Article

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

Running head: physical activity and COVID-19

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Abstract

Purpose: To determine the potential associations between physical activity and risk of SARS-CoV-2 infection, severe illness from COVID-19, and COVID-19-related death using a nationwide cohort from South Korea.

Methods: Data regarding 212,768 Korean adults (age $\geq$20 years), who tested for SARS-CoV-2, from January 1, 2020 to May 30, 2020, were obtained from the National Health Insurance Service of South Korea, and further linked with the national general health examination from January 1, 2018 to December 31, 2019 to assess physical activity levels. SARS-CoV-2 positivity, severe COVID-19 illness, and COVID-19-related death were the main outcomes. The observation period was between January 1, 2020, and July 31, 2020.

Results: Out of 76,395 participants who completed the general health examination and were tested for SARS-COV-2, 2,295 (3.0%) were positive for SARS-CoV-2, 446 (0.58%) had severe illness from COVID-19, and 45 (0.059%) died from COVID-19. Adults who engaged in both aerobic and muscle strengthening activities according to the 2018 physical activity guidelines had a lower risk of SARS-CoV-2 infection (2.6% versus 3.1%; adjusted relative risk [aRR], 0.85; 95% CI, 0.72-0.96), severe COVID-19 illness (0.35% versus 0.66%; aRR, 0.42; 95% CI, 0.19-0.91), and COVID-19-related death (0.02% versus 0.08%; aRR, 0.24; 95% CI, 0.05-0.99) than those who engaged in insufficient aerobic and muscle strengthening activities. Furthermore, the recommended range of metabolic equivalent of task (MET; 500–1000 MET min/week) was associated with the maximum beneficial effect size for reduced risk of SARS-CoV-2 infection (aRR, 0.78; 95% CI 0.66-0.92), severe COVID-19 illness (aRR, 0.62; 95% CI, 0.43-0.90), and COVID-19-related death (aRR, 0.17; 95% CI, 0.07-0.98). Similar patterns of association were observed in different sensitivity analyses.

Conclusion: Adults who engaged in the recommended levels of physical activity were associated with a decreased likelihood of SARS-CoV-2 infection, severe COVID-19 illness, and COVID-19-related death. Our findings suggest that engaging in physical activity has substantial public health value and demonstrates potential benefits to combat COVID-19.

Abstract word counts: 309

Introduction

The coronavirus disease (COVID-19) caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread rapidly across the globe.[1-3] Despite dedicated efforts to end the pandemic including vaccination and antiviral therapies based on blood products and antibody, the emergence of more than 5,000 mutations and the continued second or more waves of infection have made the prevailing situation extremely complicated.[4] Baseline characteristics of patients, including old age, obesity, heavy smoking status, and underlying comorbidities, such as hypertension, respiratory disease, cardiovascular disease, and cancer have been shown to be associated with increased risk of COVID-19 and COVID-19-related death.[1-3 5 6] There is rapidly accumulating evidence on the risk factors for COVID-19 that are a function of interactions between the pathogen, host, and environment. However, there is limited information about the impact of an individual's level of physical activity, an important modifiable factor, on the potential infectivity and prognosis of COVID-19.

Physical activity is one of the leading determinants of health, and the lack of adequate physical activity is estimated to be responsible for 6–10% of the global burden of major chronic diseases and 9% of premature deaths.[7] Sufficient physical activity is known to be not only associated with substantially reduced risk for all-cause and disease-specific mortality[8], multiple chronic diseases (such as metabolic syndrome and type 2 diabetes)[7], cancer[7], cardiovascular disease[9], but also improved physical function, cognition, and quality of life[10]. It is well established that regular and sustained participation in physical activity is beneficial for almost every facet of health, and the supporting evidence continues to grow.[10] Moreover, previous studies have suggested that physical activity has a protective effect against infectivity and severity of respiratory infection due to its immunological benefits.[11-13] The recently published Physical

Activity Guidelines for Americans, 2nd edition, which was originally proposed for preventing chronic disease-related mortality, provides a clear guidance on the types (such as aerobic and muscle-strengthening activity) and amount (e.g. 150 minutes to 300 minutes a week of moderate-intensity of physical activity for adults) of physical activity that provides substantial health benefits.[10]

During the ongoing pandemic, measures taken by governments globally to control the transmission of COVID-19 include "lock downs" and social distancing.[14-16] This has substantially decreased people's daily behaviors, routine, and population levels of physical activity[17], which may lead to an unhealthy lifestyle[10]. Previous studies had investigated the potential association between physical activity and COVID-19 with inconsistent results; no association with SARS-CoV-2 infectivity[18] and COVID-19 severity[18], and beneficial association with COVID-19 severity[19-21] have been found by various studies. Thus, the impact of physical activity on COVID-19 infectivity and clinical outcomes remains unclear.

Previous studies had described the health benefits of physical activity including those on the immune system.[22] We established the hypothesis that this association will also apply to COVID-19, an infectious respiratory disease. Therefore, the aim of this study was to investigate the hypothesis that sufficient physical activity may reduce the risk of COVID-19 infectivity, severity, and its related mortality among patients who underwent SARS-CoV-2 testing or decrease the length of hospital stay among patients confirmed with COVID-19. We used a large-scale, population-based, nationwide claim-based cohort data that included all patients who underwent laboratory testing for SARS-CoV-2 in South Korea.

