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Association of physical activity and the risk of COVID-19 hospitalization

A dose–response meta-analysis

Dan Li, MD[a], Shengzhen Jin, PhD[b], Ziying He, PhD[c,d], Songtao Lu, PhD[a,*]

Abstract

Background: Many people have experienced a high burden due to the spread of the coronavirus disease (COVID-19) and its serious consequences for health and everyday life. Prior studies have reported that physical activity (PA) may lower the risk of COVID-19 hospitalization. The present meta-analysis explored the dose–response relationship between PA and the risk of COVID-19 hospitalization.

Methods: Epidemiological observational studies on the relationship between PA and the risk of COVID-19 hospitalization were included. Categorical dose–response relationships between PA and the risk of COVID-19 hospitalization were assessed using random effect models. Robust error meta-regression models assessed the continuous relationship between PA (metabolic equivalent [Met]-h/wk) and COVID-19 hospitalization risk across studies reporting quantitative PA estimates.

Results: Seventeen observational studies (cohort\case–control\cross-section) met the criteria for inclusion in the meta-analysis. Categorical dose-relationship analysis showed a 40% (risk ratio [RR] 0.60, 95% confidence interval [CI]: 0.48–0.71) reduction in the risk of COVID-19 hospitalization compared to the lowest dose of PA. The results of the continuous dose–response relationship showed a non-linear inverse relationship ($P_{\text{non-linearity}} < .05$) between PA and the risk of COVID-19 hospitalization. When total PA was < or >10 Met-h/wk, an increase of 4 Met-h/wk was associated with a 14% (RR = 0.83, 95% CI: 0.85–0.87) and 11% (RR = 0.89, 95% CI: 0.87–0.90) reduction in the risk of COVID-19 hospitalization, respectively.

Conclusions: There was an inverse non-linear dose–response relationship between PA level and the risk of COVID-19 hospitalization. Doses of the guideline-recommended minimum PA levels by the World Health Organization may be required for more substantial reductions in the COVID-19 hospitalization risk.

Abbreviations: COVID-19 = coronavirus disease 2019, CI = confidence interval, Mets = metabolic equivalents, MPA = moderate-intensity PA, PA = physical activity, REMR = robust error meta-regression, RR = risk ratio, VPA = vigorous-intensity PA, WHO = World Health Organization.

Keywords: COVID-19 hospitalization, dose–response, meta-analysis, physical activity (PA)

1. Introduction

The coronavirus disease 2019 (COVID-19) outbreak continues worldwide. As of December 12, 2022, COVID-19 has caused 647,972,911 infections and 6,642,832 deaths worldwide.[1] With the evolution of COVID-19, the mortality cases caused by COVID-19 are getting lower and lower. However, the number of hospitalized and severe cases caused by COVID-19 is still high. It is essential to identify high-risk groups that require special attention under these conditions.[2] For non-communicable disease outcomes, lifestyle risk factors have been consistently associated with morbidity, mortality, and loss of disease-free life.[3,4] For example, physical inactivity and smoking appear to be independently associated with a higher risk of community-acquired pneumonia morbidity and mortality.[5,6]

It is also well established that the risk of developing a respiratory disease is much higher in people with low physical activity (PA), whereas COVID-19 patients with a physically inactive lifestyle (e.g., sedentary behavior) are more likely to be hospitalized and have a greater likelihood of poor clinical outcomes.[7] Moreover, it has previously been shown that regular PA and

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[a] School of Sports, Wuhan University of Science and Technology, Wuhan, China, [b] Tennis College, Wuhan sports university, Wuhan, China, [c] Graduate School, Wuhan Institute of Physical Education, Wuhan, China, [d] School of Physical Education, Jianghan University, Wuhan, China.

* Correspondence: Songtao Lu, School of sports, Wuhan University of Science and Technology, No.16, Huangjiahu West Road, Hongshan District, Wuhan 430065, Hubei Province, China (e-mail: songtaozhenzhen@sina.com).

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higher physical fitness levels enhance immune function and, therefore, might reduce susceptibility to COVID-19 infection and infection severity.[8,9] Recent studies retrospectively evaluating cohorts of COVID-19-positive adults have described the benefit of regular PA in decreasing the incidence of adverse outcomes in confirmed cases of COVID-19.[10,11] Another recent study confirmed there were protective associations of PA for adverse COVID-19 outcomes across demographic and clinical characteristics according to a retrospective cohort study for 194,191 adults with COVID-19 infection. As this study concluded that adults, regardless of demographic category or chronic disease status, should be encouraged to increase physical exercise time as another COVID-19 mitigation strategy.[12]

Research on such topics is just emerging, and the impact of PA on the infectious and clinical outcomes of COVID-19 remains clear. However, the protective effects of different levels of PA against COVID-19 are controversial. Rahmati et al conducted a meta-analysis on this topic, which did not address the controversy regarding the protective effects of different levels of PA.[13] In addition, Rahmati et al classified the case–control group as a cross-sectional study. In a meta-analysis, they assumed cardiopulmonary function as PA, which inevitably led to unconvincing results. Finally, the study only used the binary variables of PA included in the literature to analyze the outcome variables, ignoring the moderate dose in the multi-level doses, making it difficult to explain the heterogeneity generated by the meta-analysis studies. Sittichai et al found that engaging in regular PA, even in different patterns, has beneficial effects on the severity and mortality of COVID-19 patients by meta-analysis. But he did not include the study for hospitalized cases.[14]

Consequently, no systematic review or meta-analysis has reported the exact dose–response relationship between pre-diagnosis PA and COVID-19 hospitalization. Furthermore, there is still substantial uncertainty regarding the association between pre-diagnosis PA levels and hospitalization due to COVID-19 among the general population. To precisely quantify the association between pre-diagnosis PA and the risk of COVID-19 hospitalization, we conducted a systematic review and meta-analysis of observational studies published up to May 8, 2022.

