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

Running head: Physical activity and COVID-19.

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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 Table1.

Abstract

Objective: Among 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 hospitalization, 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.

Methods: A systematic search of MEDLINE/PubMed, CINAHL, 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.

Results: 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 hospitalization (RR= 0.58, 95% CI 0.46 to 0.73, P=0.001), ICU admissions (RR= 0.65, 95% CI 0.52 to 0.81, P=0.001) and mortality (RR= 0.47, 95% CI 0.38 to 0.59, P=0.001). The protective effect of PA on COVID-19 hospitalization and mortality could be attributable to the types of exercise such as resistance exercise (RR= 0.27, 95% CI 0.15 to 0.49, P=0.001) and endurance exercise (RR= 0.41, 95% CI 0.23 to 0.74, P=0.003), respectively.

Conclusion: PA is associated with decreased hospitalization, 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 hospitalization and mortality, respectively. Further studies are warranted to determine the biological mechanisms underlying these findings.

Keywords: COVID-19, Physical activity, Exercise, Meta-analysis.

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

1. Introduction

The rapid spread of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has led to 282 million confirmed cases and 5.4 million deaths [1]. 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. [2] 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 [3]. 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)[4]. Meyer et al, [5] 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 [6,7]. 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 increase the risk of SARS-CoV-2 infection as well as the severity and mortality rate [8]. Importantly, obesity and hypertension were the most prevalent disorders reported in hospitalized and deceased patients due to COVID-19 [9-11].

Several studies have shown that a baseline sedentary lifestyle increases the mortality of hospitalized patients with COVID-19 [12-19]. Moreover, engaging in healthy lifestyle behaviors may protect against the most severe consequences of COVID-19 disease including systemic inflammation, and reduced quality of life [12,20,21]. Importantly, an unhealthy lifestyle has been considered a risk factor for COVID-19 hospital admission [15]. Different mechanisms may explain the protective effect of PA on COVID-19 outcomes and disease severity [14]. 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 [22-25]. Moreover, regular PA reduces the risk of systemic inflammation, which is considered the primary contributor to lung damage in COVID-19 patients [26]. Additionally, it has a protective impact on COVID-19 risk factors such as obesity and hypertension [9,14]. Furthermore, we previously reported that a sedentary lifestyles increase the risk of COVID-19 severity and mortality [16]. Further, high hospitalization rates have been reported in patients with less cardiorespiratory fitness [27].

Given this mortality risk in physically inactive COVID-19 patients, this meta-analysis aims to explore the hospitalization, 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 [28]. The present study's findings were reported in accordance with the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) statement (Supplementary Material S1) [29].

2.1. Search strategy

Relevant studies were systematically searched in electronic databases including MEDLINE/ PubMed, CINAHL, 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 "hospitalization" or "intensive care") and ("physical activity," or "exercise training," or "physical training," or "exercise activity") (Supplementary Material S2). Furthermore, we searched all reference lists of included studies for any other eligible articles. Language restriction was not considered.

2.2. Eligibility Criteria

The Eligibility criteria followed the PICOs question [30]. 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, hospitalization, and ICU admission. Furthermore, editorials, 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 (M.A., F.M.) 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 9 points [31]. Studies with NOS scores of 0 to 3, 4 to 6, and 7 to 9 were considered low, moderate, and high quality, respectively [32].

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 [13,16,33]. 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) [34]. 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 to 49%, 50 to 74% and 75 to 100% were interpreted as low, moderate, substantial and considerable heterogeneity [34]. 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.

3. Results

3.1. Study identification and characteristics

A total of 1956 potentially relevant articles were identified in our literature search. Four hundred and sixty 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) [35]. Finally, twelve 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) were included in the meta-analysis. Publication ranged from 2020 to 2021 and the majority of these were from European countries, Iran, China, US, Korea, and Brazil; Characteristics of comorbidity for different groups among the included studies were reported in four studies [16-19] and are listed in Table 2. All included studies were of high quality with NOS scores equal to or greater than 7 (Table 3). The designs of the included studies were as follows: cohort (n = 6) and cross-sectional (n = 6) and we performed a subgroup analysis based on different study types.

3.2. Physical activity and the risk of COVID-19 hospitalization

Six studies involving 441,651 cases (360,605 physically active cases and 81,046 control cases) reported COVID-19 hospitalization[8,14,15,18,36,37]. Overall, PA was significantly associated with a reduction in COVID-19 hospitalization compared with control (RR= 0.58, 95% CI 0.46 to 0.73, P=0.00001). Significant heterogeneity was observed among the included studies (I^2=92%, P=0.00001) (Figure 2A). According to the study types, the pooled main effect of PA on COVID-19 hospitalization 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 hospitalization, but it did not reach a statistically significant difference (RR= 0.90, 95% CI 0.35 to 2.34, P=0.83). Resistance exercise was significantly associated with reduction in COVID-19 hospitalization (RR= 0.27, 95% CI 0.15 to 0.49, P=0.0001; Figure 2B).

3.3. Physical activity and risk of COVID-19 ICU admissions

Six studies involving 130,774 cases (77,435 physically active cases and 53,339 control cases) were included [8,14,16-19]. 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 to 0.81, P=0.0001). The value of I^2=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 (RR= 0.78, 95% CI 0.45 to 1.35, P=0.38 and RR= 0.75, 95% CI 0.50 to 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 to 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 to 0.89, P=0.006 and RR= 0.62, 95% CI 0.48 to 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 COVID-19 mortality

