Preventive Medicine Reports 32 (2023) 102130

Contents lists available at ScienceDirect

Preventive Medicine Reports

journal homepage: www.elsevier.com/locate/pmedr

Review article

Baseline physical activity and the risk of severe illness and mortality from COVID-19: A dose–response meta-analysis

Junjie Liu [a,1], Zhiguang Guo [b,1], Songtao Lu [a,*]

[a] School of Sports, Wuhan University of Science and Technology, Wuhan 430081, China
[b] School of Sports Health, HuBei University of Chinese Medicine. Wuhan 430081, China

ARTICLE INFO

Keywords:
Physical activity
COVID-19
Mortality
Severe illness
Meta-analysis
Dose–response

ABSTRACT

To provide a scientific basis for improved exercise-based immunity, a *meta*-analysis was used to explore the dose–response relationship between physical activity (PA) and the risk of severe illness and mortality related to COVID-19 (coronavirus disease 2019). To this end, we searched PubMed, Web of Science databases from January 2020 through April 2022. 14 observational studies met the criteria for inclusion in the *meta*-analysis, including 2840 cases of severe illness and death from COVID-19. Categorical dose–relationship analysis showed that the risks of severe illness and mortality from COVID-19 were, respectively, 46% (risk ratio (RR): 0.54; confidence intervals (CIs): 0.41–0.68) and 59% (RR = 0.41; 95%CI: 0.23–0.58) lower for the highest dose of PA compared with the lowest dose of PA. The results of the continuous dose–response analysis show an inverse nonlinear relationship ($P_{non\text{-}linearity} < 0.05$) between PA and both the risk of severe illness and mortality from COVID-19. For PA below 10 MET-h/week (MET-h/week: metabolic equivalent of task-hours/week), an increase of 4 MET-h/week (1 h of moderate-intensity or 0.5 h of high-intensity PA) was associated with 8% and 11% reductions in the risk of severe illness and mortality from COVID-19. PA above 10 MET-h/week lowered the risk of severe illness and mortality from COVID-19 by 7% and 9%, respectively, for each 4 MET-h/week increase. Doses of WHO-recommended PA levels (10 MET-h/week) may be required for more substantial reductions in the risk of severe illness and mortality from COVID-19.

1. Introduction

The coronavirus disease 2019 (COVID-19) continues to spread worldwide. As of July 15, 2022, COVID-19 had caused 6,356,812 deaths worldwide (WHO, 2022a,b). Governments and medical institutions worldwide are committed to controlling, limiting, and ending this pandemic, via, for example, vaccination and antiviral treatments based on blood products and antibodies. However, the emergence of >5000 mutations of COVID-19 and the second and subsequent waves of the infection in various countries make the current situation extremely complex (HAAs et al., 2021). Baseline characteristics of patients with COVID-19, such as old age, obesity, heavy smoking status, and potential comorbidities (such as hypertension, respiratory disease, cardiovascular disease, and cancer), are associated with a higher risk of COVID-19-related mortality (Lee et al., 2022). Moreover, whether baseline physical activity (PA) is an essential factor that can change the symptoms of COVID-19 illness is a question that has attracted extensive attention from scholars.

Physical activity (PA) had been proved as one of the main factors in promoting health (Ekelund et al., 2019; Piercy et al., 2018; Chastin et al., 2020). The lack of adequate PA is associated with 6% to 10% of the major chronic diseases and a 9% higher risk of premature mortality worldwide (Lee et al., 2012). As we all know, adequate PA can significantly reduce all-cause and disease-specific mortality (such as death from pneumonia) (Kyu et al., 2016; Lu et al., 2022). Studies have shown that PA significantly improves human immunity and protects against severe and infectious respiratory tract infections. (Piercy et al., 2018; Chastin et al., 2020). In addition, PA may positively impact inflammation and is a potential causal factor for chronic diseases such as cardiovascular disease and cancer. Higher PA doses have a more positive link with disease inflammation impact (Zbinden-Foncea et al., 2020). Bizuti et al., 2022 assume the regular practice of moderate-intensity physical activity is responsible for promoting a reduction in the concentrations of pro-inflammatory cytokines (IL-6, TNF-α and IL-1β), as

* Corresponding author at: No.16, Huangjiahu West Road, Hongshan District, Wuhan City, Hubei Province, China.
E-mail address: songtaozhenzhen@sina.com (S. Lu).
[1] These authors contributed equally as first-author.

https://doi.org/10.1016/j.pmedr.2023.102130
Received 19 September 2022; Received in revised form 21 January 2023; Accepted 6 February 2023
Available online 8 February 2023

well as triggering the increase in the production of anti-inflammatory cytokines (IL-4 and IL-10) (Bizuti et al., 2022).

However, previous studies have investigated the potential link between PA and COVID-19, with inconsistent results. Recent studies have found that physical activity is not associated with SARS-CoV-2 infectivity and COVID-19 infection but is significantly associated with COVID-19 severity and mortality (Rowlands et al., 2021). Pinto et al. (2021) found that baseline PA of hospitalized COVID-19 patients was not independently associated with the length of stay or any other clinically relevant outcome (severe illness and mortality). The authors concluded that the underlying diseases and ages of COVID-19 patients had attenuated the protective effect of PA against the risk of COVID-19 symptoms (Pinto et al., 2021). Research on this topic is just emerging, and the impact of PA on the risk of COVID-19 is still unclear, requiring systematic reviews and *meta*-analyses of relevant research data.

Rahmati et al. (2022) conducted a *meta*-analysis of studies on this topic. Although the effect of PA was calculated on the basis of the original data in this study, the actual cause of the impact of PA on severe COVID-19 and mortality was difficult to analyze from the results because confounding factors such as age, body weight, and related underlying diseases were not included in the analysis (Rahmati et al., 2022). In addition, this study took cardiopulmonary function as one measure of physical activity level, which made the results inconclusive. Finally, this study did not address the controversy regarding the protective effects of different levels of physical activity (Rahmati et al., 2022). Furthermore, A recent systematic review assumed the regular practice of adequate intensity is suggested as an auxiliary tool in strengthening and preparing the immune system for COVID-19 (da Silveira et al., 2021). However, no systematic review of the above empirical studies has been known to quantify the preventive effects of various doses of physical activity against severe illness and mortality from COVID-19. Therefore, to take into account the current international guidelines for physical activity that specifically aim to reduce the risk of COVID-19 illness burden, in our study, we conducted a dose–response *meta*-analysis to quantify the relationship between different physical exercise doses and the risk of severe illness and mortality from COVID-19.

For this study, baseline physical activity refers to the physical activity status of COVID-19 patients prior to infection. Metabolic equivalent of task (MET) used as dose in this study is a physiological indicator describing the body's metabolic equivalent of PA energy, defined as energy consumption per kilogram of body weight per hour: 1 MET = 1 kcal/kg * h.

2. Methods

This study was conducted following the structured reporting procedures prescribed by PRISMA (International Prospective Register of Systematic Reviews Database Management Organization) (Page et al., 2021) and registered with PROSPERO; the number is CRD42022344701.

2.1. Eligibility criteria

The criteria for inclusion and each article determined for inclusion were discussed by the three authors. The inclusion criteria were as follows: (1) The studies were published as epidemiological observational cohort studies, case controls, and cross-sectional design investigation studies. (2) The studies provide the odds ratio, the relative risk (RR or HR), and the 95% confidence interval (95%CI) of physical activity levels related to the risk of severe illness and mortality from COVID-19 (or provide raw data to calculate these indicators). Duplicates were excluded. Only the latest studies were selected if they were studied at different time points in the same cohort. In addition, if multiple articles were published in the same group, we chose papers that were conducted for a longer period of time or with a larger sample size. First, two authors decided to include the literature independently. Then, the three authors discussed the inconsistencies to determine whether to include the literature.