2. Materials and methods

2.1. Inclusion criteria

The criteria for inclusion, and each article determined for inclusion, were discussed by 3 authors, and the discussions on inclusion and exclusion occurred >3 times. The inclusion criteria were as follows: studies published as epidemiological observational cohort studies, case–controls, and cross-sectional design investigation studies; studies providing at least an odds ratio, relative risk (RR or hazard ratio), and 95% confidence interval (CI) between the level of PA and the risk of hospitalization for COVID-19, or raw data provided to calculate these indicators. The repeated literature was excluded. Only the latest studies were selected if they were conducted at different time points in the same cohort. Additionally, if multiple articles were published in the same group, we chose articles where subjects were followed for a longer time or with a larger sample size.

2.2. Search strategy

We searched PubMed (1980 to the present) and the Web of Science database (1980 to the present) for literature on the relationship between PA and the risk of COVID-19 hospitalization. The search strategy used keywords such as "exercise or PA or sport or walking or motor activity," "COVID-19 or SARS-CoV-2," and "severe or hospitalization." These searches were screened for cohort studies, case controls, and cross-sectional design studies. The latest search date was April 2022, and there was no language limit. The reference lists of the selected and related review articles were screened to identify potentially relevant studies. All searches were conducted independently by 2 authors, and the differences were resolved by group discussion.

2.3. Quality assessment

The Newcastle–Ottawa Scale was used to evaluate literature quality, and scores of 0 to 3, 4 to 6, and 7 to 9 were determined as low, moderate, and high quality, respectively.[15] Each article was evaluated independently by 2 authors and cross-checked. In the group meeting, the results were publicized, and the reasons for the score of each item were specified. If the evaluation of the literature quality was inconsistent, the group focused on solving the final score of its quality.

2.4. Synthesis methods

Stata 16.0 software (StataCorp LLC) was used for the meta-analysis. The P value was set at $P < .05$, and all tests were double-sided. The effect value-adjusted RR and 95% CI of the group with the highest dose of PA compared to the control group with the lowest dose of PA in each study were combined. The combined effect values were calculated using a random-effects model. Heterogeneity was assessed and described using I^2 statistics as the percentage of variation in the study; I^2 values of 25%, 50%, and 75% represented low, moderate, and high levels of heterogeneity, respectively.[16] Egger and Begg tests were used to determine publication bias. During the sensitivity analysis, each study was deleted one by one to check whether the combined effect of the remaining studies had changed.[16] The subgroup meta-analysis was conducted according to PA intensity classification (low-intensity PA, vigorous-intensity PA [VPA], moderate-to-vigorous PA, moderate-intensity PA [MPA]), sex, age, study area, study quality, and adjustment for confounding factors. Meta-regression was used to examine the heterogeneity among studies.

According to categorical and continuous dose PA, this study analyzed the dose–response relationship with the risk of COVID-19 hospitalization. Categorical doses were divided into dichotomous and multi-classified doses shown in the study, and the combined effect value RR was generated by comparing the highest and lowest doses. To analyze the continuous dose–response relationship, we calculated the total weekly dose of PA for each effect value RR based on the PA intensity, duration, and weekly frequency of the baseline survey provided in the literature. Furthermore, we assumed that the dose remained at this level during the follow-up survey. To determine the exposure value of the included dose, the median was set as the determined dose. If the development interval was <0.5, it was set to 0.25. If the upper open interval was ≥1, the difference between the intermediate dose intervals was 0.25, and the exposure value was set to 1.25.[17] Metabolic equivalent (Met)-h/wk was considered as the final unit of analysis. These are combined absolute indices of intensity, duration, and frequency used to calculate exposures to Met units not directly reported in the literature. Met, a physiological measure of PA energy, is defined as energy expenditure per kilogram of body weight per hour: 1 Met = 1 kcal/kg * h. To address the differences in PA units in different studies, we used Ainsworth et al's classification, classifying PA into low-intensity PA (3 Mets, such as walking exercise, moderate-intensity MPA (4 Mets), and high-intensity VPA (8 Mets).[18] We then converted the duration of a particular PA intensity (h/wk) to Met-h/wk in combination with the frequency of the week.

To establish the dose–response relationship between PA and the risk of hospitalization for COVID-19, robust error meta-regression (REMR) was used for model fitting.[19] The REMR approach is based on a "one-stage" framework that treats each study as a cluster and fits the revised regression to the average

PA dose across the entire dataset. In addition, the method also uses the inverse variance method to weigh each dose-specific effect in the data and balances heteroscedasticity in the REMR model to ensure unbiased estimation of parameters. Finally, we used restricted cubic splines as connection functions to fit the linear and non-linear dose–response models. Based on the dose-centralization treatment, the independent variable PA dose of the model was set as 3 nodes (0, 6.75, and 21), including 2 regression splines. The χ^2 test was used to test the hypothesis that the regression coefficient of the second regression spline is significant ($P < .05$), indicated by a linear or non-linear dose–response relationship. A dose–response relationship curve was drawn using the Stata software XBLC command.[17]

3. Results

3.1. Study selection and characteristics

In total, 170 articles were preliminarily identified. According to the literature inclusion and exclusion criteria formulated in this study, 17 studies, including seven cohort studies, 5 case–control studies, and 5 cross-sectional design studies, were finally included. There were 1,038,768 subjects and about 3022 hospitalized COVID-19 cases (some studies had not reported the number of cases). The steps for retrieval and inclusion are shown in Figure 1. The characteristics of the literature are listed in Table 1. Among the 17 studies, 3 were from North America,[10,20,21] 7 were from Asia,[11,22–27] 6 were from Europe,[28–33] and 1 was from Oceania.[34] Eight studies were considered high quality, as indicated by their Newcastle–Ottawa Scale quality scores of ≥7. The other 9 studies were considered of moderate quality.