Methods

Data Source

We performed a high quality, population-based, nationwide study using the data from the Korean National Health Insurance Service (NHIS) that includes data of all individuals who underwent SARS-CoV-2 testing in South Korea through services facilitated by the Korea Disease Control and Prevention Agency (KDCA) and Ministry of Health and Welfare, South Korea, between January 1, 2020 and May 30, 2020. The following link can be used to access the Korean NHIS site: https://nhiss.nhis.or.kr/bd/ab/bdaba000eng.do/. The dataset links and consists of general health examination results, national COVID-19-related registers, including COVID-19-related outcomes and death records, and health insurance data for the past five years, including insurance eligibility data, outpatient and inpatient healthcare records, and pharmaceutical visits. The cohort dataset has the following characteristics: 1) the Korean government provided complimentary and mandatory health services and insurance to all Korean patients with COVID-19 [1-3 5]; 2) COVID-19-related death and outcome records were obtained by national COVID-19-related registers generated by the KDCA; and 3) all patient-related data were anonymized to ensure confidentiality from the Korean government. The study protocol was approved by the Institutional Review Board of Sejong University, and the requirement for written consent was waived by the ethics committee due to urgent medical needs to be met amid the COVID-19 pandemic (no. SJU-HR-E-2020-003).

Study population

The study population comprised all Korean individuals aged ≥20 years who underwent the SARS-CoV-2 testing between January 1, 2020 and May 15, 2020 by medical or KDCA referral

(excluding self-referral [self-referred patients were tested anonymously for their privacy]; n=212,768). Subsequently, we linked their national general health examination data between January 1, 2018 and December 31, 2019 to obtain the assessment on their level of physical activity. If the participants had multiple health examination data, the most recent was used. The total observational period was from January 1, 2015 to July 30, 2020, and individual index data was the data of the first SARS-CoV-2 testing for each patient. SARS-CoV-2 infection was confirmed by nasal and pharyngeal swabs using the laboratory real-time reverse transcriptase–polymerase chain reaction assay, which was authorized by the KDCA.[1-3] [5]

Age, gender, household income, and region of residence were obtained from insurance eligibility data. Smoking habits, frequency of alcohol consumption, physician diagnosed history of diabetes mellitus, tuberculosis, stroke, cardiovascular disease, hypertension, dyslipidemia, and previous use of medication for hypertension, dyslipidemia, diabetes mellitus, and cardiovascular disease were obtained from general health examination, including self-reported questionnaires and personal medical interview. Body mass index and systolic and diastolic blood pressure were measured. Blood glucose and creatinine for estimating glomerular filtration rate and total cholesterol were obtained from fasting serum samples during general health examination. The Charlson comorbidity index was considered as reported previously.[23]

Exposures and outcomes

The leisure-time physical activities of each participant was estimated during the general health examination and personal medical interview.[23] Participants were asked to report the frequency

of physical activity weekly in two categories: vigorous-intensity physical activity defined as intense exercise that causes severe shortness of breath (i.e. running) and moderate-intensity physical activity defined as exercise that causes mild shortness of breath (such as brisk walking and bicycling). We calculated the time of physical activity in minutes/week by multiplying the frequency (times/week) and duration (minutes/time). Muscle strengthening was considered by frequency (times/week) using the following question according to physical activity guidelines[10]: "How often do you do muscle strengthening activities in a week, such as lifting weights or push-ups (times/week)"

Aerobic physical activity was divided into two categories: recommended aerobic physical activity ($\geq$ 150 minutes/week of moderate intensity activity or $\geq$ 75 minutes/week of vigorous intensity activity or greater than an equivalent combination) and insufficient aerobic physical activity (< 150 minutes/week of moderate intensity activity, < 75 minutes/week of vigorous intensity activity, and less than an equivalent combination). Equivalent combination was calculated using the general rule that two minutes of moderate-intensity activity counts the same as one minute of vigorous-intensity activity.[10] Muscle strengthening activity was divided into two categories: recommended muscle strengthening activity ($\geq$ 2 times/week) and insufficient muscle strengthening activity (< 2 times/week). Using these categories for aerobic and muscle strengthening physical activity, the level of physical activity was categorized into four; 1) insufficient aerobic activity and muscle strengthening; 2) muscle strengthening only (insufficient aerobic activity and recommended muscle strengthening activity); 3) aerobic only (recommended aerobic activity and insufficient muscle strengthening activity); and 4) aerobic and muscle strengthening (both recommended activity).

In addition, we categorized physical activity according to metabolic equivalent task (MET) score on the energy cost. Each category of activity was assigned a MET score on the energy cost, and the weighted MET-minutes per week was calculated by multiplying the standard MET score, duration, and frequency per week.[24][25] Ratings of 4.0 and 8.0 METs were assigned for moderate and vigorous intensity activity, respectively.[24][25] The level of physical activity was categorized into four: 1) inactive (0 MET min/week), 2) insufficiently active (0 to < 500 MET min/week), 3) active (500 to < 1000 MET min/week), and 4) highly active (more than 1000 MET min/week).

We linked the study participants to the national COVID-19-related registers generated by Korea Disease Control and Prevention Agency. The outcomes examined were SARS-CoV-2 infection (positive laboratory SARS-CoV-2 testing result), severe clinical outcomes of COVID-19 (ICU admission, administration of invasive ventilation) [1-3][5], COVID-19-related death, and/or length of hospital stay.

Eight cohorts studied

We generated the eight cohorts for robustness and generalization of our results (Table S1 and Figure S1): 1) cohort A was the main study that consisted of participants who received general health examination between 2018 and 2019 (Figure S2-3; n=76,395); 2) propensity score matched cohort A was performed by matching two groups (insufficient aerobic and muscle strengthening versus aerobic and muscle strengthening; n=5,298); 3) cohort B consisted of only COVID-19 confirmed patients in cohort A (n=1293); 4) cohort C was conducted differential

conditions of "exposure" using the MET score (Figure S4-5; n=76,395); 5) propensity score matched cohort C was performed by matching two groups (insufficient physical activity group [0 to 500 MET min/week] versus sufficient physical activity group [more than 500 MET min/week]; n=59,986); 6) cohort D consisted of participants who received general health examination between 2015 and 2019 (Figure S6-7; n=118,768); 7) propensity score matched cohort D was performed by matching two groups (insufficient physical activity group [0 to 500 MET min/week] versus sufficient physical activity group [more than 500 MET min/week]; n=23,860); and 8) cohort E consisted of only COVID-19 confirmed patients in cohort C (n=3,882).

