

The relationship between physical activity and severity of covid-19 symptoms in non-hospitalised individuals

MITROPOULOS, Alexandros, GOODWILL, Simon <<http://orcid.org/0000-0003-0638-911X>>, COPELAND, Robert <<http://orcid.org/0000-0002-4147-5876>> and KLONIZAKIS, Markos <<http://orcid.org/0000-0002-8864-4403>>

Available from Sheffield Hallam University Research Archive (SHURA) at:
<http://shura.shu.ac.uk/30421/>

This document is the author deposited version. You are advised to consult the publisher's version if you wish to cite from it.

Published version

MITROPOULOS, Alexandros, GOODWILL, Simon, COPELAND, Robert and KLONIZAKIS, Markos (2022). The relationship between physical activity and severity of covid-19 symptoms in non-hospitalised individuals. *European Journal of Public Health*: ckac097.

Copyright and re-use policy

See <http://shura.shu.ac.uk/information.html>

The relationship between physical activity and severity of COVID-19 symptoms in non-hospitalized individuals

Alexandros Mitropoulos¹, Simon Goodwill², Robert Copeland², Markos Klonizakis¹

¹ Lifestyle, Exercise and Nutrition Improvement (LENI) Research Group, Department of Nursing and Midwifery, College of Health Wellbeing and Life Science, Sheffield Hallam University, Sheffield, UK

² Advanced Wellbeing Research Centre, Sheffield Hallam University, Sheffield, UK

Correspondence: Alexandros Mitropoulos, Lifestyle, Exercise and Nutrition Improvement (LENI) Research Group, Department of Nursing and Midwifery, College of Health Wellbeing and Life Science, Collegiate Campus, S10 2BP, Sheffield Hallam University, Sheffield, UK, Tel: +44 0114 225 3923, e-mail: alexandros.mitropoulos@shu.ac.uk

Background: The study explored the relationship between physical activity (PA) behaviour and severity of symptoms in people infected by coronavirus disease 2019 (COVID-19). **Methods:** Five hundred and thirty-three people [16% males, mean age: 45 ± 11 years, body mass index (BMI): 23.3 ± 20] took part in the study. All participants were post-COVID-19 infection. An online questionnaire was used to gather data on; participants demographics, comorbidities and treatment, symptomatology of COVID-19, quality of life (QoL) and pre- and post-COVID-19 infection PA. **Results:** Logistic regression revealed that only a high BMI (>25) increased the severity of (odds ratio 1.01; 95% confidence interval, 0.99–1.03) symptoms from none to mild-to-moderate. Weekly PA behaviour (min/week) did not affect the primary outcome (symptom severity) as a predictor variable and neither differ ($P > 0.05$) between symptomatology for both moderate (no symptoms: 181.3 ± 202.1 vs. mild-to-moderate symptoms: 173 ± 210.3) and vigorous (no symptoms: 89.2 ± 147 vs. mild-to-moderate symptoms: 88.9 ± 148.3) PA. QoL (i.e. mobility, self-care, usual activities, pain/discomfort, anxiety/depression and perceived health) was significantly ($P < 0.05$) worse post-COVID-19 infection. **Conclusions:** Our findings did not present an association between PA levels and mild-to-moderate COVID-19 symptoms. However, all participants exceeded the lower limit of the World Health Organization recommended, adult PA dose. This might explain the lack of PA effect, on mild-to-moderate symptoms post-COVID-19 infection. Future studies should explore the effects of PA levels in more severe cases (e.g. hospitalizations) and assess the effectiveness of PA to reduce hospitalizations, and mortality rates as a result of COVID-19 infection.