2.2. Search strategy

We searched PubMed and the Web of Science database (from January 2020 through April 2022) for any literature on the relationship between physical activity and COVID-19. The terms "exercise or physical activity or sport or walking or motor activity" and "COVID-19 or SARS-CoV-2″ and "severe or ICU or mortality or die or death survival" were used to search for the relevant literature. The last of the search was conducted in April 2022, and there was no language limit. The reference lists of selected and related review articles were screened step by step to identify potentially relevant studies. All searches were conducted independently by two authors, and differences were resolved by a group discussion. When the same population or cohort data were included in several works of literature, only the most recent literature or literature using the largest population was used in the *meta*-analysis.

2.3. Quality of evidence

The Newcastle–Ottawa Scale (NOS) was used to evaluate literature quality, and scores of 0 ~ 3, 4 ~ 6, and 7 ~ 9 were determined as low, medium, and high quality, respectively (Wells et al., 2009). Each article was evaluated independently by two 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 literature quality was inconsistent, the group focused on solving the issue and identifying a final score in terms of its quality.

2.4. Data synthesis and analysis

Stata16.0 software was used for the *meta*-analysis. P values$<$0.05 were considered statistically significant, and all tests were double-sided. The effect sizes (adjusted or not adjusted), the risk ratios (RRs), and the 95% confidence intervals (CIs) of the group with the highest dose of PA compared with the group with the lowest dose of PA were combined and the combined effect values were calculated using a random effect model. Heterogeneity was assessed and described by I^2 statistics as the percentage of variation in the study; I^2 values of 25%, 50%, and 75% indicate low, moderate, and high levels of heterogeneity, respectively (Higgins and Green, 2011). Egger and Begg tests were used to determine any publication bias. During sensitivity analysis, each study was deleted one by one to check whether the combined effect of the remaining studies had changed (Higgins and Green, 2011). Subgroup *meta*-analysis was conducted by PA dose categories, gender, age, study area, study quality, and adjustment for confounding factors, and *meta*-regression was used to examine the heterogeneity among studies.

The categorical dose–response relationships were divided into dichotomous and multi-categorical doses, shown in the study. The combined effect value RR was generated by comparing the highest and lowest doses. For the analysis of 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. We assumed that their dose of PA remained at this level in the follow-up survey. As for determining the exposure value of the included dose, we set the median as its determined dose. If the development interval was $<$ 0.5, we set it as 0.25. If the upper open interval was greater than or equal to 1, the difference between the intermediate dose interval was 0.25, so the exposure value was set as 1.25 (Zhang et al., 2015). These are combined absolute indices of intensity, duration, and frequency and are also used to calculate exposures to MET units that are not directly reported in the literature. To address the differences in PA units in different studies, we adopted the classification method by Ainsworth et al.(2011), classifying PA into light

PA (3 of MET-h, such as walking exercise), moderate PA (4 MET-h), and vigorous PA (8 MET-h). We then converted the duration of a particular PA intensity (h/week) to MET-h/week in combination with the frequency of the week (Ainsworth et al., 2011).

We used robust error *meta*-regression (REMR) (Xu and Doi, 2018) for model fitting. The REMR approach is based on a "one-stage" framework, treating each study as a cluster and fitting the revised regression to the average PA dose across the entire dataset. In addition, the method uses the inverse variance method to weight each dose–specific effect in the data and balances heteroscedasticity in the REMR model to ensure the unbiased estimation of parameters. Finally, we used restricted cubic splines as connection functions to fit linear and nonlinear dose–response models. On the basis of dose-centralization treatment, the independent variable PA dose of the model was set as three nodes (0, 6.75, and 21), including two regression splines. The $\chi 2$ test was used to test the hypothesis that the regression coefficient of the second regression spline is significant ($p < 0.05$), indicated by a linear or nonlinear dose–response relationship. A dose–response relationship curve was drawn using the Stata software XBLC command (Zhang et al., 2015).

3. Results

3.1. Description of included studies

Preliminarily, 270 items from the literature were detected. According to the literature inclusion and exclusion criteria formulated in this study, 8 cohort studies, 4 case–control studies, and 2 cross-sectional studies were finally included, involving a total of 560,078 subjects and about 2864 cases of severe illness and mortality related to COVID-19 (there were studies but no reported cases). Fig. 1 displays the steps for retrieval and inclusion. Table 1 shows literature features. Of the 14 works of literature, 2 are from North America (Brandenburg et al., 2021; Sallis et al., 2021), 6 are from Asia (Baynouna AlKetbi et al., 2021; Cho et al., 2021; Halabchi et al., 2021; Lee et al., 2022; Tavakol et al., 2021; Yuan et al., 2021), 5 are from Europe (Ahmadi et al., 2021; Ekblom-bak et al., 2021; Hamrouni et al., 2021; Katsoulis et al., 2021; Salgado-aranda et al., 2021), and 1 is from Oceania (Steenkamp et al., 2022). The NOS scale was used to score the included literature. The most problematic domains of study quality were selection for ascertainment of exposure, Comparability for outcome assessment, and follow-up rate. 4 studies did not report ascertainment of exposure, 3 did not report Confounding factors, and 3 cohort studies did not report follow-up rates, respectively. In all, 9 works of literature were of high quality, or equal to 7 points, and the others were of medium quality (see Supplementary A Table 1).

3.2. Categorical dose–response relationship between PA and the risk of severe COVID-19 illness

Compared with the lowest dose of PA, the highest dose of PA can reduce the risk of severe COVID-19 by 46% (RR = 0.54; 95%CI: 0.41–0.68), and the heterogeneity test result is $I^2 = 69.03\%$ ($p < 0.01$), showing that there is significant heterogeneity in the research results (as shown in Fig. 2). On excluding each study-one by one, no significant change was found in the results of the combined effect. Published bias analysis with the Begg test ($p = 0.54 > 0.05$), the Egger test ($p = 0.70 > 0.05$), and the funnel diagram also showed no significant published bias (see Supplementary B Fig. 1).

