Electronic supplementary material

Physical activity and risk of infection, severity and mortality of COVID-19: a systematic review and nonlinear dose–response meta-analysis of data from 1,853,610 adults

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PubMed

#1 ("COVID-19" OR "COVID-19"[MeSH Terms] OR "COVID-19 Vaccines" OR "COVID-19 Vaccines"[MeSH Terms] OR "COVID-19 serotherapy" OR "COVID-19 serotherapy"[Supplementary Concept] OR "COVID-19 Nucleic Acid Testing" OR "covid-19 nucleic acid testing"[MeSH Terms] OR "COVID-19 Serological Testing" OR "covid-19 serological testing"[MeSH Terms] OR "COVID-19 Testing" OR "covid-19 testing"[MeSH Terms] OR "SARS-CoV-2" OR "sars-cov-2"[MeSH Terms] OR "Severe Acute Respiratory Syndrome Coronavirus 2" OR "NCOV" OR "2019 NCOV" OR (("coronavirus"[MeSH Terms] OR "coronavirus" OR "COV") AND 2019/11/01[PDAT] : 3000/12/31[PDAT]))

#2 "exercise"[MeSH Terms] OR "exercise"[All Fields] OR ("physical"[All Fields] AND "activity"[All Fields]) OR "physical activity"[All Fields] OR ("exercise"[MeSH Terms] OR "exercise"[All Fields] OR "exercises"[All Fields] OR "exercise therapy"[MeSH Terms] OR ("exercise"[All Fields] AND "therapy"[All Fields]) OR "exercise therapy"[All Fields] OR "exercise s"[All Fields] OR "exercised"[All Fields] OR "exerciser"[All Fields] OR "exercisers"[All Fields] OR "exercising"[All Fields]) OR ("life style"[MeSH Terms] OR ("life"[All Fields] AND "style"[All Fields]) OR "life style"[All Fields] OR "lifestyle"[All Fields] OR "lifestyles"[All Fields]) OR ("sedentary behavior"[MeSH Terms] OR ("sedentary"[All Fields] AND "behavior"[All Fields]) OR "sedentary behavior"[All Fields] OR ("physical"[All Fields] AND "inactivity"[All Fields]) OR "physical inactivity"[All Fields])

#3 #1 AND #2

#4 "mortality"[MeSH Terms] OR "mortality"[All Fields] OR "mortalities"[All Fields] OR "mortality"[MeSH Subheading] OR "death"[MeSH Terms] OR "death"[All Fields] OR "deaths"[All Fields] OR "covid 19"[MeSH Terms] OR "covid 19"[All Fields] OR "covid 19 infection"[All Fields] OR "hospital s"[All Fields] OR "hospitalisation"[All Fields] OR "hospitalization"[MeSH Terms] OR "hospitalization"[All Fields] OR "hospitalising"[All Fields] OR "hospitality"[All Fields] OR "hospitalisations"[All Fields] OR "hospitalised"[All Fields] OR "hospitalizations"[All Fields] OR "hospitalized"[All Fields] OR "hospitalize"[All Fields] OR "hospitalizing"[All Fields] OR "hospitals"[MeSH Terms] OR "hospitals"[All Fields] OR "hospital"[All Fields] OR "sever"[All Fields] OR "severe"[All Fields] OR "severed"[All Fields] OR "severely"[All Fields] OR "severer"[All Fields] OR "severes"[All Fields] OR "severing"[All Fields] OR "severities"[All Fields] OR "severity"[All Fields] OR "severs"[All Fields]

#5 #4 AND #3

Web of Science

#1 TOPIC: ("COVID-19" OR "SARS-CoV-2" OR “severe acute respiratory syndrome coronavirus 2” OR “coronavirus”)

#2 TOPIC: ("physical activity" OR “”exercise” OR “lifestyle” OR “physical inactivity”)

#3 #2 AND #1

#4 TOPIC: ("mortality" OR “death” OR "hospitalization" OR "hospitalisation", "infection" OR "severe COVID-19”)

#5 #4 AND #3

SportsDiscus

S1 (MH "COVID-19") OR (MH "SARS-CoV-2") OR (MH "severe acute respiratory syndrome coronavirus 2") OR (MH "coronavirus")

S2 (MH "physical activity") OR ‘exercise OR ‘lifestyle’ OR ‘physical inactivity’

S3 ((MH "physical activity") OR ‘exercise OR ‘lifestyle’ OR ‘physical inactivity’) AND (S1 AND S2)

S4 (MH "mortality") OR ‘death’ OR ‘hospitalization’ OR ‘hospitalisation’ OR ‘infection’ OR ‘severe COVID-19’

S5 S4 AND S3

Online supplemental emethod 2. Excluded studies and reasons for exclusion.