Introduction

As of 11 March 2020, the World Health Organization (WHO) declared coronavirus disease 2019 (COVID-19) a public health emergency of international concern.¹ The pathogen was identified as a novel, enveloped RNA betacoronavirus² named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which has a phylogenetic similarity to SARS-CoV.³ As of April, 2022, 511 million people have been infected, and 6.2 million have died from COVID-19 worldwide according to the Centre for Systems Science and Engineering at John Hopkins University.⁴

Adverse outcomes (e.g. ~50% of hospitalizations)⁵ of COVID-19 and higher mortality⁶ have been associated with comorbidities, including hypertension,⁷ cardiovascular⁶ and lung disease.⁸ These conditions are also linked to health risk behaviours such as smoking⁸ and drinking alcohol.⁹ Moreover, increasing age and male gender demonstrate a higher risk of mortality during hospitalization with COVID-19.⁶ Overall COVID-19 symptomatology seems to influence the individual's health-related quality of life (QoL).¹⁰

Angiotensin-converting enzyme 2 (ACE2) was identified as a functional receptor for SARS-CoV.¹¹ ACE2 expression and its modulation by conditions and underlying comorbidities (e.g. cardiovascular disease, obesity, hypertension) may enhance tissue susceptibility to COVID-19.⁵ In addition, the ACE/ACE2 physiological balance is disrupted by SARS-CoV-2 and simultaneously the Ang II/AT1R pathways are activated, leading to severe complications of the disease. A recent paper by Varga *et al.*¹² confirms the critical role of ACE2 expression leading to endotheliitis and the concomitant

systemic vascular and immune dysfunction ending to multi-organ failure during the infection by COVID-19.

Regular, low- to moderate-intensity physical activity (PA) improves ejection fraction in cardiovascular and metabolic diseases¹³ delaying the age-associated vasculopathy.¹⁴ Moreover, exercise immunology has demonstrated the link between PA and immune function. For example, recent epidemiological evidence¹⁵ suggests a decreased mortality and incidence rates for influenza and pneumonia as well as improved antibody responses to influenza immunization in elderly adults who engage in regular exercise training regimens. The current weekly PA guidelines¹⁶ by U.K.'s chief medical office (CMO) recommend a dose of either moderate PA ≥ 150 min/week or vigorous PA ≥ 75 min/week.

PA is shown to be an effective therapeutic modality for mitigating endothelial dysfunction and vascular wall inflammation.¹⁷ Specifically, PA augments nitric oxide bioavailability and antioxidant defences, reduces inflammation, increases the amount of endothelial and blood mononuclear cells, and improves endothelial regenerative ability by increasing the number of circulating endothelial progenitor cells. These are important benefits, considering the suggested link between SARS-CoV-2 vascular dysfunction and disruption of vascular homeostasis and tone. Recent evidence demonstrated that maximal exercise capacity is inversely associated to hospitalization secondary to COVID-19.¹⁸ These findings indicate that exercise capacity could prevent hospitalization and thus related deaths. A large percentage (~85%) of the infected population in UK do not present any symptoms,¹⁹ and it remains unknown whether exercise capacity could be a preventative factor for the development of symptoms.

With this in mind, the purpose of the current study was to examine the relationship between PA behaviour pre-COVID-19 infection and presentation of symptoms during COVID-19 infection. We hypothesized that individuals who were more active prior to COVID-19 infection would experience lower severity of symptoms compared to inactive individuals, accounting for demographic factors such as age and gender.

Methods

Participants

The study was completed online, by 533 people post-COVID-19 infection (table 1). Exclusion criteria included no confirmed COVID-19 diagnosis and being hospitalized with COVID-19. Participants' information sheet was attached to the questionnaire and informed consent was provided electronically prior to entry into the study. The online questionnaire was created via appropriate

software (Azure Web Apps, Microsoft Corporation, USA) and was distributed globally via social media platforms (e.g. Facebook, Instagram, LinkedIn and Tweeter) and word of mouth. To ascertain personal identification safety, names, addresses and/or personal contact information (e.g. telephone numbers, emails and social media profiles) were not requested. Participants were requested to answer the questionnaire approximately 14–21 days post-onset of COVID-19 infection. The study received ethical approval from Sheffield Hallam University (Sheffield, UK) local research ethics committee (ER24666388).