Participants in cohort A and B were categorized by exercise guideline and those in cohort C by MET score.[10] The Korean general health examination has added a questionnaire about muscle strengthening as of 2018; we could not calculate muscle strengthening by using data from 2015 to 2017. Therefore, participants in cohort D and E were categorized by MET score. If the participants had multiple health examination data, the most recent was used.

Sample size calculation

Although there has been no study on the association between SARS-CoV-2 infectivity and physical activity, we calculated the sample size based on a previous study on the relationship between COVID-19 severity and physical activity.[21] We had originally calculated that for each group to have an 80% power to show a 2.8-fold improvement of severity among COVID-19 patients (1% in inactive group versus 2.8% in active group), at a 5% significance level, we would need to enroll 900 COVID-19 patients in each group. Finally, we included 1293 COVID-19 patients who engaged insufficient physical activity and 1002 COVID-19 patients who engaged in sufficient muscle strengthening, aerobic or both physical activities.

Statistical Analyses

In the nationwide Korean cohort, "exposure" was the physical activities according to physical activity guidelines[10] in cohort A and B or those according to MET score in cohort C, D, and E. The "primary end point" was the positive SARS-CoV-2 testing results, severe COVID-19 illness, or COVID-19-related death in cohorts A to E; the "secondary endpoint" was the length of hospital stay among COVID-19 confirmed patients in cohort B and E. The "individual index data" was the data of first laboratory SARS-CoV-2 testing.

To assess the different confounding effects in our study, we used three sequential inclusion adjusting model by modified Poisson regressions presented by adjusted relative risks (aRRs) with 95% confidence intervals (CIs) or multivariable analysis of covariance presented by adjusted mean difference with 95% CIs. We also fitted a cubic spline model with four knots selected by the lowest Akaike information criterion.[26] Further, we confirmed the linearity assumption of systolic and diastolic blood pressure, fasting blood glucose, and serum total cholesterol using Box-Tidwell test (all P value >0.05), the normality assumption of length of hospital stay using Kolmogorov-Smirnov test (P value >0.05), and homogeneity of variances assumption of length of hospital stay using Levene's test (P value >0.05).

Model 1 was adjusted for age (20–39, 40–59, and ≥60 years) and sex. Model 2 was adjusted for age; sex; region of residence (Seoul Capital Area, Daegu/Gyeongbuk area, and other area); Charlson comorbidity index (0, 1, and ≥2); history of diabetes mellitus, tuberculosis, stroke, and cardiovascular disease; body mass index (continuous, using the cubic spline function); systolic blood pressure (continuous); diastolic blood pressure (continuous); fasting blood

glucose (continuous); serum total cholesterol (continuous); glomerular filtration rate ($\geq$90, 60–89, and $\leq$59 ml/min); household income (low, middle, and high); smoking (never, ex-, and current); alcoholic drinks (< 1, 1–2, 3–4, $\geq$5 days per week); medication for hypertension, diabetes mellitus, and cardiovascular disease. Finally, model 3 was adjusted for minimal selected potential confounders by directed acyclic graph approach (Figure S8; age, sex, region of residence, household income, smoking, and alcoholic drinks).

To test the stability and reliability of our results, we performed several analyses with multiple conditions. First, we analyzed two differential conditions of "exposure" such as using the physical activity guidelines[10] (cohort A and B) and MET score (cohort C, D and E). Second, we performed propensity score matching three times to reduce potential confounding effects and to balance the baseline characteristics (matched cohort A, insufficient aerobic and muscle strengthening versus aerobic and muscle strengthening; matched cohort C and D, insufficient physical activity group versus sufficient physical activity group). Propensity scores were derived using a logistic regression model with adjustment (model 2), and a "greedy nearest-neighbor" algorithm was used to match patients in the two groups in a 1:1 ratio (random selection without participant replacement within specified caliper widths [0.01 standard deviation]). We used robust standard errors to obtain 95% confidence intervals in matching analysis. Adequacy of matching was calculated by comparing standardized mean differences (SMDs) and propensity score density plot (Figure S9-11). An SMD of less than 0.1 indicates no major imbalance between the two groups.[5 27] Third, we conducted the sensitivity analysis by generating cohort B and E, including only COVID-19 patients. Fourth, to avoid overfitting issues, a directed acyclic graph approach was used to confirm adequate potential mediators, and thus, a visualization of the causal relationship between physical activity ("exposure") and

the risk of COVID-19 ("outcome") was provided. Fifth, we performed the subgroup analysis, in which there was stratification according to age, gender, smoking status, and Charlson comorbidity index, which have a statistical significance of interaction (P interaction value <0.05). Finally, we used the Sidak's correction for multiple comparisons to reduce the probability of type 1 error. Statistical analyses were performed using SPSS (version 25.0; IBM Corp, Armonk, NY), R software (version 3.1.1; R Foundation, Vienna, Austria), and SAS (version 9.4; SAS Institute Inc, Cary, NC).[23 28] Directed acyclic graphs were presented using Daggity (version 2.3; http://www.dagitty.net/). A two-sided P value of less than 0.05 was considered statistically significant.

Patient and public involvement

No patients were directly involved in designing the research question or in conducting the research. No patients were asked for advice on interpretation or writing up of the results. There were no plans to involve patients or the relevant patient community in the dissemination of study findings at this time.

Results

Cohort A

  Among 76,395 adults (age groups: 33.5% [20–39 years], 37.8% [40–59 years], and 28.7% [≥ 60 years]; male, 48.8%), we identified 41,293 (54.1%), 5,036 (6.6%), 18,994 (24.9%), and 11,072 (14.5%) adults with insufficient aerobic and muscle strengthening, muscle strengthening only, aerobic only, and aerobic and muscle strengthening, respectively (Table 1). During the observation period, 2,295 (3.0%), 446 (0.58%), and 45 (0.059%) adults were diagnosed with COVID-19 (SARS-CoV-2 test positive), severe COVID-19, and COVID-19-related death, respectively (Table S11).