Did not include physical activity data:

Af Geijerstam A, Mehlig K, Börjesson M, et al (2021) Fitness, strength and severity of COVID-19: A prospective register study of 1 559 187 Swedish conscripts. BMJ Open 11(7):1–8. https://doi.org/10.1136/bmjopen-2021-051316

Brandenburg JP, Lesser IA, Thomson CJ, Giles L V. (2021) Does higher self-reported cardiorespiratory fitness reduce the odds of hospitalization from COVID-19? J Phys Act Heal 18(7):782–788. https://doi.org/10.1123/jpah.2020-0817

Christensen RAG, Arneja J, Cyr KS, Sturrock SL, Brooks JD (2021) The association of estimated cardiorespiratory fitness with COVID-19 incidence and mortality: A cohort study. PLoS One 16(5 May):1–10. https://doi.org/10.1371/journal.pone.0250508

Maltagliati S, Sieber S, Sarrazin P, et al (2021) Muscle strength explains the protective effect of physical activity against COVID-19 hospitalization among adults aged 50 years and older. J Sports Sci 39(24):2796–2803. https://doi.org/10.1080/02640414.2021.1964721

Data from hospitalised patients:

Pinto AJ, Goessler KF, Fernandes AL, et al (2021) No independent associations between physical activity and clinical outcomes among hospitalized patients with moderate to severe COVID-19. J Sport Heal Sci 10(6):690–696. https://doi.org/10.1016/j.jshs.2021.08.001

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. https://doi.org/10.1007/s40121-021-00418-6

Data from the same study:

Rowlands A V., Kloecker DE, 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. https://doi.org/10.1016/j.mayocp.2020.10.032

Hamrouni M, Roberts MJ, Thackray A, et al. Associations of obesity, physical activity level, inflammation and cardiometabolic health with COVID-19 mortality: A prospective analysis of the UK Biobank cohort. BMJ Open 2021;11:1–9. doi:10.1136/bmjopen-2021-055003

Did not meet with the design or statistical analysis criteria:

Cunningham GB (2021) Physical activity and its relationship with COVID-19 cases and deaths: Analysis of U.S. counties. J Sport Heal Sci 10(5):570–576. https://doi.org/10.1016/j.jshs.2021.03.008

Wang J, Sato T, Sakuraba A (2021) Worldwide association of lifestyle-related factors and COVID-19 mortality. Ann Med 53(1):1531–1536. https://doi.org/10.1080/07853890.2021.1968029

Online supplemental eTable 1. Characteristics of the studies.

Author, year Location	Study design	Source of information	Study period	Follow-up (years)	N (% females) / Age (years)	PA assessment	Outcome	Events	Covariates	Measure of association
Ahmadi et al. (2021) [40] UK	Prospective cohort study	UK Biobank	[2006-2010] and 2021	11.3	468,569 (54.6%) / 56.5	IPAQ short form	Mortality	Deaths (n=387)	Age at baseline, sex, socioeconomic status based on the Townsend deprivation index, ethnicity, BMI, corticosteroid use, and comorbidities (cardiovascular diseases, cancers, diabetes, chronic respiratory disease, liver disease, end-stage renal disease, immune disorders/HIV, and hypertension)	HR
Brandenburg et al. (2021) [37] Canada	Cross-sectional	Participants responses to an online survey	July 2020 to October 2020	-	263 (57%) / NR	PA participation was assessed using the modified physical activity rating questionnaire	Hospitalisation and severe COVID-19	Infections (n=263) Hospitalisations (n=28) Severe COVID-19 (n=123)	Age, sex, relationship status, ethnic origin, education, household income, smoking, alcohol consumption, BMI, presence of physician-diagnosed COVID-19 comorbidities (including diabetes, asthma, chronic obstructive pulmonary disease, renal disease, hypertension, cardiovascular disease, and pregnancy), and time between recovery from COVID-19 and	OR

									completion of the online survey	
Cho et al. (2021) [31] South Korea	Case-control	Korean National Health Insurance database	January 2020 to July 2020 (cases), and [2014-2017] (controls)	-	132,060 (NR) / 50.7	Questionnaire for physical activity	COVID-19 infection and mortality	Infections (n=6288) Deaths (n=92)	Age, sex, economic income, medical history (obesity, hypertension, diabetes mellitus, dyslipidaemia, ischaemic heart disease, and stroke), smoking status, and alcohol consumption	OR
de Souza et al. (2021) [32] Brazil	Cross-sectional	Participants responses to an online survey	June 2020 to August 2020	-	938 (65%) / NR	IPAQ short version, through an online questionnaire.	Hospitalisation	Hospitalisations (n=91) Severe COVID-19 (n=54)	Age, sex and pre-existing diseases	PR
Ekblom-Bak et al. (2021) [33] Sweden	Case-control	Health Profile Assessment database	[1992-2020] and 2021	-	4,283 (29.6) / 49.9	Self-reported	Hospitalisation, severe COVID-19, and mortality	Infections (n=857) Hospitalisations (n=547) Severe COVID-19 (n=172) Deaths (n=138)	Sex, age, performed year, educational level, civil status, country of birth, estimated VO_2max, BMI, number of chronic diseases, exercise habits, smoking, overall stress	OR
Hamdan et al. (2021) [38] Palestine	Cross-sectional	Participants responses to a questionnaire	August 2020 to December 2020	-	300 (55%) / NR	Physical activity was self-reported, and it was coded as yes or no	Hospitalisation	Infections (n=300) Hospitalisations (n=59)	NR	OR
Hamer et al. (2020) [20] UK	Prospective cohort study	UK Biobank	[2006-2010] and 2020	NR	387,109 (55.1%) / 56.2	IPAQ	Hospitalisation	Hospitalisations (n=760)	Age, sex, education, ethnicity, diabetes, hypertension, cardiovascular disease (heart attack, angina or stroke)	RR
Latorre-	Cross-	Participants	May 2020	-	420 (52.6%) /	IPAQ	Severe COVID-19	Severe	Age	RR