Online questionnaire

The online questionnaire comprised five sections, which requested participants to provide the following information (Supplementary appendix SA); demographics (Supplementary section S1) including age, gender and ethnicity, and comorbidities (Supplementary section S2) including smoking status, co-existing comorbidities and

Table 1 Characteristics of the participants

	Total	No symptoms	Mild-to-moderate symptoms
%		47	53
Male gender (%)	84 (16)	33 (45)	41 (55)
Mean age (years)	45 ± 11	43.9 ± 10.4	45.2 ± 11
BMI (kg/m ²)	23.3 ± 20	21.5 ± 5*	25.6 ± 28
Ethnicity (%)	% total		
British	44	63	37
Other White	46	35	65
Other mixed	5	29	71
Asian	3	31	69
African-Caribbean	2	18	82
Occupation (%)	% total		
Managers/professionals	74	46	54
Technicians	11	46	54
Clerical support	12	59	41
Skilled/craft workers	1	50	50
Machine operators/elementary	1	20	80
Armed forces	1	60	40
Employment status (%)	% total		
Employed	83	46	54
Unemployed	10	47	53
Retired	7	52	48
Age categories, N (%)^a	Total (n = 510)		
16–39 years	172 (33.7)	72 (42)	80 (58)
40–59 years	290 (56.9)	121 (42)	133 (58)
60–79 years	48 (9.4)	14 (34)	27 (66)
Medical history	Total (n = 306)		
COPD	8	4 (50)	4(50)
Asthma	85	39 (46)	46 (54)
T2DM	11	3 (27)	8 (73)
Hypertension	51	19 (37)	32 (63)
CVD	17	11 (65)	6 (35)
Other comorbidities	113	45 (40)	68 (60)
Tobacco smoking	21	10 (48)	11 (52)
Medications	Total (n = 182)		
Inhalers	60	35 (58)	25 (42)
Angiotensin receptor blockers	9	6 (67)	3 (33)
β-blockers	9	4 (44)	5 (56)
Leukotriene receptor antagonist	8	4 (50)	4 (50)
Calcium channel blockers	10	2 (20)	8 (80)
ACE inhibitors	8	3 (38)	5 (62)
PPI	11	8 (73)	3 (27)
Antihistamines	16	8 (50)	8 (50)
Anti-depressants	11	4 (36)	7 (64)
Hormones	22	13 (59)	9 (41)
Corticosteroids	18	5 (28)	13 (72)

BMI, body mass index; COPD, chronic obstructive pulmonary disease; T2DM, type 2 diabetes mellitus; CVD, cardiovascular disease; ACE, angiotensin-converting enzyme; PPIs, proton-pump inhibitors.

*: $P < 0.05$.

a: The total number of participants who provided their date of birth equals to 510. The percentages of participants in different age groups have calculated accordingly.

medication. [Supplementary section S3](#) consisted of information related to COVID-19 including testing and/or diagnosis of COVID-19, symptomatology and severity of symptoms. The severity of symptoms was defined as (i) asymptomatic, (ii) mild-to-moderate symptoms that hospitalization was not required, (iii) severe symptoms that hospitalization was required and (iv) very severe symptoms that intensive care unit (ICU) admission was required. [Supplementary section S4](#) assessed the quality of life (QoL) of participants pre- and post-COVID-19 infection using a validated health-related QoL questionnaire (EQ-5D-5L²⁰). Finally, [Supplementary section S5](#) explored PA behaviour before and after COVID-19 infection using the global PA questionnaire (GPAQ).²¹

Quality of life

The EQ-5D-5L questionnaire was the main outcome used to assess the participants' QoL pre- and post-COVID-19 infection. This questionnaire is a generic measure of health state by considering five key dimensions of daily living (mobility, self-care, ability to undertake usual activities, pain, anxiety/depression).²² Participants were asked to describe their level of health on each dimension using one of five levels: no problems, slight problems, moderate problems, severe problems and extreme problems. Participants were also asked to rate their perceived health pre-COVID-19 infection and current (e.g. day of survey completion) scoring, from 0 (means the worst health you can imagine) to 100 (means the best health you can imagine).