3.2. Categorical analysis between PA and COVID-19 hospitalization

Compared with the lowest PA dose, the highest PA in the included studies reduced the risk of COVID-19 hospitalization by 40% (RR = 0.60, 95% CI: 0.48, 0.71). The heterogeneity test result was $I^2 = 66.22\%$ ($P < .01$), indicating substantial heterogeneity of the study results (Fig. 2). The pooled effect size results did not change significantly after excluding each study from the sensitivity analysis (online supplemental appendix A S1, Supplemental Digital Content, http://links.lww.com/MD/I415). Published bias analysis with Begg test $P = .54 > .05$, Egger test $P = 1.330 > .05$, and funnel diagram also showed no significant published bias (online supplemental appendix B S2, Supplemental Digital Content, http://links.lww.com/MD/I416).

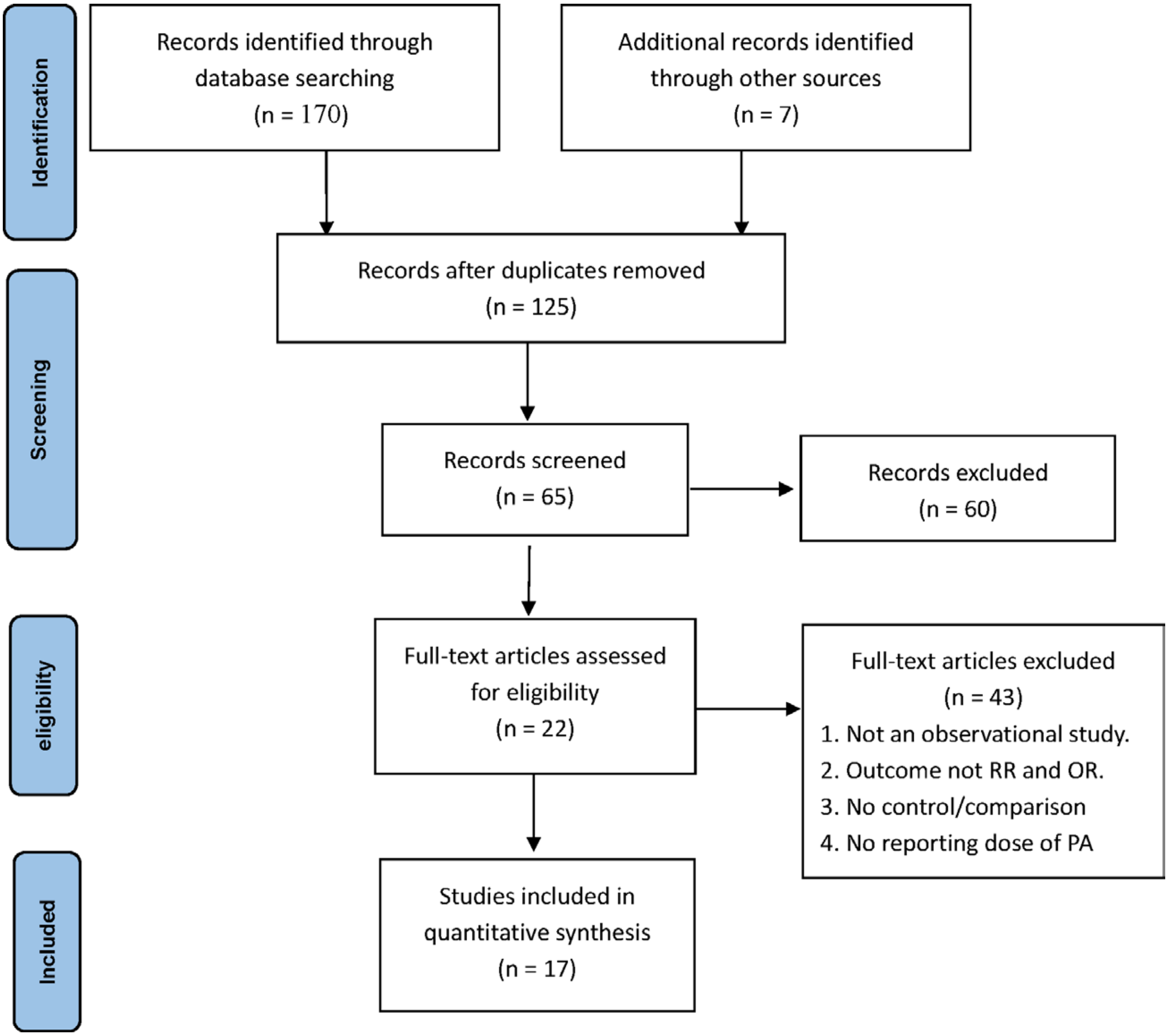

Figure 1. Flow diagram of studies considered for inclusion in the systematic review.

Table 1

Summary of the extracted studies.