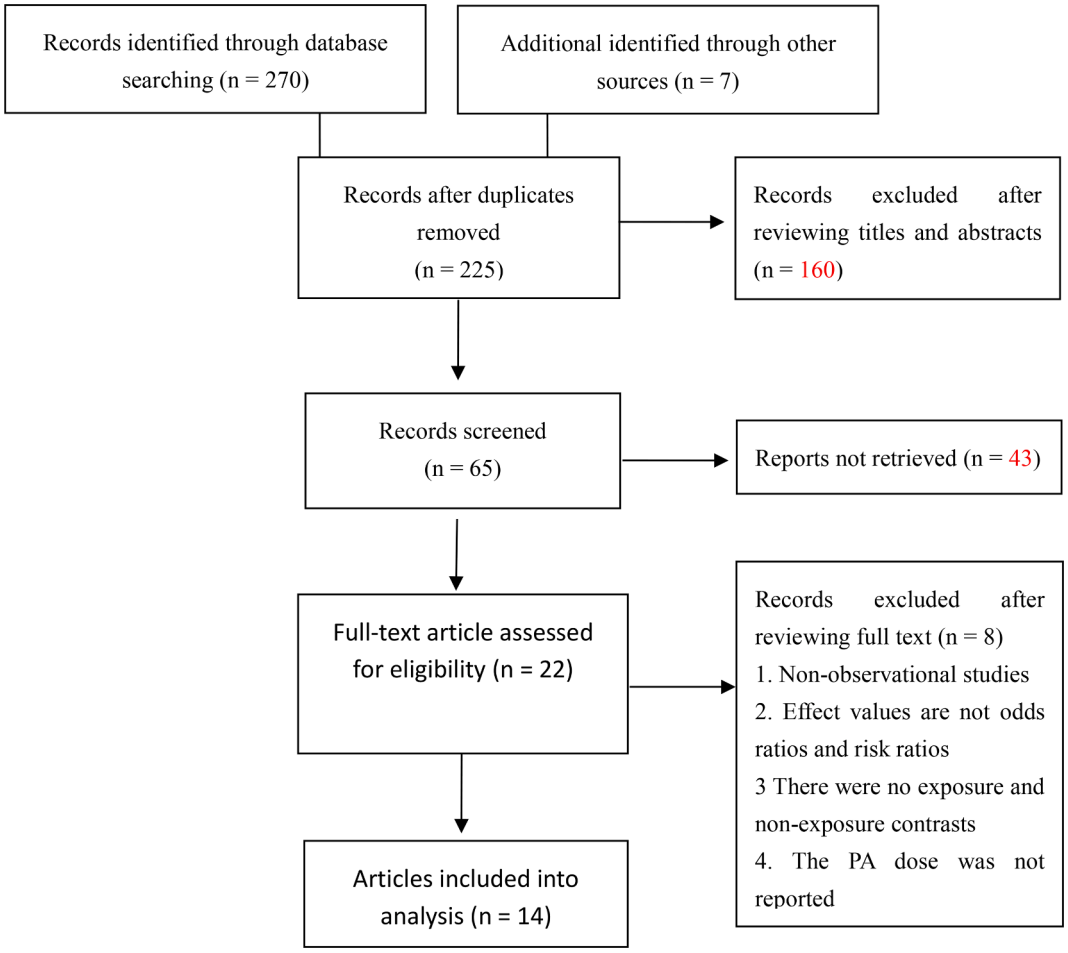

Fig. 1. Flow chart of study selection.

Table 1
Summary of Included Studies.

Study (year)	Country	Research type	Case\total	Age	Gender (Female %)	Dose of PA	Adjusted factor*	Outcome	Research Quality
Ahmadi(2021)	UK	Cohort	387\468569	56.5 ± 8.1	54.6%	3 doses:High, medium, and low	1–15	Mortality	8
Baynouna(2021)	AUH	Cohort	135、16\641	average 44	36%	5 doses:exercise times	NP*	Mortality, Severe	6
Brandenburg (2021)	CA	Case-control	NP\263	86%<65	57%	4 dose:High, medium, low, and no	2 5 6 8 9 12 15	Severe	7
Cho(2021)	KR	Case-control	75\ 125,780	50.7 ± 14.3	60.9%	5 doses:MET-min/week	1–3 9 14 16 17	Mortality	9
Ekblom-Bak (2021)	SWE	Case-control	172、138/ 407131	average 49.9	30%	3 doses:exercise times	1 2 5 16	Mortality, Severe	7
Hamrouni(2021)	UK	cohort	397\ 259 397	37–73	55.1%	3 doses:High, medium, and low	1 2 4 5 16 17	Mortality	8
Halabchi(2021)	Iran.	Cross-section	60\79\4694	36.45 ± 9.77	55%	2 dose:sedentary and physically active	NP	Mortality, Severe	6
Katsoulis(2021)	UK	cohort	NP\ 85,308	18–69	NP	3 doses:High, medium, and low	1 2 7 9	Severe	7
Lee (2021)	KR	cohort	277\118 768	NP	51.2%	4 dose:High, medium, low, and no	1 2 5–9 14 16	Mortality, Severe	9
Salgado(2021)	ESP	cohort	45\552	18–70	NP	2 dose:sedentary and physically	NP	Mortality	7
Sallis(2021)	USA	cohort	1199、771 \2970	47 ± 16.97	61.9%	3 doses:High, medium, and low	1–15	Mortality, Severe	9
Steenkamp (2021)	ZA	cohort	NP\65361	41 ± 12.1	48.2%	3 doses:High, medium, and low	1 2 6 8 9 14 15	Mortality, Severe	8
Tavakol(2021)	Iran	Cross-section	64\188	18–75	52.7%	2 dose:sedentary and physically	NP	Severe	6
Yuan(2021)	CN	Case-control	29\164	61.8 ± 13.6	48.8%	2 dose:sedentary and physically	NP	Mortality, Severe	6

*Case\total: number of cases and total sample size; Age characteristics: A single value indicates the average age, and the others are age ranges. * Correction for confounding factors: 1 age, 2 gender, 3 socioeconomic status, 4 race, 5BMI, 6 cardiovascular disease, 7 cancer, 8 diabetes, 9 hypertension, 10 use of antihypertensive drugs, 11 use of corticosteroids, 12 chronic lung/respiratory disease, 13 liver disease, 14 HIV, 15 end-stage kidney and immune diseases, 16 smoking, 17 alcohol consumption. NP*: Not reported. ZA: South Africa, UK: United Kingdom, AUH: United Arab Emirates, CA: Canada, SWE: Switzerland, Iran, KR: South Korea, ESP: Spain, USA, ZA: New Zealand, CN: China。.

As for the source of heterogeneity, between-groups heterogeneity appeared in dose categories, adjusted confounding BMI factors indicating that these factors affected the overall effect value and that different levels of PA had significantly different effects on the risk of severe COVID-19 illness (as shown in Table 2). The results of heterogeneity within subgroups showed that there was significant heterogeneity within the subgroups of overall effect value, high vS low dose comparison, moderate vS low dose comparison, PA Questionnaire for measurement, case–control group, high-quality research papers, European population, adjusted confounding factors (age, sex, and BMI), and unadjusted comorbidities hypertension(NO), diabetes, Cancer indicating that the research results of these subgroups may be affected by other factors.

3.3. Categorical dose–response relationship between PA and the risk of COVID-19 mortality

Compared with the lowest-dose PA, the highest-dose PA can reduce the risk of COVID-19 mortality by 59% (RR = 0.41; 95%CI: 0.23–0.58) and the heterogeneity test result is $I^2 = 82.43\%$ ($p < 0.01$), showing that the research results have significant heterogeneity (as shown in Fig. 3). In the sensitivity analysis, on excluding each study-one by one, no significant change was found in the results of the combined effect quantity. Published bias analysis with the Begg test ($p = 0.65 > 0.05$) and the Egger test ($p = 1.1420 > 0.05$) indicated no significant release bias (see Supplementary B Fig. 2).