  Table 2 and Figure 1 show that adults with aerobic and muscle strengthening had a lower risk of COVID-19 infection (3.1% for insufficient aerobic and muscle strengthening versus 2.6% for aerobic and muscle strengthening; aRR [model 2] 0.85; 95% CI 0.72–0.98), severe COVID-19 (0.66% versus 0.35%; aRR [model 2] 0.42; 95% CI 0.34–0.91), and COVID-19-related death (0.08% versus 0.02%; aRR [model 2] 0.23; 95% CI 0.06–0.99). In subgroup analysis stratified by the covariates (Table 3), the effect sizes of risk of COVID-19 infection between patients with insufficient aerobic and muscle strengthening and those with aerobic and muscle strengthening were stronger among middle aged adults (40–59 years; aRR 0.85; 95% CI 0.70–0.99), men (aRR, 0.81; 95% CI 0.64–0.98), never smokers (aRR 0.79; 95% CI 0.58–0.94), and those having low Charlson comorbidity index (0 score; aRR 0.74; 95% CI 0.58–0.94) than in other groups. Similar effect sizes and patterns of severe COVID-19 were found among older adults (≥60 years; aRR 0.16; 95% CI 0.02–0.96), never smokers (aRR 0.44; 95% CI 0.23–0.99), and those having low Charlson comorbidity index (0 score; aRR 0.23; 95% CI 0.09–

0.80). Moreover, we also found similar patterns after Sidak's correction (Table S12).

Matched cohort A

After 1:1 propensity score matching in cohort A (2,649 for insufficient aerobic and muscle strengthening versus 2,649 for aerobic and muscle strengthening), there were no major imbalances of baseline characteristics assessed by SMDs (Table S2; all SMDs ≤0.04). Those with aerobic and muscle strengthening had 27% lower risk of COVID-19 (aRR [model 2] 0.73; 95% CI 0.54–0.99) and 57% lower risk of severe COVID-19 (aRR [model 2] 0.43; 95% CI 0.20–0.95) than those with insufficient aerobic and muscle strengthening (Table 4).

Cohort B

Among COVID-19 confirmed patients in cohort A (Table 4 and S2; n=2,295), we found that those with aerobic and muscle strengthening had a decreased risk of severe COVID-19 (aRR [model 2] 0.66; 95% CI 0.47–0.90) and length of hospital stay (adjusted mean difference, -2.08 days; 95% CI -4.04 to -0.14).

Cohort C

The 76,395 adults in cohort C were stratified according to MET score (Table 4 and S4). The active group (500 to <1000 MET min/week) was found to have 22% lower risk of COVID-19 infection (aRR [model 2] 0.78; 95% CI 0.66–0.92), 38% lower risk of severe COVID-19 (aRR [model 2] 0.62; 95% CI 0.43–0.90), and 83% lower risk of COVID-19-related death (aRR [model 2] 0.17; 95% CI 0.07–0.98) than the inactive group. The insufficiently active group and highly active group had a modest 9% and 6% lower risk of COVID-19 infection, 22% and 21%

lower risk of severe COVID-19, and 19% and 21% lower risk of COVID-19-related death than the inactive group, respectively (Figure S1).

Matched cohort C

We conducted a propensity score-matched analysis to compare low physical activity group (0 to 500 MET min/week) with sufficient physical activity group (≥500 MET min/week). There were no major imbalances in baseline characteristics assessed by SMDs (Table 4 and S6; all SMDs<0.07). In model 2, there was less SARS-CoV-2 infection (aRR 0.90; 95% CI 0.83–0.99) and severe COVID-19 (aOR 0.77; 95% CI 0.63–0.95) in the high physical activity group than in the low physical activity group. Moreover, we also found similar patterns after Sidak's correction (Table S13).

Cohort D

Among 118,768 included adults, we identified 22,811 (19.2%), 50,052 (42.1%), 25,932 (21.8%), and 19,973 (16.8%) adults who were inactive, insufficiently active, active, and highly active, respectively (Table S7). During the observation period, 3,882 (3.3%), 277 (0.23%), and 122 (0.10%) adults were diagnosed with COVID-19 (SARS-CoV-2 test positive), severe COVID-19, and COVID-19-related death, respectively.

Table S8 and Figure S12 show that the active group (500 to <1000 MET min/week) had 15% lower risk of COVID-19 infection (aRR [model 2] 0.85; 95% CI 0.75–0.96), 46% lower risk of severe COVID-19 (aRR [model 2] 0.54; 95% CI 0.35–0.79), and 65% lower risk of COVID-

19-related death (aRR [model 2] 0.35; 95% CI 0.20–0.64) than the inactive group. However, the insufficiently active group and highly active group had a modest 11% and 15% lower risk of COVID-19 infection, 35% and 34% lower risk of severe COVID-19, and 40% and 63% lower risk of COVID-19-related death than the inactive group, respectively (Table 4).

Matched cohort D

We conducted a propensity score-matched analysis to compare low physical activity group (0 to 500 MET min/week) with sufficient physical activity group (≥500 MET min/week). There were no major imbalances in baseline characteristics assessed by SMDs (Table 4 and S9; all SMDs<0.015). In model 2, there was less SARS-CoV-2 infection (aRR 0.87; 95% CI 0.76–0.99), severe COVID-19 (aOR 0.58; 95% CI 0.35–0.99), and COVID-19 related mortality (aOR 0.46; 95% CI 0.22–0.96) in the high physical activity group than in the low physical activity group.