In total, nine studies involving 867,978 cases (670,357 physically active cases and 197,621 control cases) were included within this meta-analysis [8,12-14,16-19,38]. There was a statistically significant association between PA with reduction in COVID-19 mortality compared with control (RR= 0.47, 95% CI 0.38 to 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 to 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 to 2.06, 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 to 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 to 0.84, P=0.0004 and RR= 0.56, 95% CI 0.49 to 0.64, P=0.00001, respectively; in cross-sectional studies: RR= 0.42, 95% CI 0.24 to 0.75, P=0.003 and RR= 0.34, 95% CI 0.21 to 0.54, P=0.00001, respectively). By stratifying studies based on different PA levels, heterogeneity decreased to I^2=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 hospitalization, 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 hospitalization, 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 hospitalization 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 [39,40]. 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 hospitalization [41-43]. Additionally, regular PA has been shown to boost innate immune system responses, including the production of macrophages, natural killer cells, and neutrophils [25,44]. More importantly, there is an improvement in acquired immune system function including T cells and antibody responses following regular PA [45,46]. 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 [47]. 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 [48]. According to the present results, increased muscle strength was associated with a reduced risk of COVID-19 hospitalization. Considering the effects of age on increasing hospitalization [49] and the observed anti-sarcopenia effects of PA [50], participating in regular PA can promote muscle strength while maintaining muscle mass, which effectively prevents the occurrence of severe cases of disease [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 [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 [53,54]. Taken together, the present findings and discussed mechanisms indicate that improved muscle strength may be protective from hospitalization 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 [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 [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 Cardiovascular Disease Prevention Guidelines, 500-100 MET per week is enough to reduce the risk of cardiovascular diseases [57]. 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 [58]. 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 [59]. 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-organized studies are warranted to determine the leading cause of hospitalization and mortality in COVID-19 patients and evaluate the impact of different etiologies and clinical factors on prognosis. Second, most of the included studies used the International Physical Activity Questionnaire to measure PA behavior 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.

CONFLICT OF INTERESTS

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 Table1.

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Figure Legends

Figure 1. PRISMA flow diagram of study selection.

Figure 2. Forest plot of the relationship between physical activity and the risk of COVID-19 hospitalization based on different (A) study type and (B) physical activity- induced adaptations.

Figure 3. Forest plot of the relationship between physical activity and the risk of COVID-19 ICU admissions based on (A) study type, (B) physical activity- induced adaptations and (C) physical activity levels.

Figure 4. Forest plot of the relationship between physical activity and the risk of COVID-19 mortality based on (A) study type, (B) physical activity- induced adaptations and physical activity levels in cohort (C) and (D) cross-sectional studies.

Figure 5. Funnel plots for publication bias on fatal outcomes of COVID-19.

Tables

Table 1. General characteristics of included studies.

Study	Design	Country	Physical activity documentation	Age (year)	Gender	COVID-19 diagnosis	Outcome			
							Group (n)	Hospitalization, 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) Insufficient (140 609) Sufficient (232 603)	NR	NR	112 (12%) 115 (0.08%) 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) Light (1752) Moderate (861) Vigorous (2362) Moderate to vigorous (3223)	NR	NR	31 (33.7%) 27 (29.3%) 4 (4.3%) 13 (14.1%) 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) 1 times/week (192) ≥2 times/week (261)	36 (13.8%) 19 (9.9%) 36 (7.4%)	NR	NR
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) 1–2 times/week (254) ≥3 times/week (232)	181 (36%) 157 (32%) 159 (32%)	67 (43%) 49 (31%) 41 (26%)	45 (36%) 48 (38%) 32 (26%)
Halabchi et al. 2021 [8]	Cross-sectional	Iran	Electronic health record	492.3 ± 11.9	F= 2629 M= 2065	RT-PCR	Inactive (4445) Active (249)	820 (18.4) 28 (11.2)	58 (1.3) 2 (0.8)	79 (1.8) 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) Insufficient (108 707) Sufficient (209 489)	186 (27%) 192 (17%) 382 (18%)	NR	NR
Hamrouni et al. 2021 [38]	Prospective cohort	UK	International physical activity questionnaire	37-73	F= 135 884 M= 123 603	RT-PCR	Low (47 827) Moderate (105 564) High (106 006)	NR	NR	109 (27%) 150 (38%) 138 (34%)
Lee et al. 2021 [16]	Nationwide cohort	Korea	Personal medical interview	20-60	F= 37 272 M= 39 123	RT-PCR	Insufficient training (41 293) Resistance training (18 994) Endurance training (5036) Combined training (11 072)	NR	273 (21.1) 25 (16.7) 109/561 (19.4) 39/291 (13.4)	32 (2.5) 0 (0.0) 11 (2.0) 2 (0.7)
Maltagliati et al. 2021 [37]	Cross-sectional	27 European countries	Self-reported questionnaire	69.3 ± 8.5	F= 1763 M= 1376	RT-PCR	Hardly ever or never (1167) 1 times/week (541) >1 times/week (1161) 1-3 times/month (270)	36 (54%) 10 (15%) 15 (23%) 5 (/%)	NR	NR
Salgado-Aranda et al. 2021 [17]	Retrospective cohort	Spain	Rapid physical activity questionnaire	54.3±10.7	F= 236 M= 284	RT-PCR	Inactive (297) Active (223)	NR	26 (8.8%) 14 (6.3%)	41 (13.8%) 4 (1.8%)
Sallis et al. 2021 [18]	Retrospective observational cohort	US	Electronic health record	47.5 ±16.97	F= 29 992 M= 18 447	RT-PCR	Consistently inactive (6984) Some activity (38 338) Consistently meeting PA guidelines (3118)	732 (10.5%) 3405 (8.9%) 99 (3.2%)	195 (2.8%) 972 (2.5%) 32 (1%)	170 (2.4%) 590 (1.5%) 11 (0.4%)
Yuan et al. 2021 [19]	Cross-sectional	China	Personal medical interview	61.8±13.6	F= 80; M= 84	RT-PCR	Inactive (103) Active (61)	NR	26 (25.2) 3 (4.9)	6 (5.8) 0 (0.0)

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 (%)
		Comorbidity factor					
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)	NR	44 (14.8)	10 (3.4)	107 (36)	20 (6.7)	20 (6.7)
	Active (223)		25 (11.2)	6 (2.7)	55 (24.7)	5 (2.2)	8 (3.6)
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)	NR	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)

BMI, body mass index; CVD, cardiovascular disease; COPD, chronic obstructive pulmonary disease.