As for the source of heterogeneity, between-groups heterogeneity

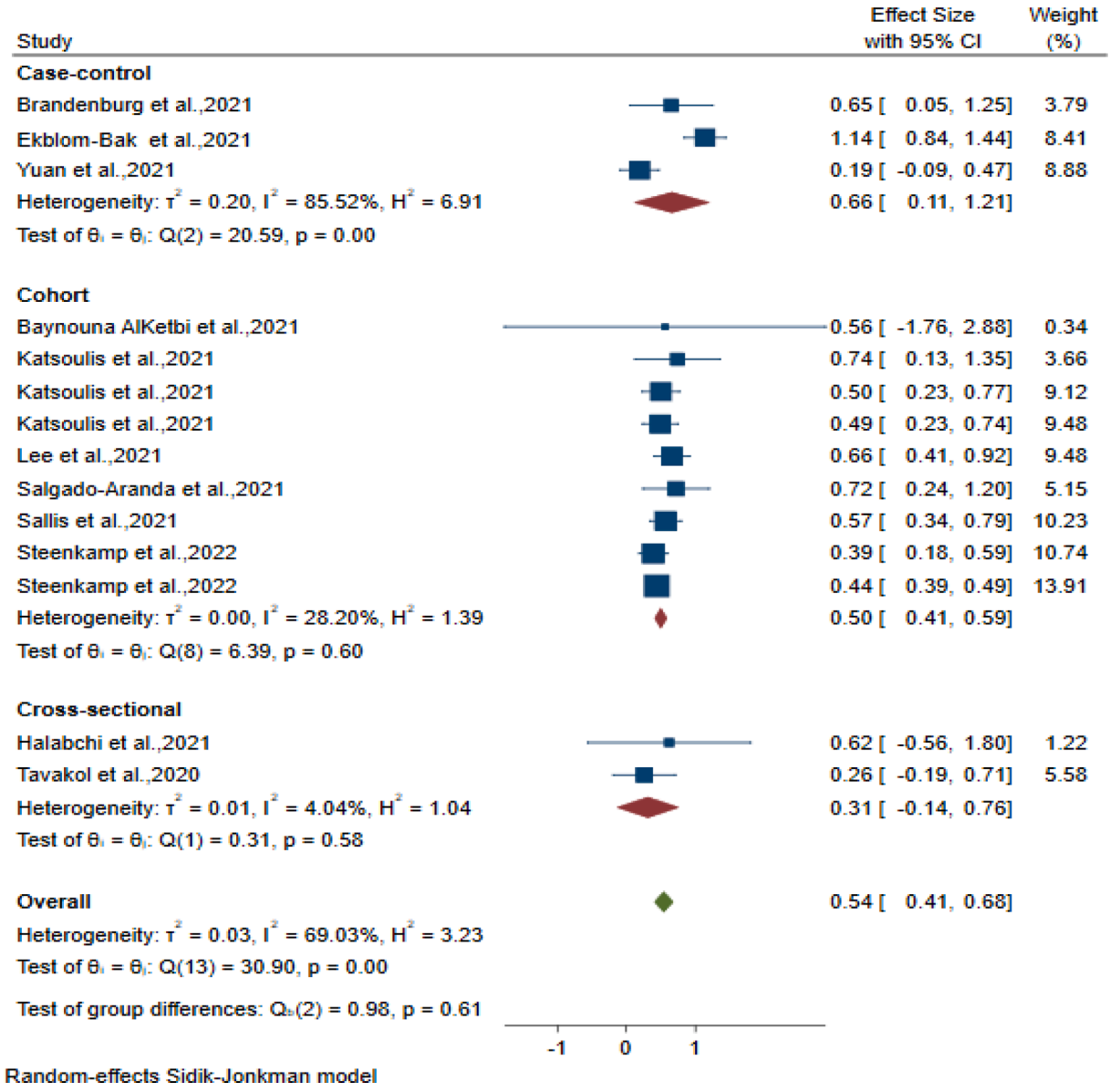

Fig. 2. The relationships of PA and Covid-19 illness severe.

appeared in Multiple dose comparison, Research quality, Different continent, adjusted confounding factors (age, sex, and BMI), which means that these factors may affect the overall effect value and that different levels of PA had significantly different effects on the risk of COVID-19 mortality (as shown in Table 2). The results of heterogeneity within subgroups showed that there was significant heterogeneity in total effect values, high vS low dose comparison, Questionnaire, Europe cohort studies, high-quality research papers, European population subgroups, adjusted confounding factor (age, gender, and BMI(no)), and unadjusted comorbidities (hypertension, diabetes,and cardiovascular disease), indicating that the research results of these subgroups may be affected by other factors.

3.4. Continuous dose–response relationship between PA and severe COVID-19 and the risk of mortality

Fig. 4 shows a negative nonlinear response relationship between PA and the risk of severe COVID-19 ($p_{non\text{-}linearity} < 0.05$). When PA was lower than 10 MET-h/week (the lowest physical activity dose recommended by the WHO), the effect size RR of severe COVID-19 lowered by 8% for each increase of 4 MET-h/week (medium intensity for 1 h or high intensity for 0.5 h) ($p < 0.01$; RR = 0.92; 95%CI: 0.88–0.97). When PA was higher than 10 MET-h/week, the RR of severe COVID-19 lowered by 7% for each increase of 4 MET-h/week ($p < 0.01$; RR = 0.93; 95%CI: 0.90–0.96).

Fig. 5 shows a negative nonlinear response relationship between PA and the risk of COVID-19 mortality ($p_{non\ linearity} < 0.05$). When PA was lower than 10 MET-h/week, the risk of COVID-19 mortality lowered by 11% for each increase of 4 MET-h/week (medium intensity for 1 h or high intensity for 0.5 h) ($p < 0.01$; RR = 0.89; 95%CI: 0.88–0.90). When PA was higher than 10 MET-h/week, the risk of COVID-19 mortality lowered by 9% for each increase of 4 MET-h/week ($p < 0.01$; RR = 0.91; 95%CI: 0.90–0.92).

4. Discussion

This study is the first dose–response *meta*-analysis on the relationship between PA and the risk of severe illness and mortality from COVID-19. Included are the cohort, case–control, and cross-sectional studies on the relationship between PA and the risk of severe illness and mortality from

Table 2
Results of the subgroup analysis.