Author(yr)	Country	Study type	Case\total	Age(SD)	Female %	Measurement and categories of PA	Adjustment *	QA
AlKetbi(2021)	AUH	Cohort	135\641	44(NP)	36%	Self-report PA: five Categories(-times\w)	NP	5
Brandenburg(2021)	CA	Case–control	NP\263	86%<65	57%	PA-R: No, Moderate, <1 h of vigorous, >1 h of vigorous	2 5 6 8 9 12 15	7
Bielik (2021)	SLK	Cohort	104\2343	18–65	49%	Physically active(≥3 times\w), cold-water swim	NP	5
Ekblom-Bak (2021)	SWE	Case–control	172/407131	49.9(NP)	30%	Never/irregular, 1–2 times/w, ≥ 3 times/w	1 2 5 16	7
Katsoulis(2021)	UK	Cohort	NP\ 85308	18–69(NP)	NP	Self-report PA: Low, Gentle, Moderate, Vigorous	1 2 7 9	7
Hamer (2020)	UK	Cohort	760\387109	56.2 ± 8.0	55.1%	IPAQ: Sufficient\ Insufficient\ None	1 2 6 8 9	7
Halabchi(2021)	Iran	Cross-section	60\4694	36.45 ± 9.77	55%	Regular sports participation (yes/no)	NP	6
Hamdan (2021)	PLE	Cross-section	59\300	30.5 ± 12.2	55.0%	PA questionnaire: yes\no	NP	5
Lee (2021)	KR	Cohort	277\118768	NP	51.2%	Self-report PA: None, Gentle, Moderate, Vigorous	1 2 5–9 14 16	
Latorre–Roman (2021) al.,2021	Spanish	Cross-section	NP\420	33 (20–54)	52.6%	IPAQ: Moderate PA > 150 min\w, 30–150 min\w, None	1	6
Malisoux (2022)	LUX	Cohort	106\452	42 (31–51)	48%	PA questionnaire: yes\no	1 2 3 5 16 18 19	7
Maltagliati (2021)	France	Case–control	66\3139	69.3 ± 8.5	53%	4-point PA scale ranging (>1, 1; <1; 0\week)	1 2 5 7 8 12 19	9
Souza et al (2021)	Brazil	Cross-section	91\938	NP	33.4%	IPAQ: Sufficient > 150 min/w(moderate), Insufficient	1 2 19	7
Sallis(2021)	USA	Cohort	1199\2970	47 ± 16.97	61.9%	UPAG: Active, inactive, some activity	1–15	9
Steenkamp(2021)	ZA	Cohort	NP\65361	41 ± 12.1	48.2%	Low activity, Moderate activity, High activity	1 2 6 8 9 14 15	8
Tavakol (2021)	Iran	Cross-section	64\188	18–75(NP)	52.7%	GPAQ: Low, Moderate to high	NP	6
Yuan (2021)	CN	Case–control	29\164	61.8 ± 13.6	48.8%	Self-report PA: Inactivity, activity	NP	6

Case/ total: Number of cases and total sample size. Age characteristics: Single value indicates mean age, others are age range.

NP = Not reported. AUH = United Arab Emirates, CA = Canada, CN = China, ESP = Spain, GPAQ = Global physical activity questionnaire, IPAQ = International Physical Activity Questionnaire, KR = Korea, LUX = Luxembourg, PA = physical activity, PA-R = physical activity rating questionnaire, PLE = Palestine, SLK = Slovak, SWE = Switzerland, UPAG = US Physical Activity Guidelines, ZA = New Zealand.

* Adjustment factors: 1 age, 2 gender, 3 socioeconomic status, 4 race, 5 body mass index (BMI), 6 cardiovascular disease, 7 cancer, 8 diabetes, 9 hypertension, 10 use of antihypertensive drugs, 11 corticosteroids, 12 chronic lung/ respiratory disease, 13 liver disease, 14 human immunodeficiency virus (HIV), 15 end-stage renal disease and immune disease, 16 smoking, 17 alcohol,18 sedentary behavior, 19 comorbidities.

The effect values of the cohort study, case–control study, and cross-sectional design study were 0.63 (95% CI: 0.54, 0.71), 0.59 (95% CI: 026, 0.91), and 0.58 (95% CI: 0.42, 0.74), respectively.

As for the source of heterogeneity (presented in Table 2), between-group heterogeneity only appeared in the comparative analysis of the relationship between PA at different dose levels and the risk of hospitalization for COVID-19 ($P < .01$), indicating that PA at different doses significantly reduces the risk of hospitalization. Within-group heterogeneity appeared in the multi-dose PA, case–control study, high quality, European, adjustment for age, sex, adjustment for high blood pressure, adjustment for diabetes, adjustment for cancer, and cardiovascular diseases subgroup, illustrating that the subgroup study effect value of the results may not be stable. The results may be affected by other factors.

3.3. Continuous dose-response relationship between PA and COVID-19 hospitalization

Figure 3 shows the continuous dose–response relationship. The results showed a negative non-linear relationship between PA and the risk of hospitalization for COVID-19 ($P_{\text{non-linearity}} < .01$). When PA < 10 Met-h/wk, an increase of 4 Met-h/wk (1 hour of moderate-intensity or 1/2 an hour of high-intensity) was associated with a 14% reduction in the risk of hospitalization for COVID-19 ($P < .01$, RR = 0. 86, 95% CI: 0.85–0.87). When PA > 10 Met-h/wk, the risk of hospitalization for COVID-19 decreased by 11% for each additional 4 Met-h/wk ($P < .01$, RR = 0.89, 95% CI: 0.87–0.90).

4. Discussion

This study is the first dose–response meta-analysis of the relationship between PA and the risk of COVID-19 hospitalization. The literature included observational studies on the relationship between PA and the risk of COVID-19 hospitalization. Through a meta-analysis of the categorical dose, our main conclusion is that the risk of COVID-19 hospitalization is reduced by 40% compared with the lowest dose of PA. For continuous dose–response analysis, we confirmed that the relationship between PA and the risk of COVID-19 hospitalization is non-linear and inverse. For every 4 Met-h\wk PA increase, the risk of COVID-19 hospitalization decreased by 11 to 14%. Sensitivity and published bias analyses further support these results, and these main quantitative features have important clinical significance.