Román et al. (2021) [28] Spain	sectional	responses to an online survey	to June 2020		33.0			COVID-19 (n=139)		
Lee et al. (2021) [10] South Korea	Prospective cohort study	National Health Insurance Service of South Korea	January 2020 to July 2020 (cases), and [2018-2019] (controls)	NR	76,395 (51.2%) / NR	Questionnaire (weekly minutes of moderate and vigorous physical activity, aerobic physical activity and muscle strengthening) and then estimation of METs according to it.	COVID-19 infection, severe COVID-19, and mortality	Infections (n=2,295) Severe COVID-19 (n=446) Deaths (n=45)	Age, sex, region of residence, Charlson comorbidity index, history of diabetes mellitus, tuberculosis, stroke and cardiovascular disease, BMI, systolic blood pressure, diastolic blood pressure, fasting blood glucose, serum total cholesterol, glomerular filtration rate, household income, alcoholic drinks, medication for hypertension, diabetes mellitus and cardiovascular disease	RR
Li-Hua et al. (2021) [34] Multi-country (COVID-19 Host Genetic Initiative)	Case-control	Genome-wide association studies	NR	-	1,019,301 (NR) / NR	Accelerometer	Hospitalisation and severe COVID-19	Infections (n=6,492) Hospitalisations (n=6,492) Severe COVID-19 (n=2,972)	NR	OR
Maltagliati et al. (2021) [29] Multi-country (European	Prospective cohort study	Survey of Health, Ageing and Retirement in Europe (SHARE)	[2004-2017] and [2020]	NR	3,139 (56.2%) / 69.3	Self-reported	Hospitalisation	Infections (n=266), Hospitalisations (n=66)	Age, height, sex, BMI, cardiovascular disease, diabetes, cancer, chronic kidney disease, rheumatoid arthritis, respiratory disease and weak	OR

adults)									muscle strength	
Rowlands et al. (2021) [35] UK	Prospective cohort study	UK Biobank	[2013-2015] and linked with data from March 2020 to March 2021	5.6	82,253 (55%) /68.0	Accelerometer	Severe COVID-19	Infections (n=2,388) Hospitalisations (n=434) Severe COVID-19 (n=434)	Age, follow-up time, season of accelerometer wear, sex, ethnicity, Townsend score, employment status, cardiovascular disease or cancer diagnosis before accelerometer baseline	OR
Sallis et al. (2021) [21] USA	Retrospective cohort study	Electronic health records of Kaiser Permanente South California (KPSC)	2018-2020	2	48,440 (61.9%) / 47.5	Self-reported	Hospitalisation, severe COVID-19, and mortality	Infections (n=48,440) Hospitalisations (n=4,236) Severe COVID-19 (n=1,199) Deaths (n=771)	Age, sex, race, underlying medical conditions (history of cancer, chronic kidney disease, chronic obstructive pulmonary disease, cardiovascular disease, history of organ transplant), obesity, class 3 obesity, pregnancy, current smoking status, diabetes, history of hypertension and an emergency department visit or hospitalisation in the 6 months prior to COVID diagnosis	OR
Steenkamp et al. (2021) [26] South Africa	Retrospective observational study	Discovery Health and Vitality client data (DHMS)	2018-2020	2	65,361 (48.2%) / 41.0	Directly measured recording of physical activity through the Vitality programme (via smart	Hospitalisation, severe COVID-19, and mortality	Infections (n=65,361) Hospitalisations (n=7,255) Severe COVID-19 (n=1,569) Deaths (n=1046)	Age, sex, comorbidities (hypertension, diabetes, ischaemic heart disase, chronic lung disease, chronic renal failure and HIV), and patient complexity	RR

						devices, clocked gym attendance or recorded mass sports event participation)				
Tavakol et al. (2021) [39] Iran	Cross-sectional	Patients who visited the respiratory emergency department of a single centre	March 2020 to April 2020	-	206 (57.8%) / 40.9	GPAQ	Severe COVID-19	Infections (n=206) Hospitalisations (n=24) Severe COVID-19 (n=24)	Age	OR
Zhang et al. (2021) [36] UK	Prospective cohort study	UK Biobank	March 2020 to June 2020 (cases)	NR	502,504 (44.8%) / 68.6	Acceleration vector magnitude PA	COVID-19 infection and mortality	Infections (n=1,746) Hospitalisations (n=1,020) Deaths (n=399)	Age, sex, waist circumference, hip circumference, BMI, smoking status, exposure to smoking at home and exposure to smoking out of home	OR

Abbreviations: BMI, Body mass index; CRF, cardiorespiratory fitness; GPAQ, Global Physical Activity Questionnaire; HIV, Human immunodeficiency virus; HR, hazard ratio; ICU, Intensive care unit; IPAQ, International Physical Activity Questionnaire; METS, Metabolic equivalent of task; MVPA, Moderate-to-vigorous physical activity; NR, not reported; OR, odds ratio; PA, physical activity; PR, prevalence rate.

