeh Malakoutinia, Mahdieh Molanouri Shamsi and Kayvan Khoramipour selected articles and extracted data; Masoud Rahmati evaluated the quality of the literature. Masoud Rahmati, Mahdieh Molanouri Shamsi and Kayvan Khoramipour wrote the manuscript, and Wongi Woo, Seoyeon Park, Dong K Yon, Seung Won Lee, Jae Il Shin and Lee Smith edited it. All listed authors reviewed and approved the final manuscript.

DATA AVAILABILITY STATEMENT
All data relevant to the study are included in the article or uploaded as supplementary information. The data are available by accessing the published studies listed in Table 1.

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**SUPPORTING INFORMATION**

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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