The dose–response association between PA and the risk of COVID-19 hospitalization has been previously reported. As for the categorical analysis, Rahmati et al observed that PA was significantly associated with a reduction in COVID-19 hospitalization compared with control (RR = 0.58) by meta-analysis.[13] In the present study, we observed a similar RR of 0.60. However, we included multiple categorical analysis data with different PA dose levels to analyze the relationship between PA and the risk of COVID-19 hospitalization. We observed significantly different protective effects of varying PA levels on the hospitalization risk of COVID-19 by heterogeneity analysis. Compared to the results obtained by Rahmati et al, our observations are more abundant.

As for the continuous analysis, Malisoux et al observed an inverse dose–response association between PA and the risk of

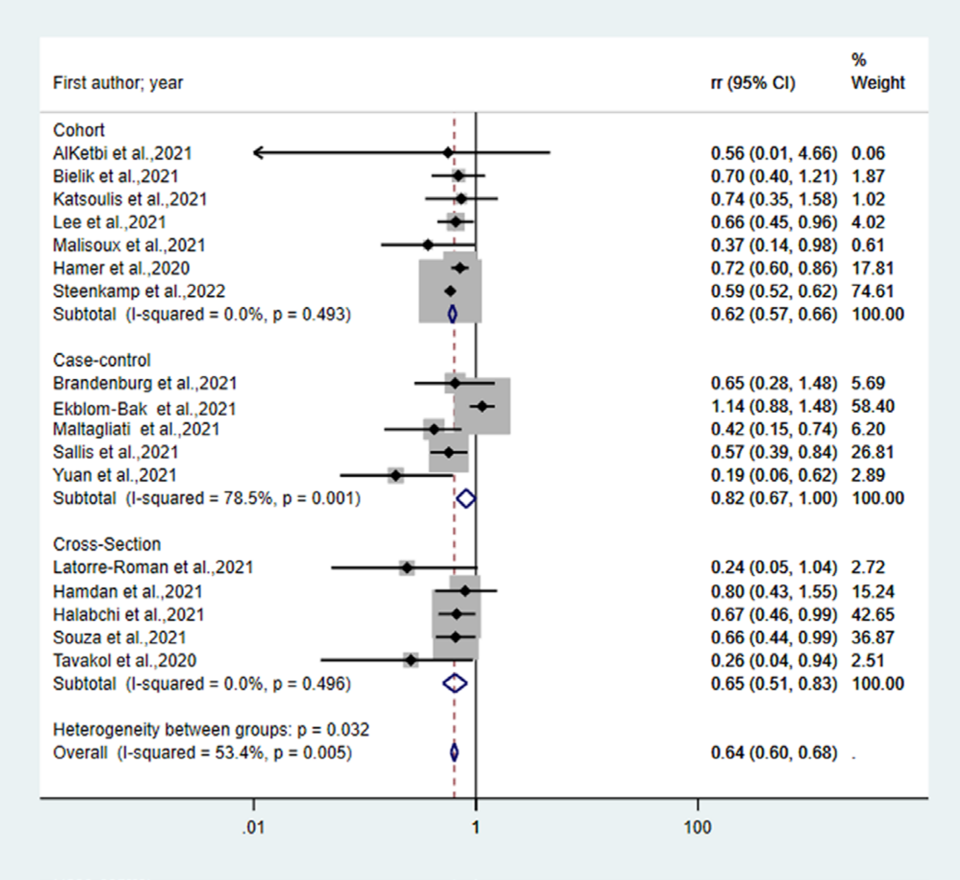

Figure 2. Forest plot showing categorical analysis between PA and the risk of COVID-19 hospitalization. COVID-19 = coronavirus disease 2019, PA = physical activity.

moderate COVID-19 illness, and increased PA was associated with a slightly lower risk of moderate illness (odds ratio: 0.99, CI: 0.98–1.00).[26] In the present study, we observed a similar inverse dose–response association between PA and the risk of COVID-19 hospitalization. An increase of 4 Met-h/wk PA was associated with a 12 to 17% (RR = 0.83–0.88) reduction in the risk of COVID-19 hospitalization. A 4 Met-h/wk PA is equivalent to 1 hour MPA or half an hour high VPA; our results are more specific and close to a practical exercise. Otherwise, the observed dose–response relationship between PA and the risk of COVID-19 hospitalization was non-linear. We assumed that after 10 Met-h/wk, the degree of enhancement in lowering the risk of moderate COVID-19 illness when PA increase is weakened. However, the threshold is 30 Met-h/wk according to the J-shaped association of PA and risk of moderate illness by Malisoux et al[26] Meanwhile, our meta-analysis findings are more robust and specific, and we observed increasing PA benefits for the inpatient burden due to COVID-19.

This difference in the magnitude of risk reduction for COVID-19 hospitalization could be related to differences in the mechanism through which PA modifies the risk of respiratory viral infections. This is supported by previous studies that showed a stronger association between maximal fitness exercise capacity and the risk of hospitalization due to COVID-19.[35] Exercise capacity is an important index for measuring overall health and the ability of the body to cope with external stressors. More specifically, it is an important index to bear the burden on the heart and lungs.[36] However, PA greatly influences exercise capacity; more specifically, regular moderate-intensity to vigorous-intensity aerobic exercise daily can improve exercise capacity. In addition, the beneficial effects of regular PA on the immune system may involve several mechanisms, including enhanced immunosurveillance, reduced systemic inflammation, improved regulation of the immune system, and delayed onset of immunosenescence.[36,37] A recent meta-analysis investigated the effects of regular PA on the immune system.[38] This study showed that moderate to vigorous intensity exercise (e.g., walking, running, cycling) is overall beneficial with a lower concentration of neutrophils and a higher concentration of CD4 T helper cells and salivary IgA. These biochemical indicator changes may be the critical mechanism for regular PA to lower the risk of hospitalization due to COVID-19.