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**	**9**
Ahmadi et al. 2021 [12]	1	1	1	1	1	0	1	1	1	8
Hamer et al. 2020 [15]	1	1	1	1	1	0	1	1	1	8
Hamrouni et al. 2021 [38]	1	1	1	1	1	0	1	1	1	8
Lee et al. 2021 [16]	1	1	1	1	1	1	1	1	1	9
Salgado-Aranda et al. 2021 [17]	1	1	1	1	1	1	1	1	1	9
Sallis et al. 2021 [18]	1	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**	**10**
de Souza et al. 2021 [36]	1	0	1	2	1		1		1	7
Maltagliati et al. 2021 [37]	1	1	1	2	1		1		1	8
Yuan et al. 2021 [19]	1	0	1	2	2		1		1	8
Cho et al. 2021 [13]	1	1	1	2	1		1		1	8
Ekblom-Bak et al. 2021 [14]	1	0	1	2	1		1		1	7
Halabchi et al. 2021 [8]	1	1	1	2	1		1		1	8

Table 4. Results of the subgroup analysis based on fatal outcomes of COVID-19.

Risk factors	Effect measures	Number of study	Effect size (95% CI)	Heterogeneity		*Begg's t*est P-value	*Egger's* test P-value
				I^2	P-value		
Hospitalization rate	RR	6	0.58 (0.46-0.73)	92%	0.00001	1.98	0.657
Hospitalization rate based on Type of exercise	RR	2	0.50 (0.22-1.10)	96%	0.00001	1.93	0.102
ICU admissions rate	RR	6	0.65 (0.52-0.81)	73%	0.0001	1.92	0.534
ICU admissions rate based on PA levels	RR	1	0.64 (0.52-0.77)	0%	0.80	1.74	0.217
ICU admissions rate based on Type of exercise	RR	4	0.74 (0.50-1.09)	85%	0.00001	1.70	0.86
Mortality rate	RR	9	0.47 (0.38-0.59)	78%	0.00001	1.85	0.141
Mortality rate based on type of exercise	RR	3	0.38 (0.22-0.67)	83%	0.00001	1.78	0.819
Mortality rate based on PA levels in cohort studies	RR	4	0.59 (0.53-0.66)	0%	0.43	1.77	0.309
Mortality rate based on PA levels in cross-sectional studies	RR	1	0.37 (0.25-0.52)	0%	0.95	1.26	0.367

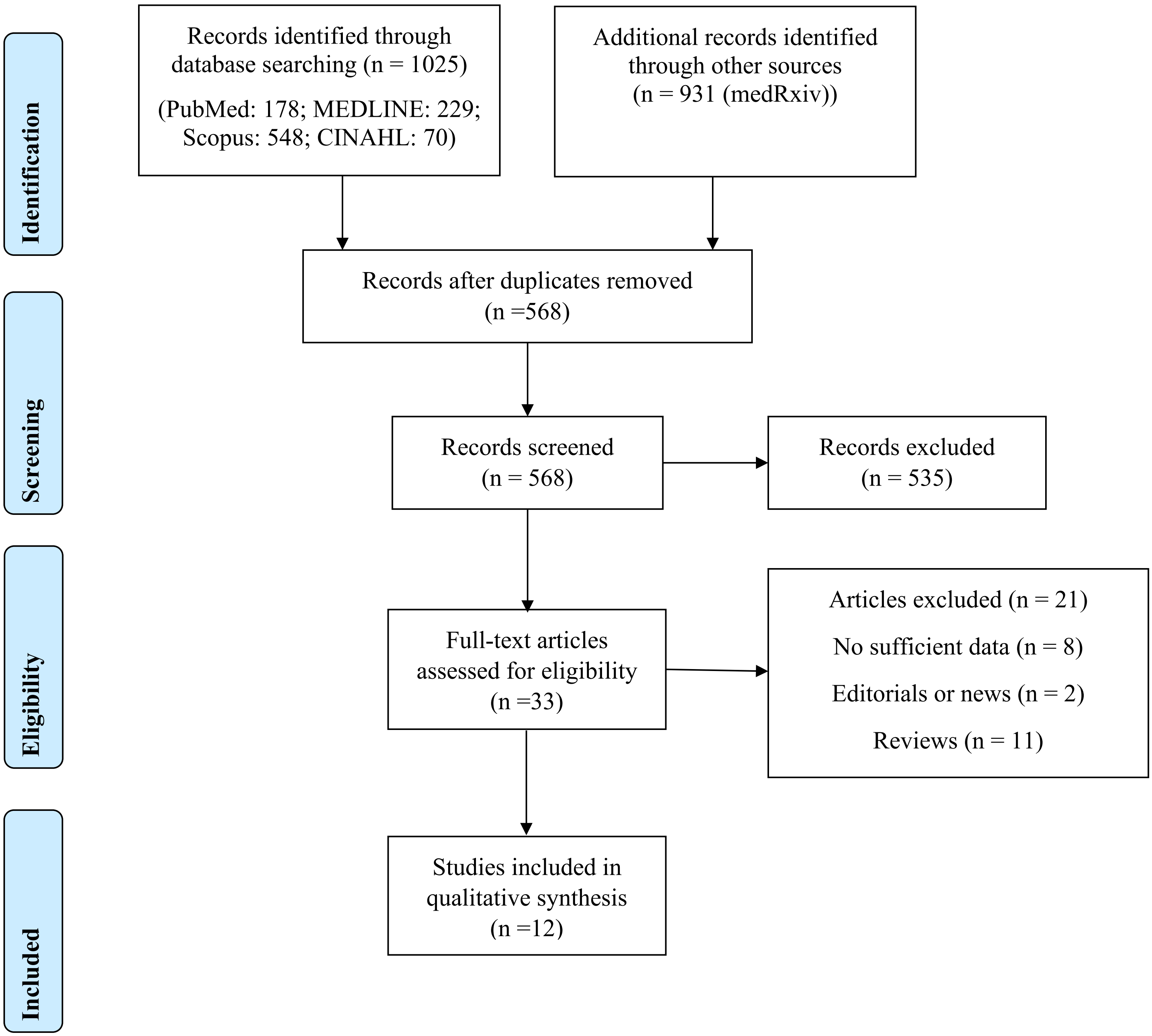
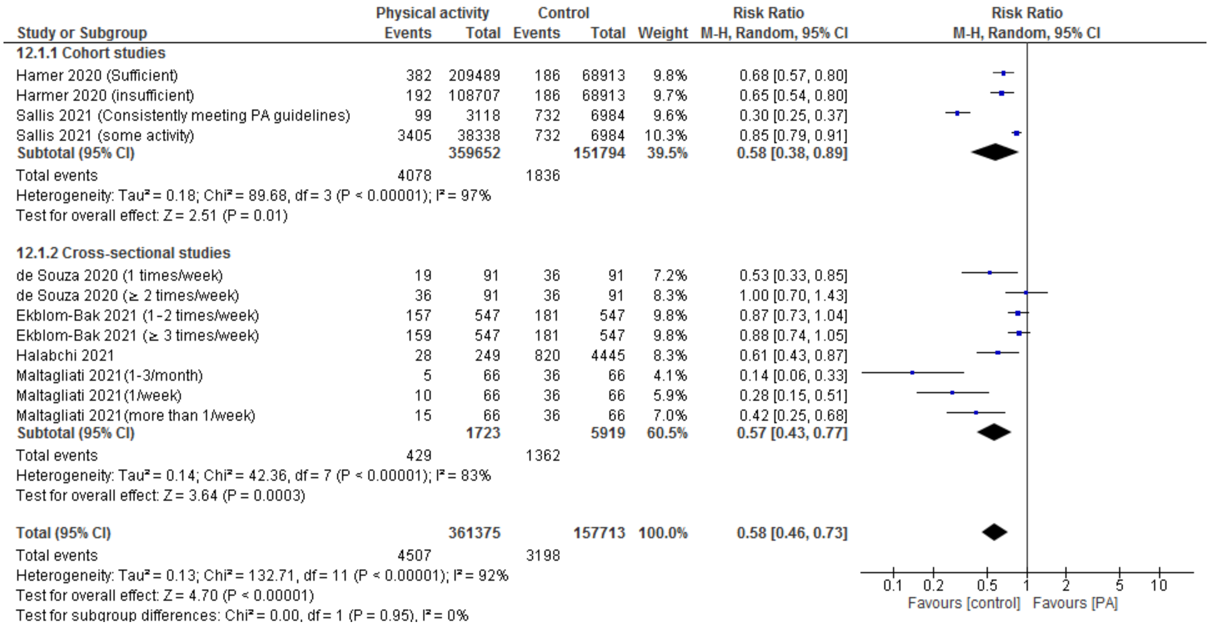