Cohort E

Among the patients diagnosed with COVID-19 (n=3,882), the risk of severe COVID-19 was less in the insufficiently active group (aRR [model 2] 0.73; 95% CI 0.53–0.99) and active group (aRR [model 2] 0.68; 95% CI 0.44–0.98) than in the inactive group. The COVID-19 related mortality among patients with COVID-19 was lower in the active group (aRR [model 2] 0.49; 95% CI 0.27–0.82) and highly active group (aRR [model 2] 0.43; 95% CI 0.22–0.83) than in the inactive group (Table 4 and S10). The length of stay in hospital of patients with COVID-19 was lower only in the active group (adjusted mean difference, -1.85 day; 95% CI, -3.63 to -0.05) than the inactive group, while no further benefits were observed in the

insufficiently and highly active groups.

Discussion

Findings of our study

To our knowledge, this is the first large-scale, population-based, nationwide study that investigated the relationship of physical activity with the infectivity and severity of COVID-19 and its-related death. In this nationally representative cohort study, we found that those who reported aerobic and muscle strengthening activities that met or exceeded the 2018 exercise guidelines had a lower risk of SARS-CoV-2 infection (aRR, 0.85; 95% CI, 0.72-0.96), severe COVID-19 illness (aRR, 0.42; 95% CI, 0.19-0.91), and COVID-19-related death (aRR, 0.24; 95% CI, 0.05-0.99) than those who did not. The effect sizes of these associations were significant among the elderly, men, never smokers, and those having low Charlson comorbidity index. Furthermore, the recommended key target range of MET score (500–1000 MET min/week) was associated with the maximum beneficial effect size for the reduced risk of SARS-CoV-2 infection (aRR, 0.78; 95% CI 0.66-0.92), severe COVID-19 illness (aRR, 0.62; 95% CI, 0.43-0.90), and COVID-19-related death (aRR, 0.17; 95% CI, 0.07-0.98). Interestingly, the length of stay in hospital was shortened about approximately two days in patients who performed both aerobics and muscle strengthening (adjusted mean difference, -2.08 day) or with MET 500–1000 MET min/week (adjusted mean difference, -1.85 day). These findings were consistent across a broad range of sensitivity and subgroup analyses using cohort A to E or propensity score matching.

Comparison with previous studies

While several studies describe the health benefits of physical activity, most studies focused on non-communicable diseases[8]. Few studies on physical activity and risk of respiratory infectious diseases have shown inconsistent results: beneficial association in USA (n=78,062)[11] and

Poland (n=1028)[13] and no association in Denmark (n=5368)[29], Sweden (n = 2038)[30], and USA (n=83,165)[31]. Furthermore, several intervention trials conducted in the USA, Brazil, Canada, Portugal, Spain, and Turkey have produced nonconclusive and inconsistent results.[32] Small sample size, heterogeneity of the study population, short-term follow-up period, and inappropriate study design (i.e., cross-sectional or uncontrolled cohort design) contributed to low levels of evidence and inconsistent results.[11 13 29-32] However, a recent meta-analysis of 14 intervention trials suggested that exercise had a significant effect on the severity of symptoms and number of symptom days (mean difference −2.24 days), similar to our results. Moreover, a recent large meta-analysis including 55 studies suggested that physical activity is associated with a 31% and 37% risk reduction of community acquired infectious disease and its related mortality, respectively, which is consistent with our results.[12]

   Though there are previous studies on the association between physical activity and the risk of COVID-19, the results are inconsistent; no association of physical activity with SARS-CoV-2 infectivity[18] and COVID-19 severity[18]; and beneficial association with COVID-19 severity[19-21]. Small sample size (COVID-19 patients, n=207[18] or 246[19]), uncontrolled cohort design[18-21], non-various definitions of physical activity[18-21], non-sophisticated statistical techniques to reduce several biases[18-21], and different methods of collecting data for measuring exercise (24-hour movement patterns and self-reported questionnaire) contributed to inconsistent results in these studies (Table S14). Furthermore, most of the studies were conducted in the UK and USA[18-21]; the findings in Asia was unknown. These studies had explained the association using the hypothesis that regular physical activity is an important contributor to exercise capacity and favorably influences biologic pathways that are involved with the body's response to an infection, which is a consistent hypothesis supporting our results. Moreover, our study was

primarily demonstrated the beneficial relationship between SARS-CoV-2 infectivity and physical activity.

Possible explanations of our results

Habitual exercise has the following beneficial effect on the immune system[33]: 1) enhanced immunosurveillance with an immune defense activity and metabolic health by increased immunoglobulins, anti-inflammatory cytokines (interleukin [IL]-6, IL-1ra, and IL10), neutrophils, cytotoxic T, immature B, and natural killer cell subsets; 2) reduced systemic inflammation promoted by the recirculation of immune cells and mediates an anti-inflammatory and antioxidant state through multiple pathways; and 3) improved regulation of the immune system and delayed onset of immunosenescence. In addition, a previous study demonstrated that physical activity inhibits lung inflammation and bacterial colonization in respiratory infectious disease involving Il-10/NF-κB.[34] Recently, a study reported that physical activity helps to shift the balance of the angiotensin-converting enzyme 2 (ACE2) axis.[35] It means that physical activity induces expression of ACE2 in skeletal muscle which leads to reduced circulating ACE2 that may have protective effect in susceptibility to SARS-CoV-2 and severity of COVID-19.[35] The above-mentioned immunological benefits of exercise may prevent the infection, severity, and death due to COVID-19.

Policy implication

Recent studies reported that total physical activity significantly decreased between immediately before and during the COVID-19 pandemic worldwide and across all age groups.[17] Although research evidence continues to mount that decreased in physical activity during the COVID-19 pandemic is a critical threat to public health, its impact on infectivity

and clinical outcomes has not been clearly defined. The results of this study demonstrated the importance of physical activity in decreasing the risk of infectivity, severity, and mortality of COVID-19, so that it can be reflected in future guidelines. The World Health Organization launched "#HealthAtHome" campaign, including the recommendation of physical activity, to help manage weight and reduce the risk of non-communicable diseases such as cardiometabolic disease, that can increase susceptibility to or severity of COVID-19.[36] World Health Organization recommended that people of all ages and abilities need to be as active as possible and encouraged people to engage in regular aerobic physical activity and bone and muscle strengthening activity[36].