As for the analysis of the confounding factors, results on between-subgroup heterogeneity showed significant heterogeneity in all subgroups adjusted for underlying disease. Thus, confounding factors of underlying disease significantly affected the association between PA and the risk of hospitalization. However, contrary to expectations, heterogeneity was observed in the within-subgroup analysis adjusted for age, sex, and body mass index. This indicated that our data failed to demonstrate significant differences in the impact of PA on the risk of hospitalization for COVID-19 according to age, sex, and body weight. This may be because the overall heterogeneity of this meta-analysis was precisely concentrated in these subgroups. The other possible reason is that the effect of PA on reducing the risk of COVID-19 hospitalization is very stable among these different demographic characteristics.

The World Health Organization's global recommendation on the health benefits of PA states that adults have at least 150 minutes of moderate-intensity aerobic PA per week, at least 75 minutes of high-intensity aerobic PA per week, or a combination of moderate and high-intensity activities; this is equivalent to 10 met h/wk.[1] Our analyses also show that when the PA level is >10 met h/wk, the risk of hospitalization for COVID-19

Table 2

Subgroup analysis.

Subgroup		N	RR (95% CI)	I^2 (%)	P^a	P^b
Total effect size (highest vs lowest)		17	0.60(0.48, 0.71)	66.22	.01	
PA categories	Binary dose*	7	0.51 (0.33,0.69)	45.43	.09	.24
	Multi-dose*	10	0.65 (0.51.0.79)	68.34	.02	
Multi-class dose comparison*	Highest versu lowest	12	0.59 (0.55,0.63)	0	.86	<.01
	Moderate versu lowest	13	0.75 (0.65,0.85)	26.88	.33	
Study type	Cohort	7	0.63 (0.54,0.71)	20.83	.53	.85
	Case–control	5	0.59 (026,0.91)	82.07	.00	
	Cross-section	5	0.58 (0.42,0.74)	2.05	.28	
Study quality	»7	8	0.67 (0.53,0.81)	70.32	.02	.1
	7<	9	0.49 (0.32,0.66)	38.93	.15	
Different continent	Europe	6	0.68 (0.43,0.94)	68.68	.02	.46
	Asia	7	0.49 (0.30,0.68)	46.31	.11	
	Others (America)	4	0.59 (0.54,0.64)	0	.96	
Adjusted confounding factor						
Age	Yes	10	0.63 (0.51,0.75)	66.73	.01	.36
	No	7	0.51 (0.29,0.74)	43.20	.14	
Sex	Yes	10	0.65 (0.54,0.78)	59.93	.03	.15
	No	7	0.47 (0.25,0.69)	44.89	.12	
BMI	Yes	7	0.66 (0.48,0.84)	67.76	.02	.29
	No	10	0.54 (0.40,0.87)	43.12	.15	
Adjusted baseline disease						
Hypertension	Yes	8	0.58 (0.31,0.85)	10.28	.57	.83
	No	9	0.61 (0.55,0.67)	71.22	.00	
Diabetes	Yes	8	0.61 (0.55,0.87)	11.67	.49	.91
	No	9	0.59 (0.34,0.84)	67.09	.00	
Cardiovascular	Yes	8	0.61 (0.55,0.87)	11.67	.49	.91
	No	9	0.59 (0.34,0.84)	67.09	.00	
Cancer	Yes	6	0.57 (0.45,0.69)	0	.70	.75
	No	11	0.61 (0.43,0.79)	80.95	.00	

P^a and P^b represent heterogeneity within and between subgroups, respectively.

BMI = body mass index, CI = confidence interval, PA = physical activity, RR = risk ratio.

Multi-dose comparison *: The highest dose is >10 h-met/wk and the lowest dose, and the moderate dose is <10 h-met/wk. The binary dose is generally expressed as exercise and non-exercise.

* Multiple dose grouping represents the highest, relative and lowest dose comparison, at least 3 levels.

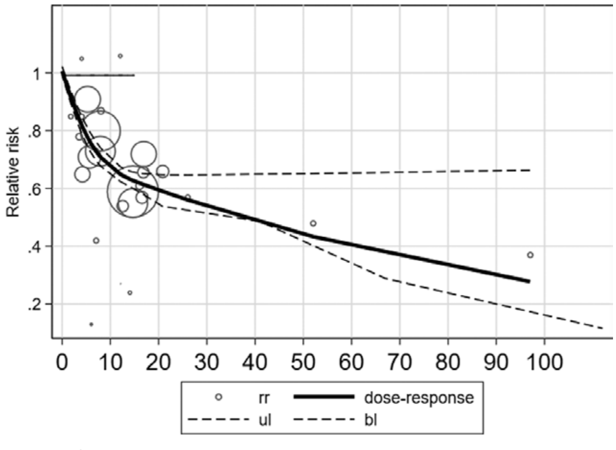

Figure 3. Continuous dose-response relationship between PA and the risk of COVID-19 hospitalization. COVID-19 = coronavirus disease 2019, PA = physical activity.

is reduced, but the degree of reduction becomes significantly smaller. The practical significance of this conclusion is that PA or exercise within 10 met h/wk has the most apparent effect on reducing the risk of hospitalization for COVID-19, with an additional benefit for reducing the risk when PA level exceeds 10 met h/wk.