subgroup		Severe risk					Mortality risk				
		N	RR(95% CI)	I^2 (%)	p^{a*}	P^{b*}	N	RR(95% CI)	I^2 (%)	p^{a*}	P^{b*}
total(highest vs lowest)		14	0.54(0.41,0.68)	69	0.01>		10	0.41(0.23,0.58)	83	0.01>	
Dose Categories	binary *	4	0.36(0.07,0.66)	35	0.28	0.01>	3	0.13(-0.02,0.28)	0	1	0.01
	H vS L *	10	0.59(0.44,0.73)	70	0.01>		7	0.47(0.27,0.67)	84	0.01>	
	M vS L *	15	0.75(0.63.0.87)	29	0.01		7	0.73(0.63,0.83)	16	0.14	
Research type	Cohort	9	0.50(0.41,0.59)	28	0.6	0.61	6	0.38(0.14,0.62)	90	0.01>	0.60
	Case-control	3	0.66(0.11,1.21)	85	0.01>		3	0.52(0.23,0.82)	44	0.23	
	Crosss-section	2	0.31(-0.14,0.76)	4	0.58		1	0.11(-0.79,1.00)			
Research quality	》7	9	0.59(0.43,0.74)	75	0.01>	0.14	7	0.47(0.28,0.67)	85	0.01>	0.01
	7<	5	0.36(0.09,0.63)	25	0.43		3	0.09(-0.10,0.28)	0	1	
Measurement of PA	Questionnaire	12	0.58(0.42,0.74)	54	0.01	0.09	9	0.40(0.20,0.60)	75	0.01>	0.80
	Objective	2	0.44(0.38,0.49)	2	0.64		1	0.43(0.36,0.49)			
Different continent	Europe	5	0.71(0.45,0.96)	62	0.01	0.17	4	0.56(0.24,0.88)	86	0.01>	0.01>
	Asia	5	0.41(0.17,0.65)	31	0.16		4	0.12(-0.06,0.29)	0	0.9	
	Others	4	0.46(0.35,0.56)	30	0.58		2	0.43(0.36,0.49)	0	0.83	
Confounding factor											
Age	Yes	8	0.59(0.42,0.76)	80	0.00	0.21	6	0.54(0.36,0.73)	74	0.01>	0.01>
	No	6	0.40(0.15,0.64)	21	0.43		4	0.12(-0.01,0.24)	0	0.9	
Sex	Yes	9	0.59(0.43,0.74)	75	0.01>	0.14	6	0.54(0.36,0.73)	74	0.01>	0.01>
	No	5	0.36(0.09,0.63)	22	0.43		4	0.12(-0.01,0.24)	0	0.9	
BMI	Yes	4	0.76(0.49,1.02)	66	0.02	0.03	4	0.64(0.44,0.85)	57	0.07	0.01>
	No	10	0.43(0.31,0.55)	40	0.68		6	0.25(0.11,0.38)	51	0.01>	
comorbidities											
hypertension	Yes	8	0.49(0.40,0.58)	29	0.58	0.60	4	0.50(0.24,0.76)	82	0.01	0.34
	No	6	0.58(0.25,0.92)	63	0.01>		6	0.33(0.09,0.56)	71	0.01>	
Diabetes	Yes	9	0.57(0.35,0.79)	59	0.01>	0.54	3	0.56(0.27,0.85)	85	0.01>	0.17
	No	5	0.49(0.38,0.60)	40	0.33		7	0.31(0.11,0.52)	65	0.01>	
angiocardiopathy	Yes	5	0.49(0.38,0.60)	40	0.33	0.54	5	0.51(0.31,0.72)	76	0.01	0.15
	No	9	0.57(0.35,0.60)	59	0.01>		5	0.26(0.00,0.53)	70	0.01	
Cancer	Yes	5	0.57(0.43,0.70)	0	0.84	0.93	2	0.64(0.20,1.08)	84	0.01>	0.21
	No	9	0.53(0.31,0.74)	75	0.01>		8	0.34(0.16,0.51)	76	0.01>	

* Note: binary is generally expressed as exercise and non-exercise, or physical activity and inactivity; * H vS L represent high vs low amounts of PA when multiple categories include the high, moderate, low or more categorical doses; M vS L represent the various subcategories of multiple categories: moderate vs low. P_a and P_b represent heterogeneity within and between subgroups, respectively.

COVID-19. Through the categorical dose *meta*-analysis, our main conclusion is that with the highest dose of PA, the risk of severe illness and mortality from COVID-19 is reduced by 46% and 59%, respectively, compared with the lowest dose of PA. The significant heterogeneity in the different dose groups (dichotomous and multiclass) indicates that the protective effects of different levels of PA against the risk of severe illness and mortality from COVID-19 are significantly different. Furthermore, we assume that the dose–response relationship between PA and the risk of severe illness and mortality from COVID-19 is nonlinear and negative for continuous dose–response analysis.

The dose of PA involves complex factors, such as intensity, time, and frequency, so we analyze the dose–response relationship according to classification and continuous dose. The two-classification dose–response relationship explains the difference between exercise and nonexercise, and the multi-classification dose–response relationship explains the dose effect of increasing PA relative to low-dose PA. This result is the same as that by Lu et al. (2022), by Kunutsor et al. (2022) on the mortality risk of general pneumonia, and by Rahmati et al. (2022) on the severity and mortality analysis of COVID-19 (Lu et al., 2022; Kunutsor et al., 2022; Rahmati et al., 2022). However, this study confirmed that the protective effect of different doses of PA against the risk of severe illness and mortality in patients with COVID-19 is significantly different. The result of this study is different from the conclusion of Rahmati et al. (2022) related to *meta*-analysis (Rahmati et al., 2022). In addition, this study included more literature, and the conclusion is more robust. The fitting of the continuous dose also makes the classified dose further confirm the results of categorical dose analysis. The higher level of PA, the stronger the protective effect against the risk of severe mortality in patients with COVID-19. There is a negative nonlinear relationship between PA and the risk of severe mortality in patients with COVID-19. The continuous dose–response analysis adds the intermediate dose to the multi-category dose for comparative analysis, which ensures that the conclusion of this research topic is more specific and systematic. A cohort study found a curvilinear association between healthy and CVRF (cardiovascular risk factors) individuals with a steep risk reduction at low to moderate MVPA volumes (Bakker et al., 2021). Moreover, a recent *meta*-analysis also confirmed a non-linear association with mortality risk reductions even for low levels of activity and a flattening of the curve at higher levels of post-diagnosis PA in adults with noncommunicable diseases (Geidl et al., 2020). Our study has the same result: low levels of PA have higher benefits for the risk of severe illness and mortality in patients with COVID-19. As shown in Fig. 5, 10 MET-h/week is almost nearby the inflection point. Furthermore, a previous dose–response *meta*-analysis of reduction in all-cause mortality from walking and cycling found the inflection point is about 11.25 MET-h/week.

The WHO global recommendation on the health benefits of PA points out that adults should perform at least 150 min of moderate-intensity aerobic PA per week, at least 75 min of high-intensity aerobic PA per week, or a combination of moderate- and high-intensity activities. These doses are equivalent to 10 MET-h/week (WHO, 2022a,b). Analysis of the continuous dose–response relationship in this study shows that PA and exercise of about 10 MET-h/week are the most obvious in reducing the risk of severe illness and mortality from COVID-19. The practical significance is that the minimum dose of 10 MET-h/week to prevent severe illness and mortality from COVID-19 is equivalent to the dose of physical activity recommended by the WHO (WHO, 2022a,b). At the same time, when the PA level exceeds 10 MET-h/week, the degree of increase in the protective effect against the risk of severe illness and mortality from COVID-19 is significantly reduced.

However, additional protective effects are still obtained, which is also consistent with the recommendations of the WHO physical activity guidelines (WHO, 2022a,b). A dose–response *meta*-analysis by Geidl et al. (2020) revealed that each 10 MET-h/week increase in PA was associated with a 22% lower mortality rate in adults with