Physical activity behaviour

The GPAQ questionnaire has been developed by the WHO and it has been validated for its use in assessing current and changes in moderate-vigorous intensity PA and sedentary behaviour.²¹ The GPAQ ([Supplementary appendix SA, section S5](#)) comprises of 16 questions designed to estimate an individual's PA in three domains (work, transport and leisure time) and time spent in sedentary behaviour.²³

Statistical analysis

Statistical analysis was performed using SPSS 24 (SPSS, SPSS IBM statistics, USA) statistical package. Binary logistic regression was used to calculate the odds ratio (OR) and 95% confidence interval (CI) for COVID-19 symptoms severity (two levels: no symptoms and mild-to-moderate symptoms) on the basis of pre-COVID-19 PA. For our primary analysis, binary logistic regression was used with symptoms severity as the dependent variable with adjustment based on reported PA behaviour (e.g. sitting time, moderate and vigorous PA and a combination of both per week), age, gender, body mass index (BMI), smoking status, ethnicity and underlying condition (e.g. chronic obstructive pulmonary disease, asthma, other respiratory condition, type 2 diabetes mellitus, hypertension, coronary artery disease, cardiovascular disease, cerebrovascular disease, chronic renal disease and immunodeficiency). GPAQ data were cleaned according to the "GPAQ analysis guide" developed by WHO.²⁴ We calculated min/week spent in moderate and vigorous activities, as well as the sum of both intensities (moderate-to-vigorous PA). Min/week spent sitting were also derived.

The α level was <0.05 . Continuous data are presented as mean \pm standard deviation. The total symptoms were also assessed as dependent variable using multiple linear regression analysis with the same predictors as in the binary logistic regression.

Sample size

The sample size calculation was performed based on previous data on correlations between PA and healthy ageing,²⁵ using G Power analysis (G*Power 3.1.7, HHU of Düsseldorf). More specifically, we used data from the dose-response association (e.g. stepwise

multiple regression analysis) between baseline moderate PA and healthy ageing at 8 years follow up [$n = 345/1692$, OR 2.67 (2.54–4.89 95% CI)] adjusted for age, gender, smoking, alcohol, marital status and wealth quintile.

Results

Demographics

Participant characteristics are described in [table 1](#). The age range of the participants was 16–79 years. Data are presented as mean (%). Many of the demographic data such as date of birth, medical history, occupation, medication and ethnicity were not reported by a percentage of participants.

Quality of life

EQ-5D-5L questionnaire outcomes, used to assess the QoL of the participants, pre- and post-COVID-19 infection, are presented in [table 2](#). All QoL components were found to be significantly worse post-COVID-19 infection.

Physical activity and COVID-19 symptomatology

Independent *t*-test with grouping variable being symptoms severity (two levels: no symptoms and mild-to-moderate symptoms), demonstrated that those with no symptoms did not differ to those with mild-to-moderate symptoms in terms of weekly time spent (in minutes) in moderate PA (no symptoms: 181.3 ± 202.1 vs. mild-to-moderate symptoms: 173 ± 210.3), in vigorous PA (no symptoms: 89.2 ± 147 vs. mild-to-moderate symptoms: 88.9 ± 148.3), in moderate and vigorous PA (no symptoms: 270.4 ± 284.9 vs. mild-to-moderate symptoms: 266.9 ± 318.4), and in sitting time (no symptoms: 384.1 ± 222.5 vs. mild-to-moderate symptoms: 387.5 ± 244.3).

Results from the logistic regression analysis with the covariates arranged by their Wald χ^2 are shown in [table 3](#). BMI (continuous variable) was associated with a higher severity of symptoms during COVID-19 infection. A unit of BMI increase was independently associated with a 1.01 (95% CI, 0.99–1.03) increase in odds of symptoms' severity. There were no significant interactions ($P > 0.05$) between the other covariates.

Results from the multiple linear regression analysis with total symptoms (continuous variable) as the dependent variable demonstrated that only gender (i.e. male; $P = 0.001$) and comorbidity (i.e. obesity and hypertension; $P = 0.001$) were significant predictors. None of the remaining independent variables showed significant correlations. These results are not presented in a table.