Increased hospitalization due to COVID-19 is a threat to health and a heavy disease burden on all aspects, such as individuals and the country. We found that increased PA significantly reduces the hospitalization risk of COVID-19, and PA should be a positive factor in decreasing the COVID-19 disease burden. However, the Global Burden of Diseases 2019 ranked low PA 19th out of 20 risk factors in terms of disability-adjusted life years, down from 10th in the equivalent 2010 Global Burden of Diseases publication.[39,40] Moreover, PA decreased in all age groups, independent of sex, due to the COVID-19 pandemic, according to a recent meta-analysis.[41] In the face of the global spread of COVID-19, we must regain the vital role of PA in reducing the burden of the disease. The conclusions of our study will undoubtedly have significant implications for public health.

Finally, our study is the first meta-analysis on the dose–response relationship between PA and the hospitalization risk of COVID-19. The results of this study are based on a large sample cohort study, case–control group study, and the advantages of a long period of follow-up investigation by cohort study; therefore, the results are relatively stable. However, this study may have limitations. First, the literature we included may be insufficient in the continuous dose–response analysis. One possible reason for this is that we set strict inclusion criteria. In addition, cohort studies require long-term follow-up surveys and extensive sample data. Therefore, few cohort studies have been conducted on related topics. Second, the methods of PA evaluation included in the literature of this study are subjective measurements, which may lead to inaccurate doses, and different measurement and observation methods of physical activities and hospitalized cases may have a significant impact on the research conclusion. In addition, exercise habit is based on the assumption that there is no change in the long-term follow-up; that is, the dose of PA is constant in the long-term observational study. This assumption may make the results inaccurate. Moreover, the results of some cohort studies included were not adjusted for confounding factors such as sex, age, and other concomitant medical conditions, which should be paid attention to in future studies.

5. Conclusions

There was an inverse non-linear dose–response relationship between PA levels and the risk of COVID-19 hospitalization. An increase in the PA dose significantly reduced the hospitalization risk of COVID-19. The degree of risk reduction is weakened when PA is >10 Met-h/wk. Doses of the guideline-recommended minimum PA levels by the World Health Organization may be required for more substantial reductions in the COVID-19 hospitalization risk. Future studies with different doses of PA or exercise interventions are needed to determine the optimum PA dose required for COVID-19 prevention.

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Author contributions

Conceptualization: Shengzhen Jin, Songtao Lu.
Data curation: Dan Li.
Formal analysis: Shengzhen Jin, Ziying He, Songtao Lu.
Methodology: Dan Li, Ziying He.
Resources: Dan Li.
Software: Dan Li, Shengzhen Jin, Songtao Lu.
Visualization: Songtao Lu.
Writing – original draft: Dan Li, Shengzhen Jin, Ziying He, Songtao Lu.
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References

[1] Physical activity guidelines. Available at: https://www.who.int/emergencies/diseases/novel-coronavirus-2019. [Access date December 12, 2022].

[2] Chen J, Qi T, Liu L, et al. Clinical progression of patients with COVID-19 in Shanghai, China. J Infect. 2020;80:e1–6.

[3] Colpani V, Baena CP, Jaspers L, et al. Lifestyle factors, cardiovascular disease and all-cause mortality in middle-aged and elderly women: a systematic review and meta-analysis. Eur J Epidemiol. 2018;33:831–45.

[4] Schlesinger S, Neuenschwander M, Ballon A, et al. Adherence to healthy lifestyles and incidence of diabetes and mortality among individuals with diabetes: a systematic review and meta-analysis of prospective studies. J Epidemiol Community Health. 2020;74:481–7.

[5] Bielik V, Grendar M, Kolisek M. A possible preventive role of physically active lifestyle during the SARS-CoV-2 pandemic; might regular cold-water swimming and exercise reduce the symptom severity of COVID-19? Int J Environ Res Public Health. 2021;18:7158.

[6] Inoue Y, Koizumi A, Wada Y, et al. Risk and protective factors related to mortality from pneumonia among middleaged and elderly community residents: the JACC Study. J Epidemiol. 2007;17:194–202.

[7] Severe outcomes among patients with coronavirus disease 2019 (COVID-19) - United States, February 12-March 16, 2020. MMWR Morb Mortal Wkly Rep. 2020;69:343–6.

[8] Duggal NA, Niemiro G, Harridge SDR, et al. Can physical activity ameliorate immunosenescence and thereby reduce age-related multi-morbidity? Nat Rev Immunol. 2019;19:563–72.

[9] Simpson RJ, Kunz H, Agha N, et al. Exercise and the regulation of immune functions. Prog Mol Biol Transl Sci. 2015;135:355–80.

[10] Sallis R, Young D, Tartof S, et al. Physical inactivity is associated with a higher risk for severe COVID-19 outcomes: a study in 48 440 adult patients. Br J Sports Med. 2021;55:1099–105.

[11] Tavakol Z, Ghannadi S, Tabesh MR, et al. Relationship between physical activity, healthy lifestyle and COVID-19 disease severity; a cross-sectional study. J Public Health. 2021;4:1–9.

[12] Young DR, Sallis JF, Baecker A, et al. Associations of physical inactivity and COVID-19 outcomes among subgroups. Am J Prev Med. 2022;12:e007.

[13] Rahmati M, Shamsi MM, Khoramipour K, et al. Baseline physical activity is associated with reduced mortality and disease outcomes in COVID-19: a systematic review and meta-analysis. Rev Med Virol. 2022;32:e2349.

[14] Sittichai N, Parasin N, Saokaew S, et al. Effects of physical activity on the severity of illness and mortality in COVID-19 patients: a systematic review and meta-analysis. Front Physiol. 2022;13:1030568.