Online supplemental eTable 2. Results of the NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies and the Quality Assessment of Case-Control Studies.

Study	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Total score
Ahmadi et al. (2021)	✓	✓	✓	✓	NR	✓	✓	✓	✓	×	✓	NR	✓	✓	11/14
Brandenburg et al. (2021)	✓	✓	✓	✓	NR	✓	✓	✓	✓	×	✓	NR	✓	✓	11/14
Cho et al. (2021) *	✓	✓	✓	✓	✓	✓	✓	NR	✓	✓	NR	✓			11/12
de Souza et al. (2021)	✓	✓	✓	✓	NR	✓	✓	✓	✓	×	✓	NR	NA	✓	10/14
Ekblom-Bak et al. (2021) *	✓	✓	✓	✓	✓	✓	✓	NR	✓	✓	NR	✓			10/12
Hamdan et al. (2021)	✓	✓	✓	✓	NR	✓	✓	×	×	×	✓	NR	NA	×	7/14
Hamer et al. (2020)	✓	✓	✓	✓	NR	✓	✓	✓	✓	×	✓	NR	✓	✓	11/14
Latorre-Román et al. (2021)	✓	✓	✓	✓	NR	✓	✓	✓	✓	×	✓	NR	NA	✓	10/14
Lee et al. (2021)	✓	✓	✓	✓	NR	✓	✓	✓	✓	×	✓	NR	✓	✓	11/14
Li-Hua et al. (2021) *	✓	✓	✓	✓	✓	✓	✓	NR	✓	NR	NR	NR			8/12
Maltagliati et al. (2021)	✓	✓	✓	✓	NR	✓	✓	×	×	×	✓	NR	✓	✓	9/14
Rowlands et al. (2021)	✓	✓	✓	✓	NR	✓	✓	✓	✓	×	✓	NR	✓	✓	11/14
Sallis et al. (2021)	✓	✓	✓	✓	NR	✓	✓	✓	✓	×	✓	NR	✓	✓	11/14
Steenkamp et al. (2021)	✓	✓	✓	✓	NR	✓	✓	✓	✓	×	✓	NR	✓	✓	11/14
Tavakol et al. (2021)	✓	✓	✓	✓	NR	✓	✓	✓	✓	×	✓	NR	NA	✓	10/14
Zhang et al. (2021)	✓	✓	✓	✓	NR	✓	✓	✓	✓	×	✓	NR	✓	✓	11/14

✓ indicates “yes”, × indicates “no”, NA indicates “not applicable”, and NR indicates “not reported”.
* Case-control studies

Online supplemental eTable 3. Grading of Recommendations Assessment, Development and Evaluation (GRADE) assessment of overall quality of evidence.