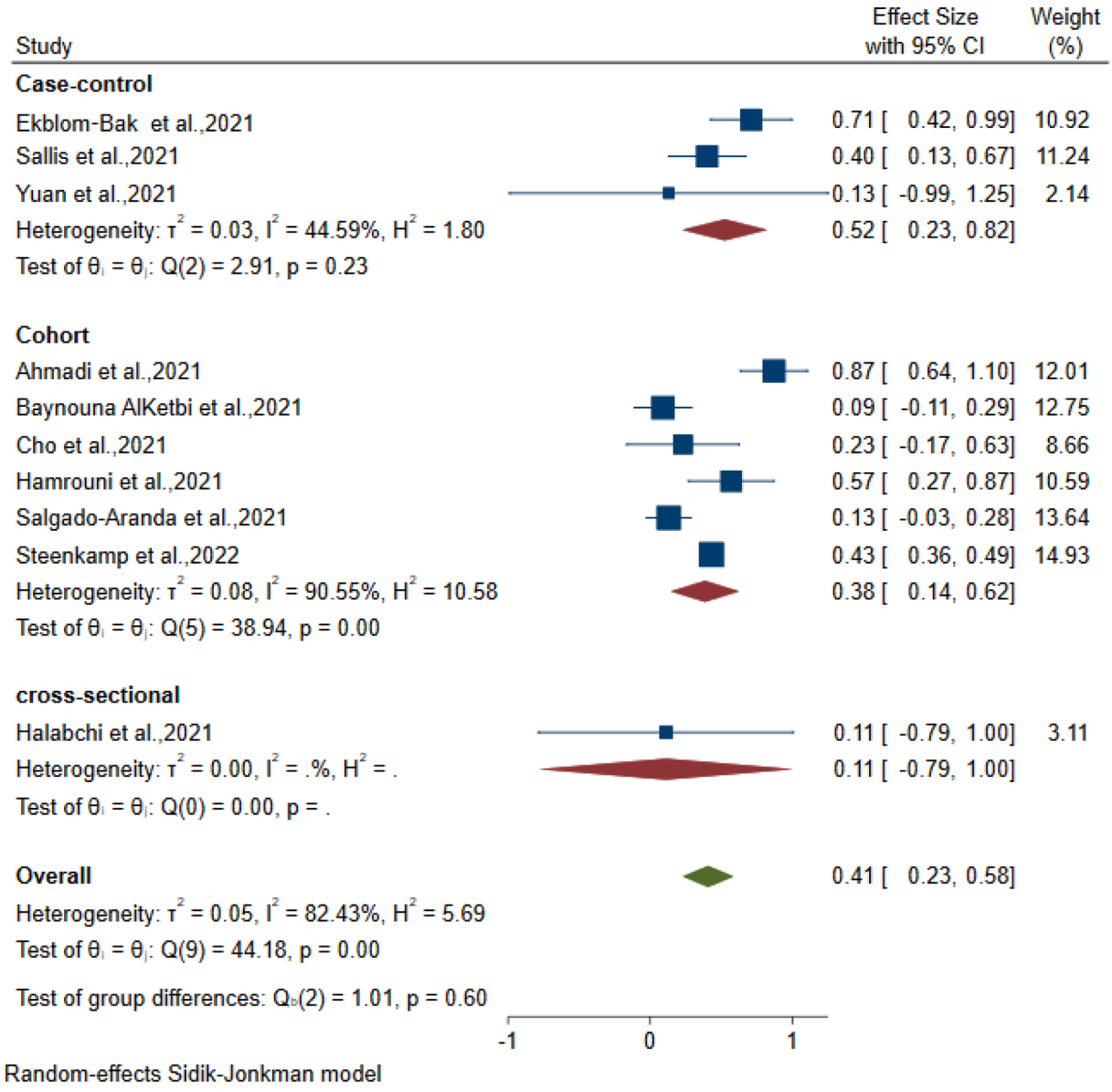

Fig. 3. The relationships of PA and Covid-19 mortality.

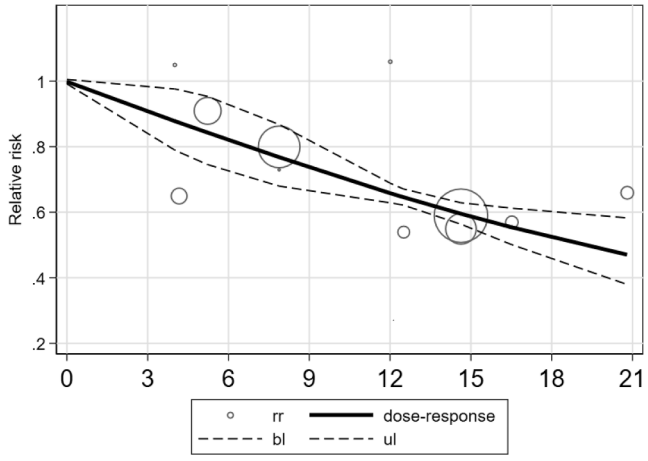

Fig. 4. The continuous dose response relationship between PA and the risk of COVID-19 severe illness.

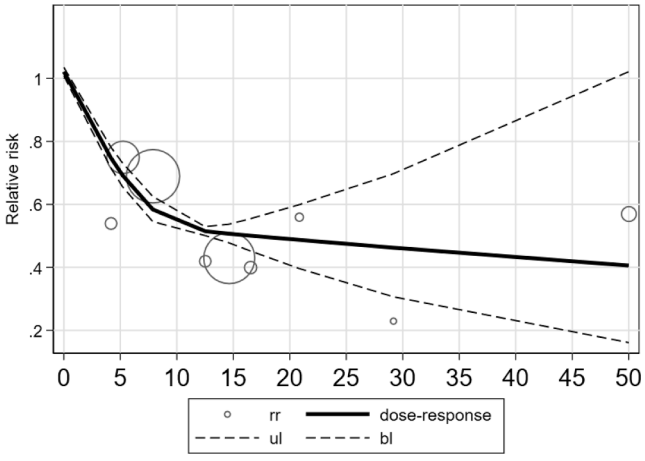

Fig. 5. The continuous dose response relationship between PA and the risk of COVID-19 mortality.

noncommunicable diseases (Geidl et al., 2020). However, 10 MET-h/week increase in PA is not practical. Our study confirmed that the practical significance of increasing the dose of PA by 4 MET-h/week per week is that exercising more than once a week (1 h of moderate PA or 0.5 h of vigorous PA) will reduce the risk of severe illness and mortality from COVID-19 by 7%-11%. Research by Williams et al. (2014) assumed that the mechanism of PA reducing mortality from general pneumonia might not only involve the root cause of the impact on pneumonia but also affect whether pneumonia leads to fatal consequences from other underlying diseases (Williams et al., 2014). For example, because pneumonia itself causes heart problems (Benson et al., 1970), such as left ventricular dysfunction (Corrales-Medina et al., 2011), or increases arrhythmias (Corrales-Medina et al., 2012), people with pneumonia and cardiac complications are more likely to die (Nieman et al., 1990). Therefore, PA may have more significant health benefits for patients with heart disease. It can enhance the mucosal immune function of patients and reduce the risk of mortality in patients with pneumonia and cardiac complications (Kimura et al., 2006). At the same time, the heterogeneity between diabetes subgroups in this study is close to significant, showing that PA may have a greater effect on the remission of diabetes in patients. PA can effectively regulate insulin and glucose metabolism, which is the protective mechanism of its health-promoting effect (Kunutsor et al., 2022). In addition, moderate PA, such as walking, enhances immune function by increasing the activity of macrophages, natural killer cells (Shephard et al., 1995), and neutrophils and regulating cytokines. These effects on systemic health may be the mechanism by which PA protects against severe illness and mortality from COVID-19 (Shephard and Shek, 1995).

The COVID-19 epidemic has led to a continuous increase in the number of severe cases and mortality, posing a threat to personal health and a heavy disease burden on all aspects of regions and countries. We found that increasing physical activity can significantly reduce the disease risk of COVID-19 and physical activity should be a positive factor in reducing the disease burden of COVID-19. However, the global burden of disease (GBD) 2019 ranked low physical activity 19th among the 20 most risky lifestyles leading to chronic diseases, lower than 10th place in the same report published in 2010 (Collaborators, 2020; Stamatakis et al., 2021). In addition, according to a recent *meta*-analysis (Wunsch et al., 2022), due to the COVID-19 pandemic, PA in all age groups of the general population has lowered. Facing the global spread of COVID-19, we must accept the vital role of physical activity in reducing the burden of the disease.