Strengths and limitations

There are several limitations in this study that need to be addressed. First, physical activity was assessed by self-report, which may lead to misclassification. Misclassification of physical activities by a self-report usually leads to regression dilution bias, which may lead to an underestimation of the magnitude of true association.[22] Second, we can only assess the binary variable of muscle strengthening activity. Although frequency of muscle strengthening activity was not available, 2018 physical activity guidelines recommend only the use of binary variable (≥ 2 times/week), not frequency data. Third, the data of physical activity status was obtained at a single point of recent general health examinations and excluded light-intensity physical activity. Furthermore, there is the possibility that individuals may tend to overestimate levels of physical activity on average with variations in possible effects, especially over longer periods of recall. However, the "exposure" of physical activity can change at index data, which may influence the magnitude of the true association. Moreover, physical activity was only collected during leisure time; household and occupation-related physical activities were

missing, which may influence the magnitude of true association.[37] Future prospective cohort or interventional studies with serial and direct measurements of physical activity (i.e., mobile exercise apps) are needed to investigate the true association between exercise and COVID-19. Fourth, although we adjusted a variety of covariates and matched using propensity score, we cannot exclude the possibility of unexpected confounding variables such as dietary patterns. To address this, we generated several cohort studies and performed several sensitivity analyses that may make our results robust and generalizable. Fifth, our results should be interpreted with caution since our study comprised only Asian patients (Korean), and ethnic prevalence of ACE2 polymorphism is different which may affect the ACE2 axis. Finally, COVID-19 outcomes have improved over time, due to improvement in management [38], and our study was performed with data from the early stages of the pandemic. Further longitudinal studies are warranted. Sixth, measurement error in some confounders such as alcohol consumption and household income can result in residual confounding. Furthermore, the estimates are biased as the study did not capture the time-varying nature of both exposure and many of the confounders.[39] Seventh, some estimated 95% CIs such as 0.05 or 0.06 in Table 2 clearly suggest sparse-data bias which should be acknowledged as an important limitation.[40] Although we used several analyses such as modified Poisson regressions model and matching analysis, it should be noted that the target effect of each analysis are different. While conditional effect is estimated in modified Poisson regressions, average effect in the exposed group is estimated in propensity score methods. Finally, patients with self-referral were tested anonymously to maintain privacy and their data were unavailable in our database; therefore, exclusion of those with self-referral may have led to increase in selection bias.

Despite these limitations, this is the first large-scale, population-based, nationwide study to

investigate the association between physical activity and risk of COVID-19 infectivity, severity, and related death. Our data were collected from a large population that contains nationwide data of physical activity of over 100,000 individuals. To date, this is the first and largest analysis that focused on these relationships. We used the validated physical activity assessment according to the 2018 physical activity guidelines for Americans, and our data (such as previous medical history, body mass index, blood pressure, and blood sample) were measured or obtained by medical staff during personal medical interview.

Conclusions

This study provides new evidence that physical activity, including both aerobic and muscle strengthening exercises led to substantial reductions in the infectivity of SARS-CoV-2, risk of poor outcomes, and death-related to COVID-19. In particular, the effect sizes of these associations were significant among elderly, men, never smokers, and those having low Charlson comorbidity index. However, the recommended key target range of MET score was associated with the maximum beneficial effect size for reduced the risk of SARS-CoV-2 infection, severe COVID-19 illness, and COVID-19-related death. Interestingly, the length of hospital stay was shortened by approximately two days in patients who reported aerobic and muscle strengthening activities that met or exceeded the 2018 exercise guidelines (adjusted mean difference, -2.08 day) or those with MET 500–1000 MET min/week (adjusted mean difference, -1.85 day). The findings of the study suggest that public health policies and strategies to increase physical activity at the population level may reduce the risk of SARS-CoV-2 infection and minimize adverse consequences in COVID-19 patients. Encouraging individuals to maintain recommended levels of physical activity during the COVID-19 pandemic should be promptly and vigorously considered at the public health level.

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Contributors

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Competing interests

All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Patient consent for publication

Not required

Ethical approval

The National Health Insurance Service-National Sample Cohort has ethical approval form the Institutional Review Board of Sejong University (SJU-HR-E-2020-003).

Data availability statement

Study protocol, *Statistical code*: Available from Dr. Yon (e-mail, yonkkang@gmail.com). *Data set*: Available from the National Health Insurance Service of Korea (NHIS-COVID-19 data) through a data use agreement.

What are the findings?

- Our results indicated that those who engaged in both aerobic and muscle strengthening activity according to 2018 exercise guidelines had a lower risk of SARS-CoV-2 infection (adjusted relative risk [aRR], 0.85; 95% CI, 0.72-0.96), severe COVID-19 illness (aRR, 0.42; 95% CI, 0.19-0.91), and COVID-19-related death (aRR, 0.24; 95% CI, 0.05-0.99) than those who did not.

- Our findings reported that the recommended key target range of metabolic equivalent of task (MET; 500–1000 MET min/week) was associated with the maximum beneficial effect size for reduced the risk of SARS-CoV-2 infection (aRR, 0.78; 95% CI 0.66-0.92), severe COVID-19 illness (aRR, 0.62; 95% CI, 0.43-0.90), and COVID-19-related death (aRR, 0.17; 95% CI, 0.07-0.98). The length of stay in hospital was shortened about approximately two days in patients with both aerobic and muscle strengthening or with 500–1000 MET min/week.

How might it impact on clinical practice in the future?

- The findings of the study suggest that public health policies and strategies to increase physical activity at the population level may reduce the risk of SARS-CoV-2 infection and minimize adverse consequences in COVID-19 patients.

- Encouraging individuals to have active level of physical activity during the COVID-19 pandemic should be promptly and actively considered at the public health level.