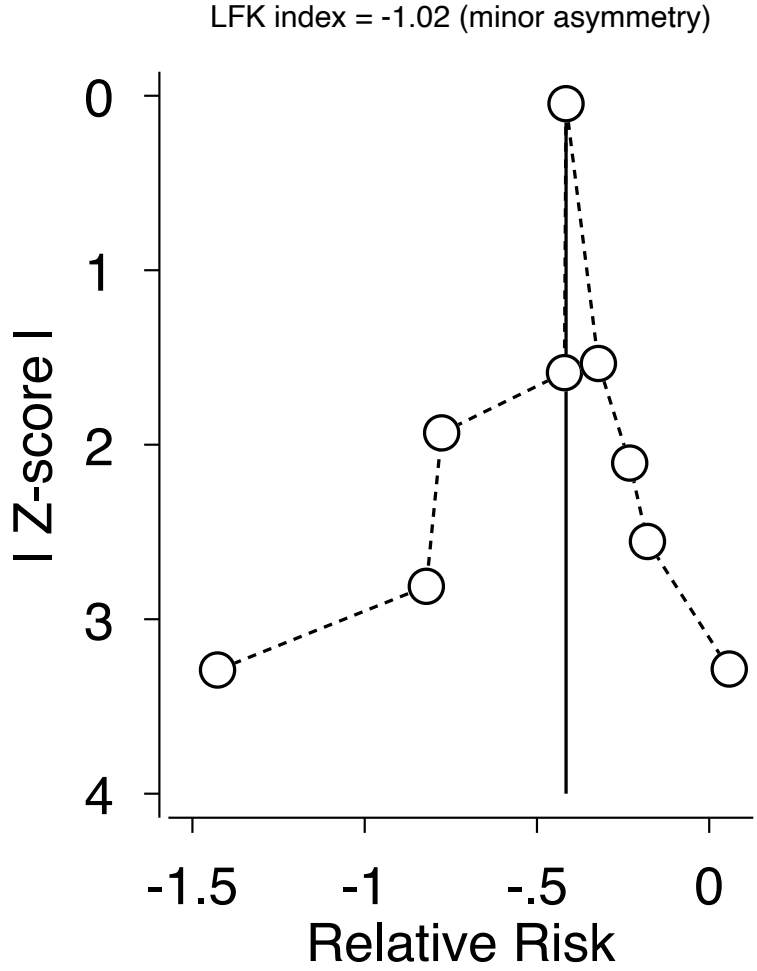
Physical activity and COVID-19 outcomes									
N° of participants (studies)	**Study design**	**Risk of bias**	**Magnitude of Effect**	**Dose-response gradient**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Quality of evidence**
SARS-CoV-2 Infection									
710,959 (3 studies)	Observational[a]	Low	RR=0.89 (no large effect)	Undetected	No serious	No serious	No serious	Detected (major)	⨁⨁◯◯ LOW
COVID-19 Hospitalisation									
1,525,271 (9 studies)	Observational[b]	Low-Moderate	RR=0.64 (no large effect)	Undetected	No serious	No serious	No serious	Detected (minor)	⨁⨁◯◯ LOW
Severe COVID-19 illness									
1,209,966 (7 studies)	Observational[c]	Low	RR=0.66 (no large effect)	Nonlinear dose–response relationship	No serious	No serious	No serious	Detected (major)	⨁⨁⨁◯ MODERATE
Mortality due to COVID-19									
824,760 (6 studies)	Observational[d]	Low	RR=0.57 (no large effect)	Nonlinear dose–response relationship	No serious	No serious	No serious	Detected (major)	⨁⨁⨁◯ MODERATE

RR, relative risk.

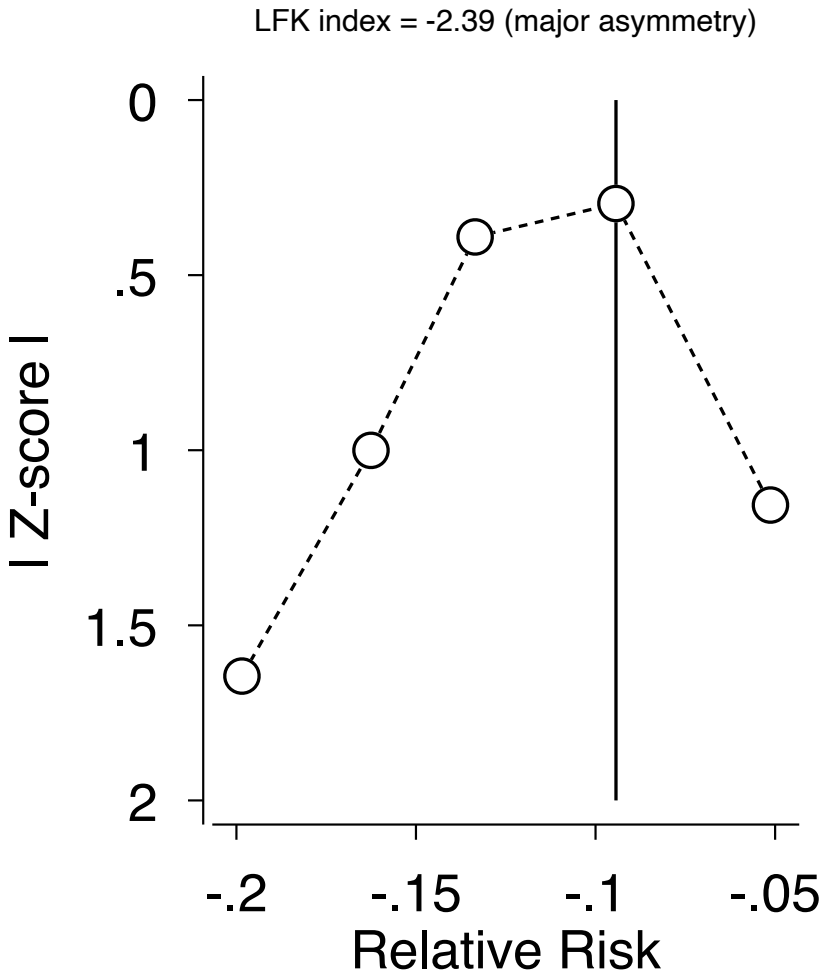
Explanations:

a. Study designs included 1 cross-sectional study and 2 prospective cohort studies
b. Study designs included 4 cross-sectional studies, 1 case-control study, 2 prospective cohort studies and 2 retrospective cohort studies
c. Study designs included 2 cross-sectional studies, 1 case-control study, 2 prospective cohort studies and 2 retrospective cohort studies
d. Study designs included 1 case-control study, 3 prospective cohort studies and 2 retrospective cohort studies