Finally, our study is the first *meta*-analysis study on the dose–response relationship between PA and severe illness and mortality from COVID-19. The results of this study are based on a large-sample cohort study and a case–control group study, as well as the advantages of years of follow-up investigation, so the results are relatively robust. However, this study may have the following limitations: (1) The literature we included may be insufficient. The possible reason is that we set strict inclusion criteria. In addition, cohort studies require long-term follow-up surveys and the requirements of extensive sample data, so there are relatively few cohort studies on related topics. Therefore, we can only set three nodes in the restrictive cubic bar to produce two regression splines to judge whether the overall study is linear or nonlinear according to the second regression spline. Such treatment may not verify the specific linear or nonlinear conclusion of PA dose after 10 MET-h/week, and we need to explain this conclusion carefully. Therefore, more in-depth studies on the protective factors of high-intensity PA against mortality from COVID-19 are required for the future. (2) The methods of PA evaluation included in the literature of this study are subjective measurements, and the dose may be inaccurate. In addition, the habit of exercise or sport is based on the assumption that there is no change in the long-term follow-up. The dose of PA is assumed to remain unchanged in the long-term observational study. This will make the results inaccurate, but some cohort studies have not been corrected or classified, which should be paid attention to in future related research.

5. Conclusion

There was a significant nonlinear negative dose–response relationship between the level of PA and the risk of severe illness and mortality from COVID-19. Various doses of PA were protective factors against severe illness and mortality from COVID-19. The higher physical activity dose significantly reduces the risk of severe illness and mortality from COVID-19. The degree of risk reduction is more significant when the total physical activity dose is lower than 10 MET-h/week, and the degree of enhancement is weakened when PA is higher than 10 MET-h/week. Doses of WHO-recommended PA levels may be required for more substantial reductions in severe illness and mortality from COVID-19.

6. Ethical compliance

The underlying work is based on systematic reviews of published data and thus does not require ethical review approval.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pmedr.2023.102130.

References

Ahmadi, M.N., Huang, B.-H., Inan-Eroglu, E., et al., 2021. Lifestyle risk factors and infectious disease mortality, including COVID-19, among middle aged and older adults: Evidence from a community-based cohort study in the United Kingdom. Brain Behav. Immun. 96, 18–27.

Ainsworth, B.E., Haskell, W.L., Herrmann, S.D., et al., 2011. 2011 Compendium of Physical Activities: a second update of codes and MET values. Med. Sci. Sports Exerc. 43 (8), 1575–1581.

Bakker, E.A., Lee, D.C., Hopman, M.T.E., Oymans, E.J., Watson, P.M., Thompson, P.D., Eijsvogels, T.M.H., 2021. Dose-response association between moderate to vigorous physical activity and incident morbidity and mortality for individuals with a different cardiovascular health status: A cohort study among 142,493 adults from the Netherlands. PLoS Med. 18 (12) https://doi.org/10.1371/journal.pmed.1003845.

Baynouna AlKetbi, L.M., Nagelkerke, N., Abdelbaqi, H., et al., 2021. Risk Factors for SARS-CoV-2 Infection Severity in Abu Dhabi. J Epidemiol Glob Health 11 (4), 344–353.

Benson, H., Akbarian, M., Adler, L.N., et al., 1970. Hemodynamic effects of pneumonia. I. Normal and hypodynamic responses. J. Clin. Invest. 49 (4), 791–798.

Bizuti, M.R., Starck, É., da Silva Fagundes, K.K., et al., 2022. Influence of exercise and vitamin D on the immune system against Covid-19: an integrative review of current literature. Mol. Cell. Biochem. 477 (6), 1725–1737.

Brandenburg, J.P., Lesser, I.A., Thomson, C.J., et al., 2021. Does higher self-reported cardiorespiratory fitness reduce the odds of hospitalization from COVID-19? J. Phys. Act. Health 18 (7), 782–788. https://doi.org/10.1123/jpah.2020-0817.

Chastin, S., Abaraogu, U., Bourgois, J., et al., 2020. Physical activity, immune function and risk of community acquired infectious disease in the general population: systematic review and meta-analysis. SSRN Electron. J. https://doi.org/10.2139/ssrn.3673184.

Cho, D.-H., Lee, S.J., Jae, S.Y., et al., 2021. Physical activity and the risk of COVID-19 infection and mortality: a nationwide population-based case-control study. J. Clin. Med. 10 (7), 1539.

Collaborators, G.R.F., 2020. 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) 396 (10258), 1223–1249.

Corrales-Medina, V.F., Suh, K.N., Rose, G., et al., 2011. Cardiac complications in patients with community-acquired pneumonia: a systematic review and meta-analysis of observational studies. PLoS Med. 8 (6), e1001048.