Figure 1. PRISMA flow diagram of study selection.

A: Effect of any type of exercise on COVID-19 hospitalization by study type



B: Effect of type of exercise on COVID-19 hospitalization.

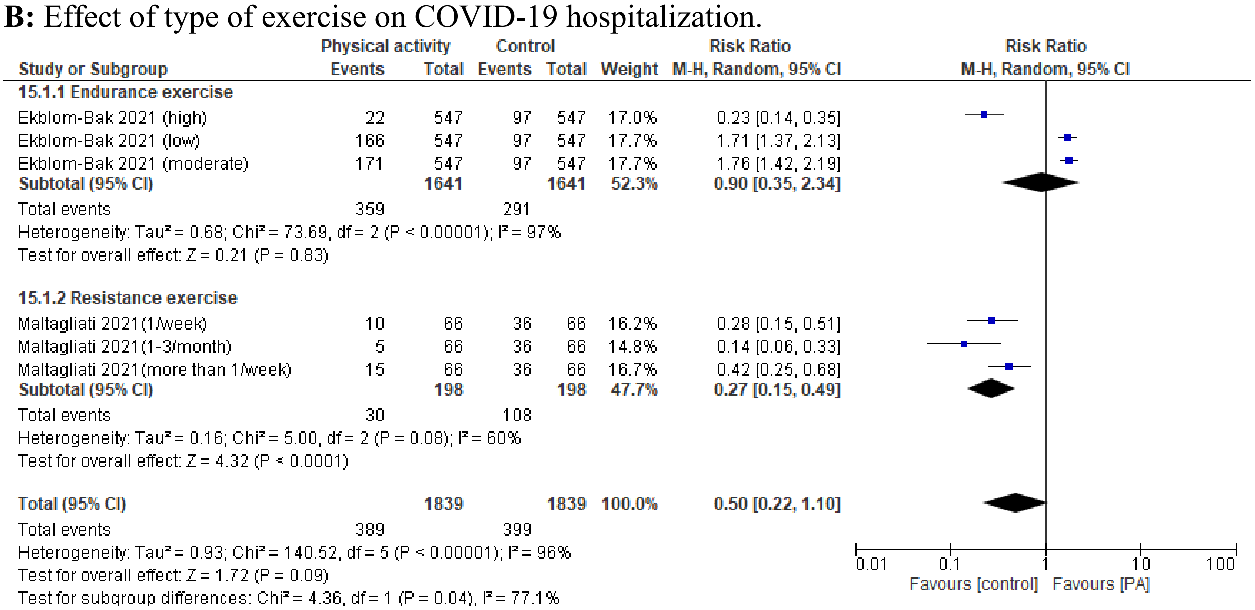
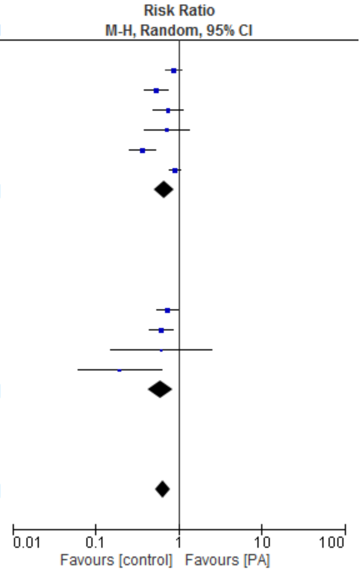