Discussion

In this study, we explored the relationship between PA behaviour and severity of symptoms in people infected but not hospitalized by COVID-19, taking into account covariates such as age, gender, BMI, smoking status and medical history. We found no association

Table 2 EQ-5D-5L outcomes

	Participants (n = 529)	
	Pre-COVID-19	Post-COVID-19
Mobility	1.05 \pm 0.3	2.21 \pm 1**
Self-care	1.03 \pm 0.2	1.55 \pm 0.8**
Usual activities	1.05 \pm 0.3	2.99 \pm 1.2*
Pain/discomfort	1.23 \pm 0.6	2.6 \pm 1.1**
Anxiety/depression	1.36 \pm 0.7	2.3 \pm 1.1**
Perceived health	87.6 \pm 15.2	53 \pm 23.6**

*: $P < 0.05$, **: $P < 0.001$.

Table 3 Results from logistic regression to assess the relationship between PA levels and COVID-19 symptoms severity

	B	SE	Wald χ^2	df	P	OR	OR 95% CI	
							Lower	Upper
MVPA	0.00	0.00	0.14	1	0.70	1.00	0.99	1.00
Vigorous PA	0.00	0.00	0.33	1	0.56	1.00	0.99	1.00
Sitting time	0.00	0.00	0.01	1	0.91	1.00	0.99	1.00
Age	0.01	0.01	2.15	1	0.14	1.01	0.99	1.03
Gender	-0.03	0.28	0.01	1	0.92	0.97	0.56	1.67
BMI	0.05	0.02	6.22	1	0.01*	1.04	1.01	1.08
Comorbidities	0.02	0.16	0.02	1	0.87	1.02	0.75	1.39
Smoking status	0.13	0.17	0.53	1	0.46	1.13	0.80	1.59
Constant	-1.64	0.89	3.37	1	0.06	0.19		

CI, confidence interval; MVPA, moderate and vigorous physical activity; OR, odds ratio; PA, physical activity; SE, standard error.

*: $P < 0.05$.

between COVID-19 symptoms severity and pre-COVID-19 PA behaviour in a diverse cohort of people (table 1), who were infected with COVID-19. All participants reported meeting the current CMO PA guidelines.¹⁶ BMI was the only factor closely associated with increased symptoms severity. QoL was found to be impacted post-COVID-19 infection, an outcome which comes in agreement with previous studies.¹⁰ To our knowledge, this is the first study to explore the associations between PA and symptomatology in non-hospitalized participants.

All of our participants, regardless of COVID-19 symptom severity, reported high PA that would be sufficient to increase overall cardiorespiratory fitness (CRF).²⁶ Indeed, the average PA time spent for both moderate and vigorous exercise from our participants exceeded the lower limit of the weekly recommended dose (e.g. moderate PA ≥ 150 min/week or vigorous PA ≥ 75 min/week) by CMO.²⁰ It is likely that cases of hospitalization or admission to ICU post-COVID-19 infection could have presented lower volumes of PA. Although hospitalizations or admissions to ICU were not reported in our current data, our results could partly be explained by a recent study that examined the effects of maximal exercise capacity on hospitalization in people infected with COVID-19. This demonstrated that maximal exercise capacity is inversely correlated with hospitalizations indicating that lower levels of CRF present higher chances of severe symptoms during COVID-19 infection.¹⁸ Studies exploring the association between maximal exercise capacity and hospitalization, secondary to COVID-19, have also reported that exercise capacity is significantly higher in those who were not hospitalized compared to those who were.²¹