Corrales-Medina, V.F., Musher, D.M., Wells, G.A., et al., 2012. Cardiac complications in patients with community-acquired pneumonia: incidence, timing, risk factors, and association with short-term mortality. Circulation 125 (6), 773–781.
da Silveira, M.P., da Silva Fagundes, K.K., Bizuti, M.R., et al., 2021. Physical exercise as a tool to help the immune system against COVID-19: an integrative review of the current literature. Clin. Exp. Med. 21 (1), 15–28.
Ekblom-Bak, E., Väisänen, D., Ekblom, B., Blom, V., Kallings, L.V., Hemmingsson, E., Andersson, G., Wallin, P., Salier Eriksson, J., Holmlund, T., Lindwall, M., Stenling, A., Lönn, A., 2021. Cardiorespiratory fitness and lifestyle on severe COVID-19 risk in 279,455 adults: a case control study. Int. J. Behav. Nutr. Phys. Act. 18 (1) https://doi.org/10.1186/s12966-021-01198-5.
Ekelund, U., Tarp, J., Steene-Johannessen, J., et al., 2019. Dose-response associations between accelerometry measured physical activity and sedentary time and all cause mortality: systematic review and harmonised meta-analysis. BMJ 366. https://doi.org/10.1136/bmj.l4570.
Geidl, W., Schlesinger, S., Mino, E., Miranda, L., Pfeifer, K., 2020. Dose-response relationship between physical activity and mortality in adults with noncommunicable diseases: a systematic review and meta-analysis of prospective observational studies. Int. J. Behav. Nutr. Phys. Act. 17 (1), 109. https://doi.org/10.1186/s12966-020-01007-5.
Haas, E.J., Angulo, F.J., McLaughlin, J.M., et al., 2021. Impact and effectiveness of mRNA BNT162b2 vaccine against SARS-CoV-2 infections and COVID-19 cases, hospitalizations, and deaths following a nationwide vaccination campaign in Israel: an observational study using national surveillance data. Lancet 397 (10287), 1819–1829. https://doi.org/10.1016/s0140-6736(21)00947-8.
Halabchi, F., Mazaheri, R., Sabeti, K., Yunesian, M., Alizadeh, Z., Ahmadinejad, Z., Aghili, S.M., Tavakol, Z., 2021. Regular sports participation as a potential predictor of better clinical outcome in adult patients with COVID-19: A large cross-sectional study. J. Phys. Act. Health 18 (1), 8–12.
Hamrouni, M., Roberts, M.J., Thackray, A., Stensel, D.J., Bishop, N., 2021. Associations of obesity, physical activity level, inflammation and cardiometabolic health with COVID-19 mortality: a prospective analysis of the UK Biobank cohort. BMJ Open 11 (11), e055003.
Higgins, P.T., Green, S., 2011. Cochrane handbook for systematic reviews of interventions. New Jerse: A Version 5.1.0. The Johu Wiley Sons, Ltd Publication.
Katsoulis, M., Pasea, L., Lai, A.G., Dobson, R.J.B., Denaxas, S., Hemingway, H., Banerjee, A., 2021. 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 191, 41–47.
Kimura, F., Shimizu, K., Akama, T., Akimoto, T., Kuno, S., Kono, I., 2006. The effects of walking exercise training on immune response in elderly subjects. Internat. J. Sport Health Sci. 4, 508–514.
Kunutsor, S.K., Seidu, S., Laukkanen, J.A., 2022. Physical activity reduces the risk of pneumonia: systematic review and meta-analysis of 10 prospective studies involving 1,044,492 participants. Geroscience 44 (1), 519–532. https://doi.org/10.1007/s11357-021-00491-2.
Kyu, H.H., Bachman, V.F., Alexander, L.T., et al., 2016. Physical activity and risk of breast cancer, colon cancer, diabetes, ischemic heart disease, and ischemic stroke events: systematic review and dose-response meta-analysis for the Global Burden of Disease Study 2013. BMJ 354. https://doi.org/10.1136/bmj.i3857.
Lee, S.W., Lee, J., Moon, S.Y., Jin, H.Y., Yang, J.M., Ogino, S., Song, M., Hong, S.H., Abou Ghayda, R., Kronbichler, A., Koyanagi, A.i., Jacob, L., Dragioti, E., Smith, L., Giovannucci, E., Lee, I.-M., Lee, D.H., Lee, K.H., Shin, Y.H., Kim, S.Y., Kim, M.S., Won, H.-H., Ekelund, U., Shin, J.I., Yon, D.K., 2022. 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. 56 (16), 901–912.
Lee, I.-M., Shiroma, E.J., Lobelo, F., Puska, P., Blair, S.N., Katzmarzyk, P.T., 2012. Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy. Lancet 380 (9838), 219–229.
Lu, S., Liu, W., Li, R., et al., 2022. Leisure time physical activity and risk of pneumonia mortality: a dose-response meta-analysis. J. Sports Med. Phys. Fitness 62 (4), 547–553. https://doi.org/10.23736/s0022-4707.21.12017-1.
Nieman, D., Nehlsen-Cannarella, S., Markoff, P., Balk-Lamberton, A., Yang, H., Chritton, D., Lee, J., Arabatzis, K., 1990. The effects of moderate exercise training on natural killer cells and acute upper respiratory tract infections. Int. J. Sports Med. 11 (06), 467–473.
Page, M.J., McKenzie, J.E., Bossuyt, P.M., et al., 2021. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. J. Clin. Epidemiol. 134, 178–189.
Piercy, K.L., Troiano, R.P., Ballard, R.M., et al., 2020. The physical activity guidelines for Americans. J. Am. Med. Assoc. 320 (19), 2020.
Pinto, A.J., Goessler, K.F., Fernandes, A.L., Murai, I.H., Sales, L.P., Reis, B.Z., Santos, M. D., Roschel, H., Pereira, R.M.R., Gualano, B., 2021. No independent associations between physical activity and clinical outcomes among hospitalized patients with moderate to severe COVID-19. J. Sport Health Sci. 10 (6), 690–696.
Rahmati, M., Shamsi, M.M., Khoramipour, K., Malakoutinia, F., Woo, W., Park, S., Yon, D.K., Lee, S.W., Shin, J.I., Smith, L., 2022. Baseline physical activity is associated with reduced mortality and disease outcomes in COVID-19: A systematic review and meta-analysis. Rev. Med. Virol. 32 (5) https://doi.org/10.1002/rmv.2349.
Rowlands, A.V., Kloecker, D.E., Chudasama, Y., et al., 2021. Association of timing and balance of physical activity and rest/sleep with risk of COVID-19: A UK Biobank Study. Mayo Clin. Proc. 96 (1), 156–164.
Salgado-Aranda, R., Pérez-Castellano, N., Núñez-Gil, I., et al., 2021. Influence of Baseline Physical Activity as a Modifying Factor on COVID-19 Mortality: A Single-Center. Retrospective Study. Infect Dis Ther 10 (2), 801–814.
Sallis, R., Young, D.R., Tartof, S.Y., et al., 2021. Physical inactivity is associated with a higher risk for severe COVID-19 outcomes: a study in 48 440 adult patients. Br. J. Sports Med. 55 (19), 1099–1105.
Shephard, R., Rhind, S., Shek, P., 1995. The impact of exercise on the immune system: NK cells, interleukins 1 and 2, and related responses. Exerc. Sport Sci. Rev. 23, 215–241.
Shephard, R.J., Shek, P.N., 1995. Cancer, immune function, and physical activity. Can. J. Appl. Physiol. = Revue canadienne de physiologie appliquee 20 (1), 1–25.
Stamatakis, E., Ding, D., Ekelund, U., Bauman, A.E., 2021. 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. 55 (21), 1222–1223.
Steenkamp, L., Saggers, R.T., Bandini, R., et al., 2022. 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. 56 (10), 568–576.
Tavakol, Z., Ghannadi, S., Tabesh, M.R., Halabchi, F., Noormohammadpour, P., Akbarpour, S., Alizadeh, Z., Nezhad, M.H., Reyhan, S.K., 2021. Relationship between physical activity, healthy lifestyle and COVID-19 disease severity; a cross-sectional study. Z Gesundh Wiss 31 (2), 267–275.
Wells GA, Peterson J, Welch V, et al., 2009. The Newcastle-Ottawa scale (NOS) for assessing the quality in nonrandomized studies in meta-analyses, Ottawa, University of Ottawa. Available from: http://www. ohri. ca/ programs/ clinical_ epidemiology/ oxford. Asp.
Williams, P., 2014. Dose-response relationship between exercise and respiratory disease mortality. Med. Sci. Sports Exerc. 46 (4), 711–717. https://doi.org/10.1249/mss.0000000000000142.
World Health Organization, 2022. Global Recommendations on Physical Activity for Health. [2022-07-15]. https://www.who.int/publications/i/item/9789241599979.
World Health Organization, 2022. Coronavirus disease (COVID-19) Numbers at a glance [R/OL]. [2022-07-15]. https://www.who.int/emergencies/diseases/novel-coronavirus-2019.
Wunsch, K., Kienberger, K., Niessner, C., 2022. Changes in Physical Activity Patterns Due to the Covid-19 Pandemic: A Systematic Review and Meta-Analysis. Int. J. Environ. Res. Public Health 19 (4). https://doi.org/10.3390/ijerph19042250.
Xu, C., Doi, S., 2018. The robust error meta-regression method for dose-response meta-analysis. Int. J. Evid. Based Healthc. 16 (3), 138–144. https://doi.org/10.1097/xeb.0000000000000132.
Yuan, Q., Huang, H.-Y., Chen, X.-L., Chen, R.-H., Zhang, Y., Pan, X.-B., Chen, J.-N., Liu, N., Du, H., 2021. Does pre-existent physical inactivity have a role in the severity of COVID-19? Ther. Adv. Respir. Dis. 15 https://doi.org/10.1177/17534666211025221.
Zbinden-Foncea, H., Francaux, M., Deldicque, L., Hawley, J.A., 2020. Does high cardiorespiratory fitness confer some protection against proinflammatory responses after infection by SARS-CoV-2? Obesity 28 (8), 1378–1381.
Zhang, T., Dong, S., Zhou, Z., et al., 2015. The advanced meta-analysis method-based on stata. Fudan Univ. Press 220–232.