Figure 2

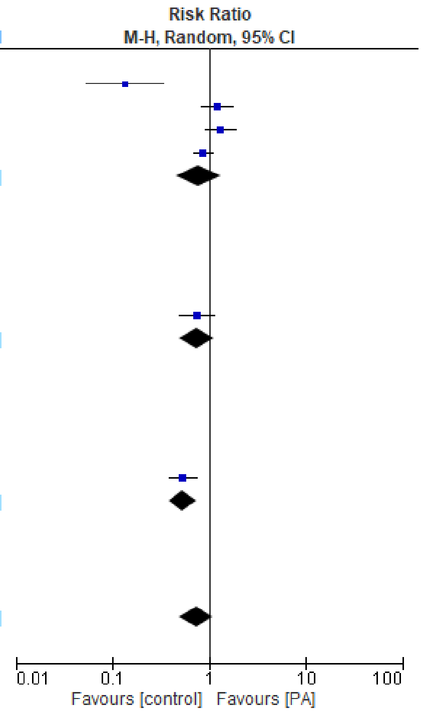
A: Effect of any type of exercise on COVID-19 ICU admission by study type.

Study or Subgroup	Physical activity Events	Physical activity Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
13.1.1 Cohort studies						
Lee 2021 (Aerobic training)	109	18994	273	41293	14.2%	0.87 [0.70, 1.08]
Lee 2021 (Combined training)	39	11072	273	41293	11.9%	0.53 [0.38, 0.74]
Lee 2021 (Strength training)	25	5036	273	41293	10.5%	0.75 [0.50, 1.13]
Salgado-Aranda 2021	14	223	26	297	7.0%	0.72 [0.38, 1.34]
Sallis 2021 (Consistently meeting PA guidelines)	32	3118	195	6984	11.2%	0.37 [0.25, 0.53]
Sallis 2021 (some activity)	972	38338	195	6984	15.4%	0.91 [0.78, 1.06]
Subtotal (95% CI)		**76781**		**138144**	**70.3%**	**0.67 [0.51, 0.89]**
Total events	1191		1235			
Heterogeneity: Tau² = 0.09; Chi² = 25.94, df = 5 (P < 0.0001); I² = 81%						
Test for overall effect: Z = 2.78 (P = 0.005)						
13.1.2 Cross-sectional studies						
Ekblom-Bak 2021 (1-2 times/week)	49	172	67	172	12.6%	0.73 [0.54, 0.99]
Ekblom-Bak 2021 (≥ 3 times/week)	41	172	67	172	12.1%	0.61 [0.44, 0.85]
Halabchi 2021	2	249	58	4445	2.1%	0.62 [0.15, 2.51]
Yuan 2021	3	61	26	103	2.9%	0.19 [0.06, 0.62]
Subtotal (95% CI)		**654**		**4892**	**29.7%**	**0.60 [0.43, 0.86]**
Total events	95		218			
Heterogeneity: Tau² = 0.05; Chi² = 5.13, df = 3 (P = 0.16); I² = 42%						
Test for overall effect: Z = 2.85 (P = 0.004)						
Total (95% CI)		**77435**		**143036**	**100.0%**	**0.65 [0.52, 0.81]**
Total events	1286		1453			
Heterogeneity: Tau² = 0.07; Chi² = 33.12, df = 9 (P = 0.0001); I² = 73%						
Test for overall effect: Z = 3.91 (P < 0.0001)						
Test for subgroup differences: Chi² = 0.22, df = 1 (P = 0.64), I² = 0%						



B: Effect of type of exercise on COVID-19 ICU admission.

Study or Subgroup	Physical activity Events	Physical activity Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
16.1.1 Endurance exercise						
Ekblom-Bak 2021 (high)	5	172	37	172	9.9%	0.14 [0.05, 0.34]
Ekblom-Bak 2021 (low)	45	172	37	172	17.5%	1.22 [0.83, 1.78]
Ekblom-Bak 2021 (moderate)	49	172	37	172	17.7%	1.32 [0.91, 1.92]
Lee 2021 (Aerobic training)	109	18994	273	41293	19.6%	0.87 [0.70, 1.08]
Subtotal (95% CI)		**19510**		**41809**	**64.7%**	**0.78 [0.45, 1.35]**
Total events	208		384			
Heterogeneity: Tau² = 0.25; Chi² = 23.82, df = 3 (P < 0.0001); I² = 87%						
Test for overall effect: Z = 0.88 (P = 0.38)						
16.1.2 Resistance exercise						
Lee 2021 (Strength training)	25	5036	273	41293	17.1%	0.75 [0.50, 1.13]
Subtotal (95% CI)		**5036**		**41293**	**17.1%**	**0.75 [0.50, 1.13]**
Total events	25		273			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.37 (P = 0.17)						
16.1.3 Combined exercise						
Lee 2021 (Combined training)	39	11072	273	41293	18.2%	0.53 [0.38, 0.74]
Subtotal (95% CI)		**11072**		**41293**	**18.2%**	**0.53 [0.38, 0.74]**
Total events	39		273			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.69 (P = 0.0002)						
Total (95% CI)		**35618**		**124395**	**100.0%**	**0.74 [0.50, 1.09]**
Total events	272		930			
Heterogeneity: Tau² = 0.19; Chi² = 33.45, df = 5 (P < 0.00001); I² = 85%						
Test for overall effect: Z = 1.52 (P = 0.13)						
Test for subgroup differences: Chi² = 2.24, df = 2 (P = 0.33), I² = 10.9%						



C: Effect of level of physical activity exercise on COVID-19 ICU admission.