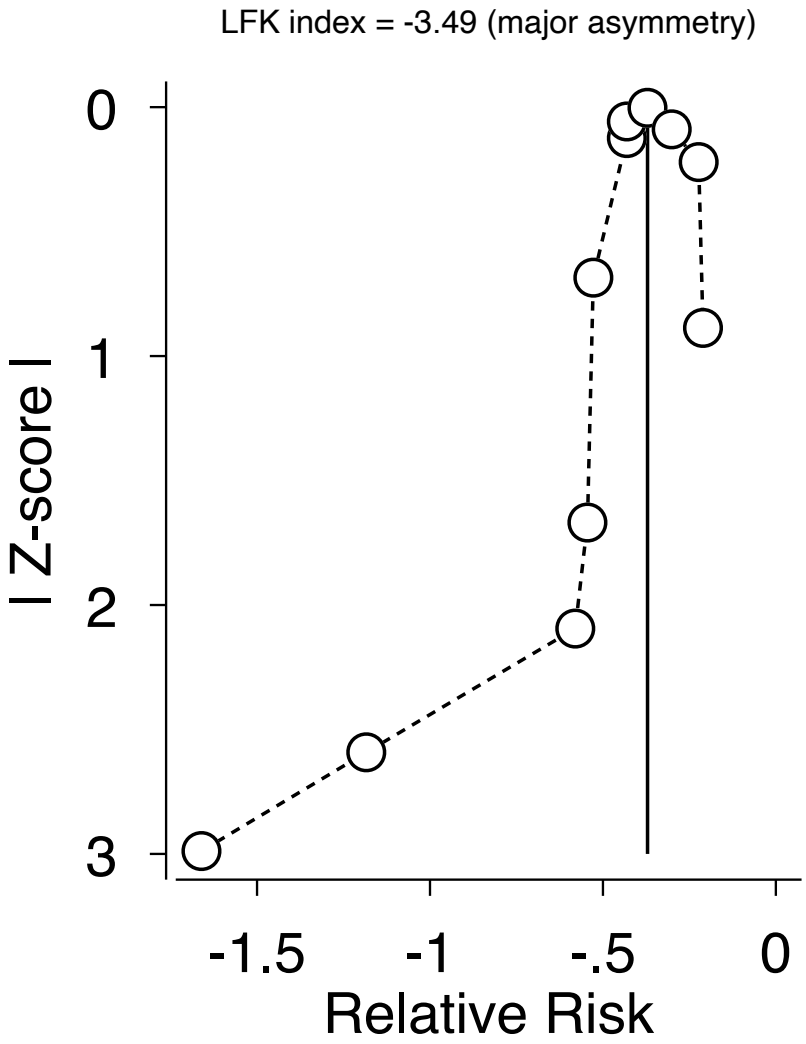
Online supplemental eFigure 1. Doi plot for hospitalisation. Relative Risk was transferred to natural logarithm form.



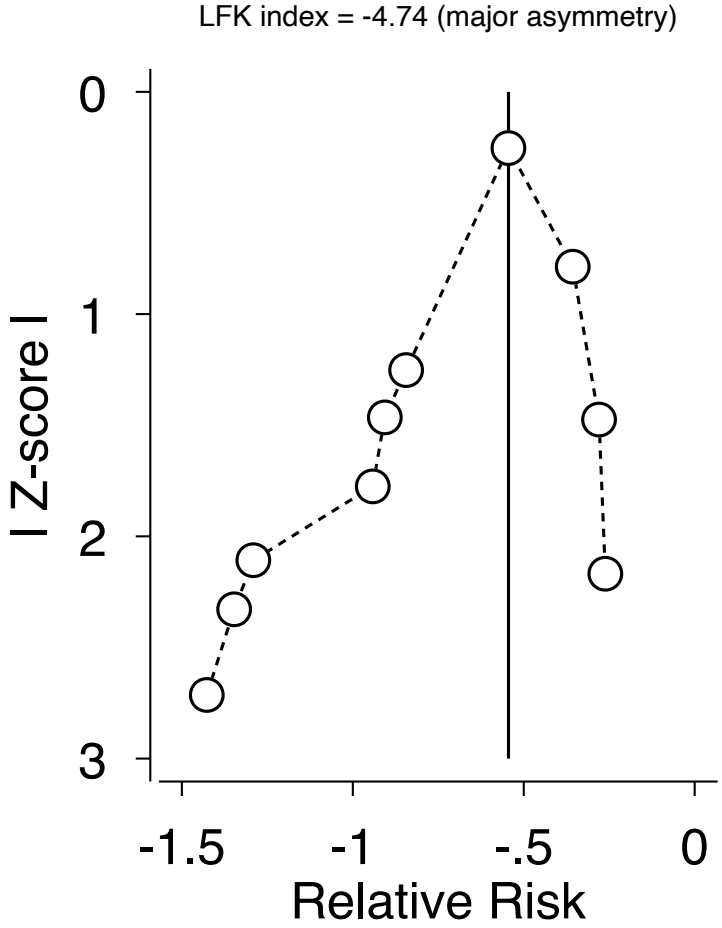
Online supplemental eFigure 2. Doi plot for COVID-19 infection. Relative Risk was transferred to natural logarithm form.