Another large cohort study ($n = 1843$) demonstrated that PA behaviour acts as a long-term predictor of peak oxygen uptake (VO_{2peak}).²⁷ VO_{2peak} testing is used to assess the CRF. CRF directly reflects a well-tempered function of the multiple organ systems and is considered a vital measurement of overall health in clinical practice.²⁸ CRF also reflects the organ systems' ability to react to external and internal stressors such as exercise, surgical operations and COVID-19. COVID-19 represents an internal stressor to respiratory and cardiovascular system potentially leading to systemic vascular inflammation,²⁹ thrombosis and stroke,³⁰ as well as acute respiratory distress syndrome³¹ and many more systemic manifestations increasing thus the overall stress. Physiologically, it has been demonstrated that those who are hospitalized or admitted to ICU due to COVID-19 often present some or all of the aforementioned manifestations which is linked to a lower CRF and body's ability to respond in this severe internal organ systems' stress.¹⁸ Therefore, those with adequate CRF (e.g. those who meet PA guidelines) are unlikely to present severe symptoms (e.g. hospitalizations and/or ICU admissions), nevertheless, they might present mild-to-moderate symptoms, that ensure, as has been reported elsewhere.

An additional physiological explanation for our findings is related to the average profile of the people, who according to our current knowledge, are more likely to be hospitalized due to COVID-19—this includes older age (≥ 65 years), obese status, hypertension, smoking status and other severe comorbidities (e.g. heart failure and stage III or IV COPD based on Gold criteria). Our findings agree with the relationship between severity of symptoms and these factors, as we observed a significantly higher BMI in those with mild-to-moderate symptoms compared to those with no symptoms, in addition to our participants being of lower age (i.e. 45 years of age), and smoke less. Our study takes our knowledge a step further, as the majority of our participants engaged in high amounts of PA, which may further explain the low impact of COVID-19 on the bodies of our participants. Indeed, it has been demonstrated that regular exercise provides multiple health benefits and strengthens the body's immune response including decreased illness incidence and dampened systemic inflammation.^{32,33}

QoL was demonstrated to be worse following COVID-19 infection in our study. Most studies have examined the effect of COVID-19 ICU admissions and/or hospitalizations on health related QoL³² and thus there is a lack of evidence for those presenting mild to moderate symptoms. However, our current study's data and evidence from previous coronaviruses, indicate that the decline on QoL due to COVID-19 could be explained by the persistent pulmonary function impairment, muscle weakness, fatigue, pain, depression and anxiety.³⁴

An association between the severity of symptoms and ethnicity was not demonstrated in our study which comes in contradiction with a recent meta-analysis which demonstrated that there is a close association between ethnicity and the clinical outcomes of COVID-19.³⁵ Namely, they found an association between increased risk of ICU admission for Asians. In our study, we did not have severe cases and that might explain the lack of association for our studied cohort. The prevalence of COVID-19 in the different ethnic groups (table 1) demonstrated a similar trend with recent evidence (e.g. 77% White, 7% Asian, 3% Black, 3% Other and 2% Mixed).³⁵

Limitations

Our study presents some limitations. First, the online distribution of our survey limited our sample in those with computer literacy. It is probable that this limitation did not include a broader range of ages and specifically those above 65 years, who would be more likely to present severe symptoms. Second, we could not balance the respondents according to gender (84% were female) due to the online nature of our study. The prevalence of symptomatic COVID-19 has been found to be higher in men than in women primarily due to the higher prevalence of alcohol and smoking,³⁶ however, the prevalence of smoking in our participants was only 4%. This survey was conducted amid an unprecedented pandemic during which three strict, government-imposed lockdowns in UK imposing severe, social distancing restrictions. Third, a large percentage of our participants presented with high PA levels; nevertheless, high PA levels in our study could be partly explained based on other research studies that have connected high cardiorespiratory levels to mild-moderate COVID-19 symptomatology. Therefore, and in order to preserve public health and follow government guidelines we conducted our study online, using a validated self-reporting PA questionnaire.

Conclusions

The present study provides further evidence that those with a high BMI (e.g. >25) are more likely to present with severe symptoms after COVID-19 infection. Additionally, our findings did not suggest a relationship between PA and the absence or the presentation of mild-to-moderate COVID-19 symptoms. It is possible that PA levels could be associated with severe COVID-19 symptomatology, and this could partially be explained by the on average high PA levels of our participants. Our research supports calls that the general population should

be encouraged to regularly engage in PA to improve or maintain their CRF, as a means of reducing COVID-19 symptom severity.³⁷ Future studies should include cases of hospitalizations and ICU admission due to COVID-19 and explore whether CRF could minimize the COVID-19-associated manifestations and mortality rates.