	Physical activity		Control			Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**
19.1.1 Low intensity						
Lee 2021 (1-500)	109	50052	75	22811	40.7%	0.66 [0.49, 0.89]
Subtotal (95% CI)		**50052**		**22811**	**40.7%**	**0.66 [0.49, 0.89]**
Total events	109		75			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.75 (P = 0.006)						
19.1.2 Moderate-vigrous intensity						
Lee 2021 (500-1000)	49	25932	75	22811	31.6%	0.57 [0.40, 0.82]
Lee 2021 (higher equal than 1000)	44	19973	75	22811	27.7%	0.67 [0.46, 0.97]
Subtotal (95% CI)		**45905**		**45622**	**59.3%**	**0.62 [0.48, 0.80]**
Total events	93		150			
Heterogeneity: Chi² = 0.34, df = 1 (P = 0.56); I² = 0%						
Test for overall effect: Z = 3.64 (P = 0.0003)						
Total (95% CI)		**95957**		**68433**	**100.0%**	**0.64 [0.52, 0.77]**
Total events	202		225			
Heterogeneity: Chi² = 0.45, df = 2 (P = 0.80); I² = 0%						
Test for overall effect: Z = 4.56 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.11, df = 1 (P = 0.74), I² = 0%						

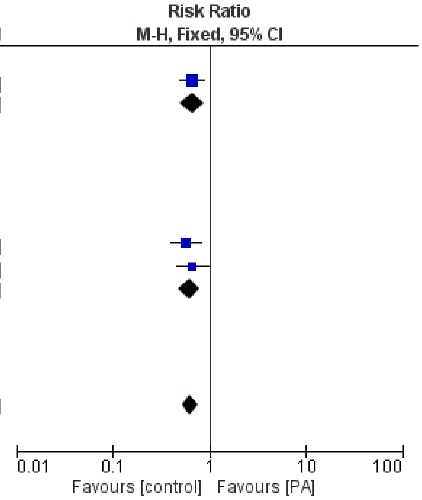
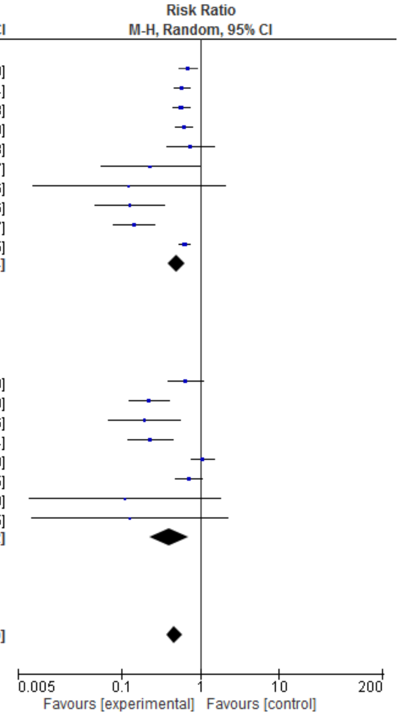


Figure 3

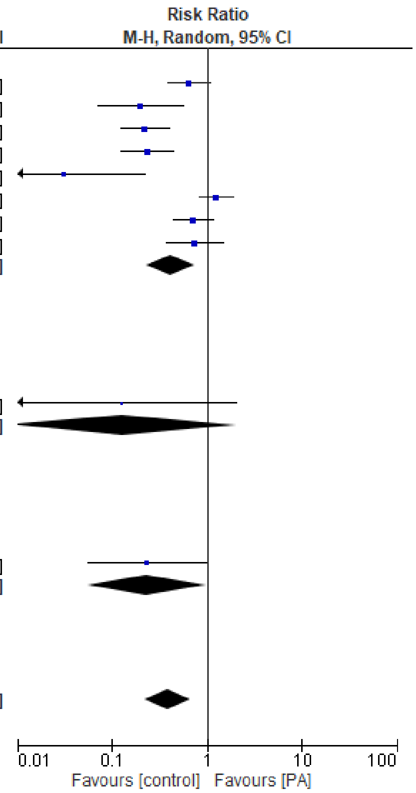
A: Effect of any type of exercise on COVID-19 mortality by study type.

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
11.1.1 Cohort studies						
Ahmadi 2021 (insufficient)	115	140609	112	95221	8.7%	0.70 [0.54, 0.90]
Ahmadi 2021 (sufficient)	160	232613	112	95221	8.9%	0.58 [0.46, 0.74]
Hamrouni 2021 (high intensity training)	138	106006	109	47827	8.8%	0.57 [0.44, 0.73]
Hamrouni 2021 (moderate intensity training)	150	105564	109	47827	8.8%	0.62 [0.49, 0.80]
Lee 2021 (Aerobic training)	11	18994	32	41293	5.2%	0.75 [0.38, 1.48]
Lee 2021 (Combined training)	2	11072	32	41293	2.0%	0.23 [0.06, 0.97]
Lee 2021 (Strength training)	0	5036	32	41293	0.6%	0.13 [0.01, 2.06]
Salgado-Aranda 2021	4	223	41	297	3.3%	0.13 [0.05, 0.36]
Sallis 2021 (Consistently meeting PA guidelines)	11	3118	170	6984	5.8%	0.14 [0.08, 0.27]
Sallis 2021 (some activity)	590	38338	170	6984	9.4%	0.63 [0.53, 0.75]
Subtotal (95% CI)		**661573**		**424240**	**61.6%**	**0.50 [0.39, 0.64]**
Total events	1181		919			
Heterogeneity: Tau² = 0.08; Chi² = 36.37, df = 9 (P < 0.0001); I² = 75%						
Test for overall effect: Z = 5.60 (P < 0.00001)						
11.1.2 Cross-sectional studies						
Cho 2021 (Light)	27	1752	31	1313	6.6%	0.65 [0.39, 1.09]
Cho 2021 (Moderate to vigorous)	17	3223	31	1313	5.9%	0.22 [0.12, 0.40]
Cho 2021 (Moderate)	4	861	31	1313	3.2%	0.20 [0.07, 0.56]
Cho 2021 (Vigorous)	13	2362	31	1313	5.5%	0.23 [0.12, 0.44]
Ekblom-Bak 2021 (1-2 times/week)	48	138	45	138	8.2%	1.07 [0.77, 1.49]
Ekblom-Bak 2021 (≥ 3 times/week)	32	138	45	138	7.7%	0.71 [0.48, 1.05]
Halabchi 2021	0	249	79	4445	0.6%	0.11 [0.01, 1.80]
Yuan 2021	0	61	6	103	0.6%	0.13 [0.01, 2.25]
Subtotal (95% CI)		**8784**		**10076**	**38.4%**	**0.41 [0.23, 0.72]**
Total events	141		299			
Heterogeneity: Tau² = 0.44; Chi² = 40.67, df = 7 (P < 0.00001); I² = 83%						
Test for overall effect: Z = 3.13 (P = 0.002)						
Total (95% CI)		**670357**		**434316**	**100.0%**	**0.47 [0.38, 0.59]**
Total events	1322		1218			
Heterogeneity: Tau² = 0.14; Chi² = 76.46, df = 17 (P < 0.00001); I² = 78%						
Test for overall effect: Z = 6.44 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.44, df = 1 (P = 0.51), I² = 0%						