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Tables and Figures

Figure 1. Association between physical activity according to 2018 physical activity guidelines for Americans and SARS-CoV-2 infection, severe COVID-19 illness, and COVID-19-related death in cohort A (A). Association between physical activity according to MET score and SARS-CoV-2 infection, severe COVID-19 illness, and COVID-19-related death in cohort C (B).

The level of physical activity was categorized into four: 1) inactive (0 MET min/week), 2) insufficiently active (0 to < 500 MET min/week), 3) active (500 to < 1000 MET min/week), and 4) highly active (more than 1000 MET min/week).

Whiskers represent 95% confidence intervals and dots indicate full adjusted relative risks.

Abbreviations: COVID-19, coronavirus disease; MET, metabolic equivalent of task; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Figure S1. Participant profile in all cohort

Abbreviations: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Figure S2. Flowchart depicting study enrollment in cohorts A and B

Abbreviations: COVID-19, coronavirus disease; KDCA, Korea Disease Control and Prevention Agency; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Figure S3. Participant profile in cohort A and B

Abbreviations: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Figure S4. Flowchart depicting study enrollment in cohort C

Abbreviations: COVID-19, coronavirus disease; KDCA, Korea Disease Control and Prevention Agency; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Figure S5. Participant profile in cohort C

Abbreviations: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Figure S6. Flowchart depicting study enrollment in cohort D and E

Abbreviations: COVID-19, coronavirus disease; KDCA, Korea Disease Control and Prevention Agency; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Figure S7. Participant profile in cohort D and E

Abbreviations: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Figure S8. Directed acyclic graph demonstrating the implicitly assumed causal association between physical activity ("exposure") and risk of COVID-19 ("outcome") in the Korean nationwide cohort before matching. Confounders, potential mediators, and exposure-outcome associations are indicated.

Abbreviations: BMI, body mass index; BP, blood pressure; CCI, Charlson comorbidity index; CVD, cardiovascular disease; COVID-19, coronavirus disease; GFR, glomerular filtration rate; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TB, tuberculosis

Figure S9. Density and distribution of propensity scores before and after matching in matched cohort A

Figure S10. Density and distribution of propensity scores before and after matching in matched cohort C

Figure S11. Density and distribution of propensity scores before and after matching in matched cohort D

Figure S12. Association between physical activity according to MET score and SARS-CoV-2 infection, severe COVID-19 illness, and COVID-19-related death in cohort D

The level of physical activity was categorized into four: 1) inactive (0 MET min/week), 2) insufficiently active (0 to < 500 MET min/week), 3) active (500 to < 1000 MET min/week), and 4) highly active (more than 1000 MET min/week).

Whiskers represent 95% confidence intervals and dots indicate full adjusted relative risks.

Abbreviations: COVID-19, coronavirus disease; MET, metabolic equivalent of task; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Table 1. Baseline characteristics of patients who performed the SARS-CoV-2 testing in the Korean nationwide cohort (cohort A)

Characteristic	Entire cohort	Types of physical activity			
		Insufficient aerobic and muscle strengthening	Muscle strengthening only	Aerobic only	Aerobic and muscle strengthening
Total, n (%)	76,395 (100.0)	41,293 (54.1)	5036 (6.6)	18,994 (24.9)	11,072 (14.5)
Age, years, n (%)					
20-39	25,614 (33.5)	13,005 (31.5)	1747 (34.7)	6072 (32.0)	4790 (43.3)
40-59	28,856 (37.8)	15,677 (38.0)	2028 (40.3)	7091 (37.3)	4060 (36.7)
≥ 60	21,925 (28.7)	12,611 (30.5)	1261 (25.0)	5831 (30.7)	2222 (20.1)
Sex, n (%)					
Male	37,272 (48.8)	17,703 (42.9)	3156 (62.7)	9217 (48.5)	7196 (65.0)
Female	39,123 (51.2)	23,590 (57.1)	1880 (37.3)	9777 (51.5)	3876 (35.0)
Region of residence, n (%)					

Seoul Capital Area	34,149 (44.7)	18,442 (44.7)	2448 (48.6)	8200 (43.2)	5059 (45.7)
Daegu/Gyeongbuk area	14,910 (19.5)	8203 (19.8)	1034 (20.5)	3704 (19.5)	1969 (17.8)
Other area	27,336 (35.8)	14,648 (35.5)	1554 (30.9)	7090 (37.3)	4044 (36.5)
Charlson comorbidity index, n (%)					
0	44,854 (58.7)	23,405 (56.7)	3137 (62.3)	10,971 (57.8)	7341 (66.3)
1	9361 (12.3)	5234 (12.7)	617 (12.3)	2277 (12.0)	1233 (11.1)
≥2	22,180 (29.0)	12,654 (30.6)	1282 (25.5)	5746 (30.3)	2498 (22.6)
History of diabetes mellitus, n (%)	6518 (8.5)	3738 (9.1)	355 (7.1)	1745 (9.2)	680 (6.1)
History of tuberculosis, n (%)	1585 (2.1)	860 (2.1)	121 (2.4)	383 (2.0)	221 (2.0)
History of stroke, n (%)	1038 (1.4)	640 (1.6)	45 (0.9)	261 (1.4)	92 (0.8)
History of cardiovascular disease, n (%)	2357 (3.1)	1372 (3.3)	151 (3.0)	601 (3.2)	233 (2.1)
History of hypertension, n (%)	14,528 (19.0)	8245 (20.0)	832 (16.5)	3866 (20.4)	1585 (14.3)
History of dyslipidemia, n (%)	5355 (7.0)	2988 (7.2)	336 (6.7)	1425 (7.5)	606 (5.5)