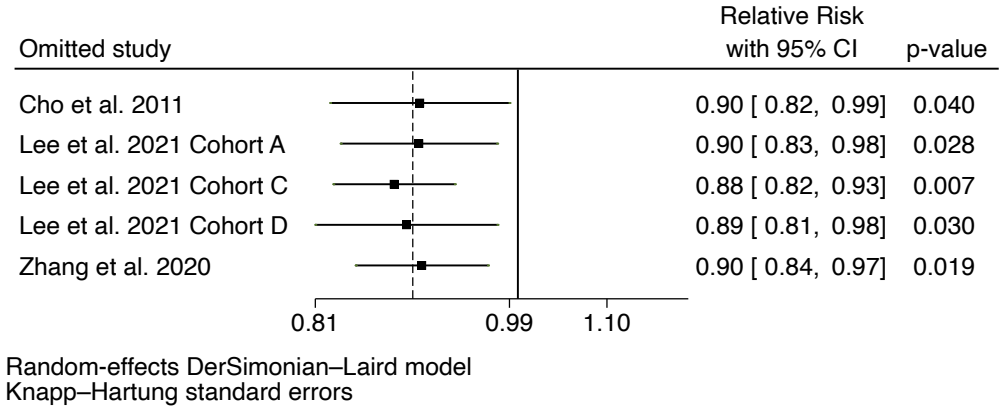
Online supplemental eFigure 3. Doi plot for severe COVID-19 illness. Relative Risk was transferred to natural logarithm form.



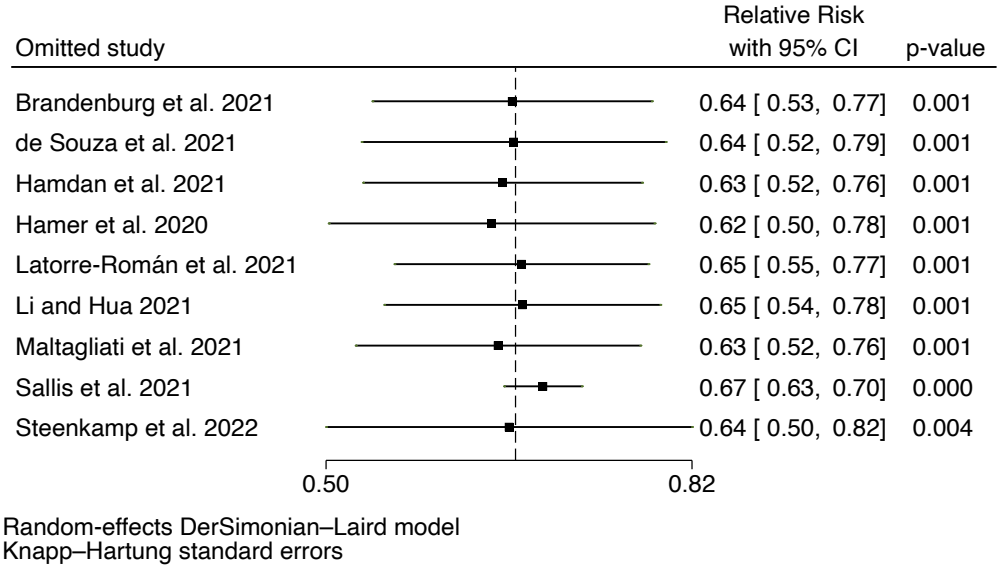
Online supplemental eFigure 4. Doi plot for death due to COVID-19. Relative Risk was transferred to natural logarithm form.



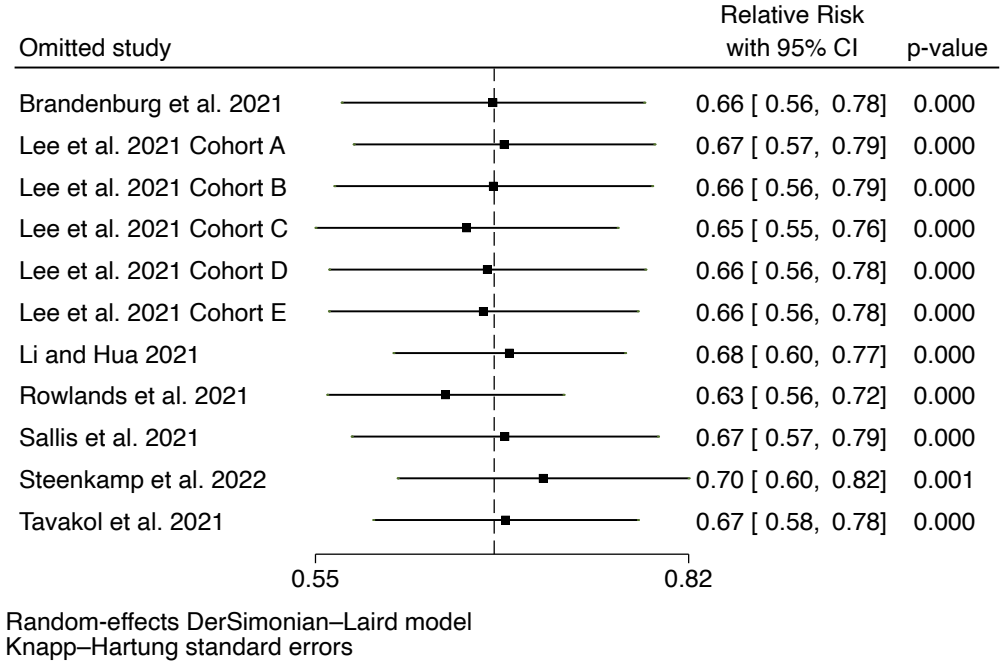
Online supplemental eFigure 5. Sensitivity analyses once each study was excluded for COVID-19 infection.