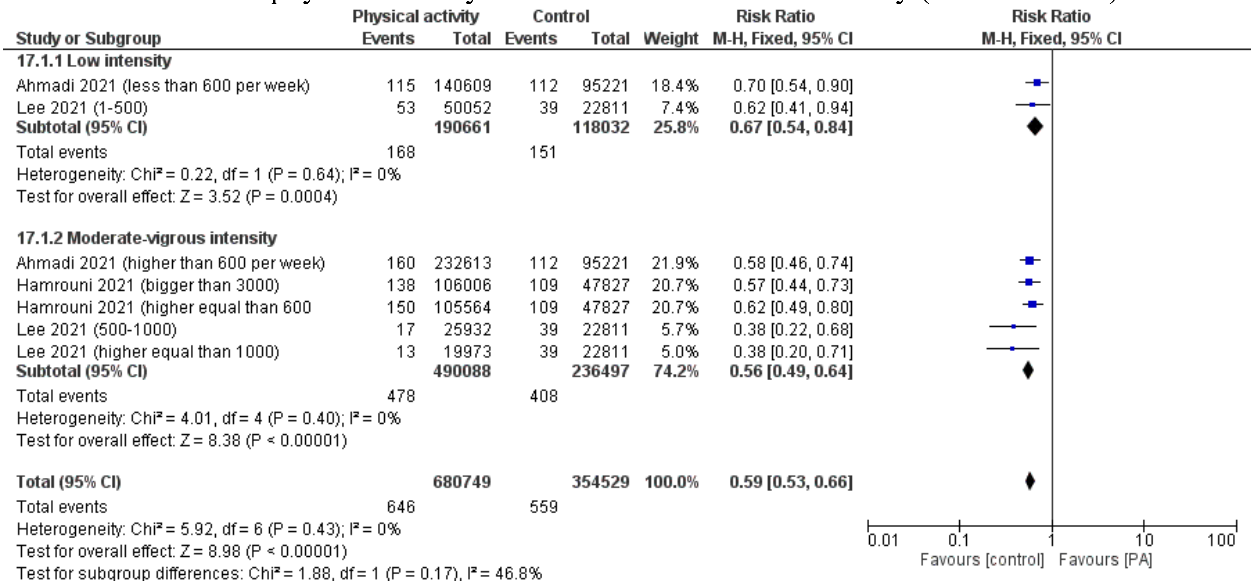


B: Effect of type of exercise on COVID-19 mortality.

Study or Subgroup	Physical activity Events	Physical activity Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
14.1.1 Endurance exercise						
Cho 2021 (Light)	27	1752	31	1313	12.7%	0.65 [0.39, 1.09]
Cho 2021 (Moderate)	4	861	31	1313	9.5%	0.20 [0.07, 0.56]
Cho 2021 (Moderate to vigorous)	17	3223	31	1313	12.3%	0.22 [0.12, 0.40]
Cho 2021 (Vigorous)	13	2362	31	1313	12.0%	0.23 [0.12, 0.44]
Ekblom-Bak 2021 (high)	1	138	32	138	5.1%	0.03 [0.00, 0.23]
Ekblom-Bak 2021 (low)	40	138	32	138	13.3%	1.25 [0.84, 1.87]
Ekblom-Bak 2021 (moderate)	23	138	32	138	12.9%	0.72 [0.44, 1.16]
Lee 2021 (Aerobic training)	11	18994	32	41293	11.7%	0.75 [0.38, 1.48]
Subtotal (95% CI)		**27606**		**46959**	**89.5%**	**0.41 [0.23, 0.74]**
Total events	136		252			
Heterogeneity: Tau² = 0.57; Chi² = 48.80, df = 7 (P < 0.00001); I² = 86%						
Test for overall effect: Z = 2.94 (P = 0.003)						
14.1.2 Resistance exercise						
Lee 2021 (Strength training)	0	5036	32	41293	3.1%	0.13 [0.01, 2.06]
Subtotal (95% CI)		**5036**		**41293**	**3.1%**	**0.13 [0.01, 2.06]**
Total events	0		32			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.45 (P = 0.15)						
14.1.3 Combined exercise						
Lee 2021 (Combined training)	2	11072	32	41293	7.4%	0.23 [0.06, 0.97]
Subtotal (95% CI)		**11072**		**41293**	**7.4%**	**0.23 [0.06, 0.97]**
Total events	2		32			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.00 (P = 0.05)						
Total (95% CI)		**43714**		**129545**	**100.0%**	**0.38 [0.22, 0.67]**
Total events	138		316			
Heterogeneity: Tau² = 0.57; Chi² = 52.11, df = 9 (P < 0.00001); I² = 83%						
Test for overall effect: Z = 3.39 (P = 0.0007)						
Test for subgroup differences: Chi² = 1.10, df = 2 (P = 0.58), I² = 0%						



C: Effect of level of physical activity exercise on COVID-19 mortality (cohort studies).



D: Effect of level of physical activity exercise on COVID-19 mortality (cross-sectional studies).