Supplementary data

Supplementary data are available at *EURPUB* online.

Acknowledgements

We would like to thank all of our participants as well as Dr Paul Smith (Senior Research Fellow; Sheffield Hallam University) who was the software developer of our study.

Conflicts of interest: None declared.

Key points

- Logistic regression revealed that individuals with a high body mass index (e.g. >25) are more likely to present severe symptoms in comparison to those with lower one.
- The current findings did not suggest a relationship between high physical activity (PA) levels and the absence or the presentation of mild-to-moderate coronavirus disease 2019 (COVID-19) symptoms.
- General population is encouraged to regularly engage in PA to improve or maintain their CRF, as a means of reducing COVID-19 symptom severity.

References

- World Health Organization. Coronavirus Disease (COVID-19) Outbreak. 2020. Available at: <https://www.who.int/emergencies/diseases/novel-coronavirus-2019> (26 May 2022, date last accessed).
- Lu R, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet* 2020;395:565–74.
- Zhu N, Zhang D, Wang W, et al.; China Novel Coronavirus Investigating and Research Team. A novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med* 2020;382:727–33.
- Johns Hopkins University & Medicine Coronavirus Resource Centre. COVID-19 World Map. 2020. Available at: <https://coronavirus.jhu.edu/map.html> (26 May 2022, date last accessed).
- Beyerstedt S, Casaro EB, Rangel É. COVID-19: angiotensin-converting enzyme 2 (ACE2) expression and tissue susceptibility to SARS-CoV-2 infection. *Eur J Clin Microbiol Infect Dis* 2021;40:905–19.
- Docherty AB, Harrison EM, Green CA, et al.; ISARIC4C investigators. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. *BMJ* 2020;369:m1985.
- Pranata R, Lim MA, Huang I, et al. Hypertension is associated with increased mortality and severity of disease in COVID-19 pneumonia: a systematic review, meta-analysis and meta-regression. *J Renin Angiotensin Aldosterone Syst* 2020;21:1470320320926899. 1470320320926899.
- Alqahtani JS, Oyelade T, Aldhahir AM, et al. Prevalence, severity and mortality associated with COPD and smoking in patients with COVID-19: a rapid systematic review and meta-analysis. *PLoS One* 2020;15:e0233147.
- Hall KS, Samari G, Garbers S, et al. Centring sexual and reproductive health and justice in the global COVID-19 response. *Lancet Invalid Date* 2020;395:1175–7.
- Chen KY, Li T, Gong FH, et al. Predictors of health-related quality of life and influencing factors for COVID-19 patients, a follow-up at one month. *Front Psychiatry* 2020;11:668.
- Li W, Moore MJ, Vasilieva N, et al. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. *Nature* 2003;426:450–4.
- Varga Z, Flammer AJ, Steiger P, et al. Endothelial cell infection and endotheliitis in COVID-19. *Lancet* 2020;395:1417–8.
- Roque FR, Hernanz R, Salaces M, et al. Exercise training and cardiometabolic diseases: focus on the vascular system. *Curr Hypertens Rep* 2013;15:204–14.
- Donato AJ, Machin DR, Lesniewski LA. Mechanisms of dysfunction in the aging vasculature and role in age-related disease. *Circ Res* 2018;123:825–48.
- Nieman DC, Wentz LM. The compelling link between physical activity and the body's defense system. *J Sport Health Sci* 2019;8:201–17.
- UK Chief Medical Officers. Physical Activity Guidelines. 2019. Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/832868/uk-chief-medical-officers-physical-activity-guidelines.pdf (26 May 2022, date last accessed).