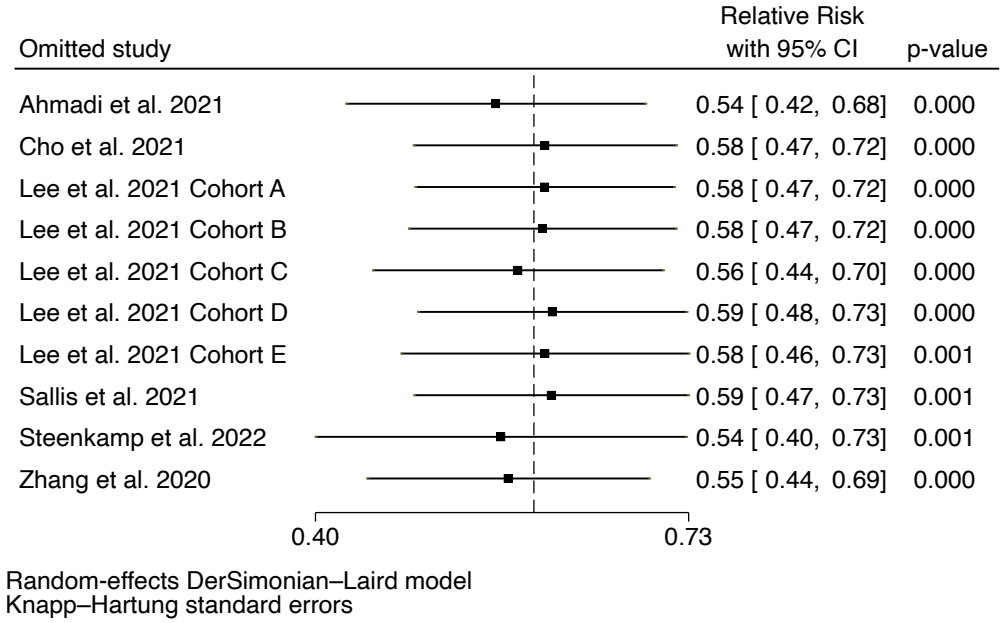
Online supplemental eFigure 6. Sensitivity analyses once each study was excluded for hospitalization due to COVID-19.



Online supplemental eFigure 7. Sensitivity analyses once each study was excluded for severe COVID-19 illness.



Online supplemental eFigure 8. Sensitivity analyses once each study was excluded for death due to COVID-19.



Online supplemental eTable 4. Subgroup analysis according to design, physical activity assessment, and measure outcome.

	N	RR	95% CI	p	I^2
SARS-CoV-2 infection					
Cross-sectional and case-control	1	-	-	-	-
Prospective and retrospective	4	0.90	0.81 to 0.99	0.044	0
Objective physical activity	0	-	-	-	-
Subjective physical activity	5	0.89	0.83 to 0.96	0.014	0
Only studies with Relative Risk	3	0.91	0.80 to 1.06	0.115	0
Hospitalisation					
Cross-sectional and case-control	5	0.66	0.44 to 0.99	0.048	0
Prospective and retrospective	4	0.64	0.54 to 0.76	0.026	74.4
Objective physical activity	2	-	-	-	-
Subjective physical activity	7	0.65	0.50 to 0.85	0.016	58.3
Only studies with Relative Risk	5	0.66	0.62 to 0.71	<0.001	0
Severe COVID-19 illness					
Cross-sectional and case-control	2	-	-	-	-
Prospective and retrospective	9	0.68	0.59 to 0.80	<0.001	52.5
Objective physical activity	3	0.65	0.24 to 1.75	0.200	88.5
Subjective physical activity	8	0.68	0.57 to 0.78	0.001	0
Only studies with Relative Risk	9	0.64	0.55 to 0.75	<0.001	17.39
Death due to COVID-19					
Cross-sectional and case-control	1	-	-	-	-
Prospective and retrospective	8	0.56	0.45 to 0.70	0.002	24.7
Objective physical activity	2	-	-	-	-
Subjective physical activity	7	0.55	0.35 to 0.69	0.007	35.4
Only studies with Relative Risk	8	0.61	0.47 to 0.80	0.003	61.30