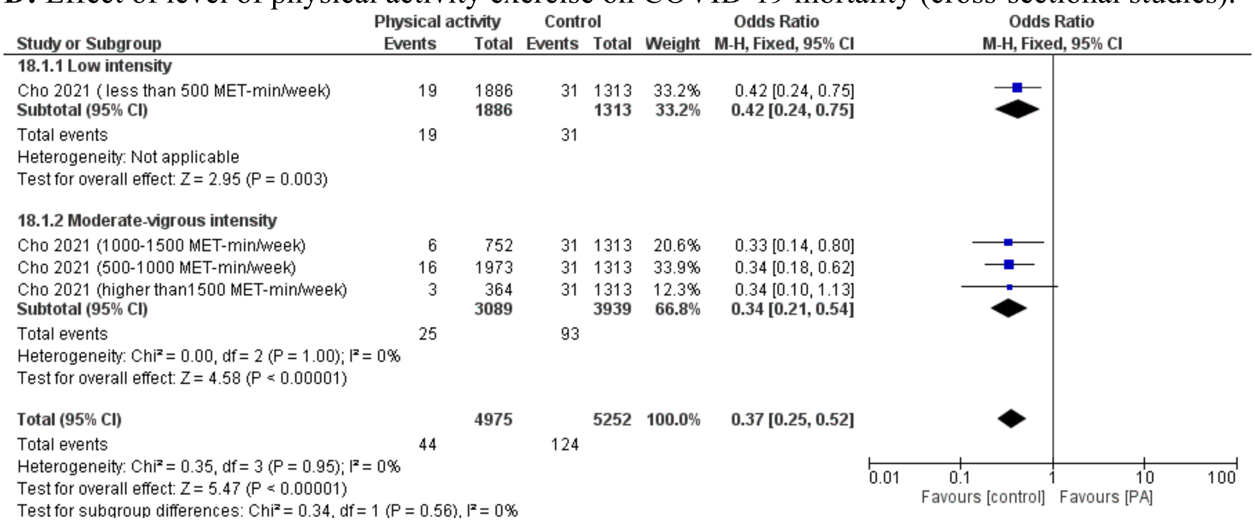
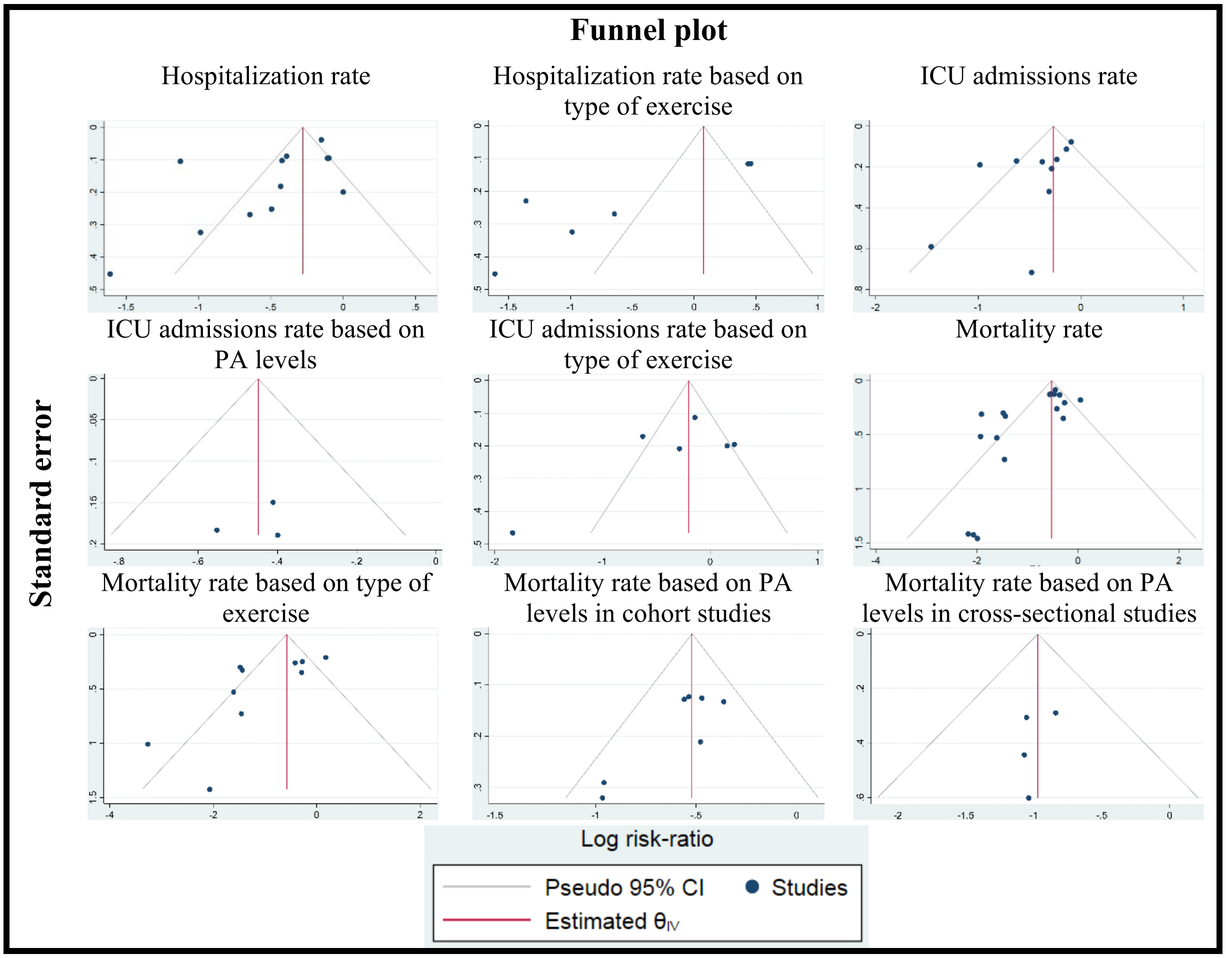


Figure 4



Funnel plot
Hospitalization rate
Hospitalization rate based on type of exercise
ICU admissions rate
ICU admissions rate based on PA levels
ICU admissions rate based on type of exercise
Mortality rate
Mortality rate based on type of exercise
Mortality rate based on PA levels in cohort studies
Mortality rate based on PA levels in cross-sectional studies
Standard error
Log risk-ratio
Pseudo 95% CI
Studies
Estimated θ_{IV}

Figure 5.