- Ribeiro F, Alves AJ, Duarte JA, et al. Is exercise training an effective therapy targeting endothelial dysfunction and vascular wall inflammation? *Int J Cardiol* 2010; 141:214–21.
- 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.
- Petersen I, Phillips A. Three quarters of people with SARS-CoV-2 infection are asymptomatic: analysis of English household survey data. *Clin Epidemiol* 2020;12: 1039–43.
- Devlin N, Shah K, Feng Y, et al. Valuing health related quality of life: an EQ-5D-5L value set for England. *Health Econ* 2018;27:7–22.
- Cleland CL, Hunter RF, Kee F, et al. Validity of the Global Physical Activity Questionnaire (GPAQ) in assessing levels and change in moderate-vigorous physical activity and sedentary behaviour. *BMC Public Health* 2014;14:1255.
- Dolan P. Modeling valuations for EuroQol health states. *Med Care* 1997;35:1095–108.
- Bull FC, Maslin TS, Armstrong T. Global physical activity questionnaire (GPAQ): nine country reliability and validity study. *J Phys Act Health* 2009;6:790–804.
- Wanner M, Hartmann C, Pestoni G, et al. Validation of the Global Physical Activity Questionnaire for self-administration in a European context. *BMJ Open Sport Exerc Med* 2017;3:e000206.
- Hamer M, Lavoie KL, Bacon SL. Taking up physical activity in later life and healthy ageing: the English longitudinal study of ageing. *Br J Sports Med* 2014;48:239–43.
- Aadahl M, Kjær M, Kristensen JH, et al. Self-reported physical activity compared with maximal oxygen uptake in adults. *Eur J Cardiovasc Prev Rehabil* 2007;14:422–8.
- Aspenes ST, Nauman J, Nilsen TI, et al. Physical activity as a long-term predictor of peak oxygen uptake: the HUNT Study. *Med Sci Sports Exerc* 2011;43:1675–9.
- Ross R, Blair SN, Arena R, et al.; Stroke Council. Importance of assessing cardio-respiratory fitness in clinical practice: a case for fitness as a clinical vital sign: a scientific statement from the American Heart Association. *Circulation* 2016;134:e653–99.
- Siddiqi HK, Libby P, Ridker PM. COVID-19—a vascular disease. *Trends Cardiovasc Med* 2021;31:1–5.
- Zakeri A, Jadhav AP, Sullenger BA, et al. Ischemic stroke in COVID-19-positive patients: an overview of SARS-CoV-2 and thrombotic mechanisms for the neuro-interventionalist. *J Neurointerv Surg* 2021;13:202–6.
- Fan E, Beitler JR, Brochard L, et al. COVID-19-associated acute respiratory distress syndrome: is a different approach to management warranted? *Lancet Respir Med* 2020;8:816–21.
- Garrigues E, Janvier P, Kherabi Y, et al. Post-discharge persistent symptoms and health-related quality of life after hospitalization for COVID-19. *J Infect* 2020;81:e4–6.
- Flynn MG, McFarlin BK, Markofski MM. State of the art reviews: the anti-inflammatory actions of exercise training. *Am J Lifestyle Med* 2007;1:220–35.
- Neufeld KJ, Leoutsakos JS, Yan H, et al. Fatigue symptoms during the first year following ARDS. *Chest* 2020;158:999–1007.
- Sze S, Pan D, Nevill CR, et al. Ethnicity and clinical outcomes in COVID-19: a systematic review and meta-analysis. *EClinicalMedicine* 2020;29:30: 100630.
- Abate BB, Kassie AM, Kassaw MW, et al. Sex difference in coronavirus disease (COVID-19): a systematic review and meta-analysis. *BMJ Open* 2020;10:e040129.
- Jimenez A, Mayo X, Copeland RJ. The positive impact of physical activity and exercise on immune function. *The critical prevention and recovery tool to fight a second wave of COVID-19*. 2020. Available at: https://www.europeactive.eu/sites/europeactive.eu/files/covid19/ThinkActive/The_positive_impact_of_physical_activity_and_exercise_Aug2020_web.pdf (26 May 2022, date last accessed).