[15] Wells GA, Peterson J, Welch V, et al. The Newcastle-Ottawa Scale (NOS) for Assessing the Quality in Nonrandomized Studies in Meta-analyses. Ottawa: University of Ottawa. 2009. Available at: https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.

[16] Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002;21:1539–58.

[17] Zhang T, Dong S, Zhou Z, et al. The Advanced Meta-Analysis Method-Based on Stata. Fudan University Press. 2015:220–232.

[18] Ainsworth B, Haskell W, Herrmann S, et al. 2011 compendium of physical activities: a second update of codes and MET values. Med Sci Sports Exerc. 2011;43:1575–81.

[19] Xu C, Doi S. The robust error meta-regression method for dose-response meta-analysis. Int J Evid Based Healthcare. 2018;16:138–44.

[20] Brandenburg JP, Lesser IA, Thomson CJ, et al. Does higher self-reported cardiorespiratory fitness reduce the odds of hospitalization from COVID-19? J Phys Activity Health. 2021;18:782–8.

[21] de Souza FR, Motta-Santos D, Dos Santos Soares D, et al. Association of physical activity levels and the prevalence of COVID-19-associated hospitalization. J Sci Med Sport. 2021;24:913–8.

[22] Yuan Q, Huang HY, Chen XL, et al. Does pre-existent physical inactivity have a role in the severity of COVID-19? Ther Adv Respir Dis. 2021;15:17534666211025221.

[23] Baynouna AlKetbi LM, Nagelkerke N, Abdelbaqi H, et al. Risk factors for SARS-CoV-2 infection severity in Abu Dhabi. J Epidemiol Global Health. 2021;11:344–53.

[24] Halabchi F, Mazaheri R, Sabeti K, et al. Regular sports participation as a potential predictor of better clinical outcome in adult patients with COVID-19: a large cross-sectional study. J Phys Activity Health. 2021;18:8–12.

[25] Hamdan M, Badrasawi M, Zidan S, et al. Risk factors associated with hospitalization owing to COVID-19: a cross-sectional study in Palestine. J Int Med Res. 2021;49:3000605211064405.

[26] Malisoux L, Backes A, Fischer A, et al. Associations between physical activity prior to infection and COVID-19 disease severity and symptoms: results from the prospective Predi-COVID cohort study. BMJ Open. 2022;12:e057863.

[27] Lee SW, Lee J, Moon SY, et al. Physical activity and the risk of SARS-CoV-2 infection, severe COVID-19 illness and COVID-19 related mortality in South Korea: a nationwide cohort study. Br J Sports Med. 2021;56:901–14.

[28] Hamer M, Kivimaki M, Gale CR, et al. Lifestyle risk factors, inflammatory mechanisms, and COVID-19 hospitalization: a community-based cohort study of 387,109 adults in UK. Brain Behav Immun. 2020;87:184–7.

[29] Maltagliati S, Sieber S, Sarrazin P, et al. Muscle strength explains the protective effect of physical activity against COVID-19 hospitalization among adults aged 50 years and older. J Sports Medicine medRxiv. 2021;39:2796–803.

[30] Baik I, Curhan GC, Rimm EB, et al. A prospective study of age and lifestyle factors in relation to community-acquired pneumonia in US men and women. Arch Intern Med. 2000;160:3082–8.

[31] Latorre-Roman PA, Guzman-Guzman IP, Delgado-Floody P, et al. Protective role of physical activity patterns prior to COVID-19 confinement with the severity/duration of respiratory pathologies consistent with COVID-19 symptoms in Spanish populations. Res Sports Med. 2021;16:e1937166.

[32] Katsoulis M, Pasea L, Lai AG, et al. Obesity during the COVID-19 pandemic: both cause of high risk and potential effect of lockdown? A population-based electronic health record study. Public Health. 2021;191:41–7.

[33] Ekblom-Bak E, Vaisanen D, Ekblom B, et al. Cardiorespiratory fitness and lifestyle on severe COVID-19 risk in 279,455 adults: a case control study. Int J Behav Nutr Phys Activity. 2021;18:135.

[34] Steenkamp L, Saggers R, Bandini R, et al. Small steps, strong shield: directly measured, moderate physical activity in 65 361 adults is associated with significant protective effects from severe COVID-19 outcomes. Br J Sports Med. 2022;56:568–78.

[35] Brawner CA, Ehrman JK, Bole S, et al. Inverse relationship of maximal exercise capacity to hospitalization secondary to coronavirus disease 2019. Mayo Clin Proc. 2021;96:32–9.
[36] Nieman DC, Wentz LM. The compelling link between physical activity and the body's defense system. J Sport Health Sci. 2019;8:201–17.
[37] Shephard R, Shek P. Potential impact of physical activity and sport on the immune system--a brief review. Br J Sports Med. 1994;28:247–55.
[38] Chastin SFM, Abaraogu U, Bourgois JG, et al. Effects of regular physical activity on the immune system, vaccination and risk of community-acquired infectious disease in the general population: systematic review and meta-analysis. Sports Med. 2021;51:1673–86.
[39] Collaborators GRF. Global burden of 87 risk factors in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet (London, England). 2020;396:1223–49.
[40] Stamatakis E, Ding D, Ekelund U, et al. Sliding down the risk factor rankings: reasons for and consequences of the dramatic downgrading of physical activity in the Global Burden of Disease 2019. Br J Sports Med. 2021;55:1222–3.
[41] Wunsch K, Kienberger K, Niessner C. Changes in physical activity patterns due to the Covid-19 pandemic: a systematic review and meta-analysis. Int J Environ Res Public Health. 2022;19:2250.