Body mass index, kg/m^2, n (%)					
Mean (SD)	23.9 (3.8)	23.8 (3.9)	23.7 (3.3)	24.1 (3.8)	24.1 (3.5)
<25	49,286 (64.5)	26,883 (65.1)	3398 (67.5)	11,881 (62.6)	7124 (64.3)
25–30	22,453 (29.4)	11,822 (28.6)	1442 (28.6)	5822 (30.7)	3367 (30.4)
≥30	4656 (6.1)	2588 (6.3)	196 (3.9)	1291 (6.8)	581 (5.3)
Systolic blood pressure, mmHg, mean (SD)	121.2 (14.8)	121.2 (15.2)	121.1 (14.4)	121.6 (13.6)	120.8 (13.7)
Diastolic blood pressure, mmHg, mean (SD)	74.9 (10.0)	74.8 (10.1)	74.9 (9.9)	75.0 (9.9)	74.8 (9.7)
Fasting blood glucose, mg/dL, mean (SD)	99.4 (24.7)	99.8 (25.9)	97.9 (21.3)	99.8 (24.3)	98.2 (22.0)
Serum total cholesterol, mg/dL, mean (SD)	191.4 (40.4)	191.7 (41.5)	191.9 (38.4)	190.5 (39.6)	191.4 (38.4)
Glomerular filtration rate, ml/min, n (%)					
≥90	40,449 (52.9)	22,168 (53.9)	26,665 (53.1)	9807 (51.9)	5809 (52.7)
60-89	31,051 (40.6)	16,026 (39.0)	2110 (42.0)	8065 (42.7)	4850 (44.0)
≤59	4580 (6.0)	2923 (7.1)	247 (4.9)	1035 (5.5)	375 (3.4)

Household income, n (%)					
Low (0–39 percentile)	21,427 (28.4)	12,186 (29.5)	1175 (23.3)	5339 (28.1)	2727 (24.6)
Middle (40–79 percentile)	33,482 (43.8)	17,927 (43.4)	2216 (44.0)	8361 (44.0)	4978 (45.0)
High (80–100 percentile)	21,486 (28.1)	11,180 (27.1)	1645 (32.7)	5294 (27.9)	3367 (30.4)
Smoking, n (%)					
Never smoker	50,227 (65.7)	28,472 (69.0)	2931 (58.2)	12,442 (65.6)	6382 (57.6)
Ex-smoker	12,492 (16.4)	5691 (13.8)	1171 (23.3)	3170 (16.7)	2460 (22.2)
Current smoker	13,676 (17.9)	7130 (17.3)	934 (18.6)	3382 (17.8)	2230 (20.1)
Alcoholic drinks, days per week, n (%)					
<1	47,769 (62.5)	27,003 (65.5)	2843 (56.5)	11,839 (62.5)	6084 (55.0)
1–2	20,375 (26.7)	9988 (24.2)	1598 (56.5)	5044 (62.5)	3745 (33.9)
3–4	6074 (8.0)	3103 (7.5)	470 (9.3)	1542 (8.1)	959 (8.7)

≥5	2075 (2.7)	1154 (2.8)	120 (2.4)	534 (2.8)	267 (2.4)
Use of medication, n (%)					
Medication for hypertension, n (%)	13,663 (17.9)	7775 (18.8)	774 (15.4)	3659 (19.3)	1455 (13.1)
Medication for dyslipidemia, n (%)	4450 (5.8)	2494 (6.0)	264 (5.2)	1206 (6.4)	486 (4.4)
Medication for diabetes mellitus, n (%)	6080 (8.0)	3494 (8.5)	325 (6.5)	1635 (8.6)	626 (5.7)
Medication for cardiovascular disease, n (%)	2153 (2.8)	1252 (3.0)	134 (2.7)	555 (2.9)	212 (1.9)

Abbreviations: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SD, standard deviation.

Table 2. Adjusted relative risk (95% confidence intervals) of SARS-CoV-2 infection, severe COVID-19 outcomes, and COVID-19 related deaths associated with study patients who engaged in physical activities according to exercise guideline (cohort A)

Event	Types of physical activity			
	Insufficient aerobic and muscle strengthening	Muscle strengthening only	Aerobic only	Aerobic and muscle strengthening
COVID-19, n (%)	1293/41,293 (3.1)	150/5036 (3.0)	561/18,994 (3.0)	291/11,072 (2.6)
Adjusted RR (95% CI)				
Model 1[*] (age and sex adjusted)	1.0 (ref)	1.08 (0.91 to 1.29)	0.98 (0.88 to 1.09)	**0.87 (0.75 to 0.98)**
Model 2[§] (fully adjusted)	1.0 (ref)	1.01 (0.73 to 1.42)	0.92 (0.77 to 1.12)	**0.84 (0.73 to 0.96)**
Model 3[‖] (selected confounders by DAGs)	1.0 (ref)	1.03 (0.86 to 1.22)	0.97 (0.88 to 1.07)	**0.85 (0.72 to 0.98)**
Severe COVID-19[‡], n (%)	273/41,293 (0.66)	25/5036 (0.50)	109/18,994 (0.57)	39/11,072 (0.35)
Adjusted RR (95% CI)				
Model 1[*] (age and sex adjusted)	1.0 (ref)	0.85 (0.56 to 1.29)	0.87 (0.70 to 1.09)	**0.59 (0.39 to 0.87)**
Model 2[§] (fully adjusted)	1.0 (ref)	0.93 (0.61 to 1.42)	0.86 (0.69 to 1.08)	**0.42 (0.19 to 0.91)**

Model 3[‖] (selected confounders by DAGs)	1.0 (ref)	0.88 (0.58 to 1.33)	0.86 (0.69 to 1.08)	**0.56 (0.34 to 0.88)**
COVID-19 related death, n (%)	32/41,293 (0.08)	0/5036 (0.00)	11/18,994 (0.06)	2/11,072 (0.02)
Adjusted RR (95% CI)				
Model 1[*] (age and sex adjusted)	1.0 (ref)	NA	0.70 (0.35 to 1.41)	**0.23 (0.06 to 0.98)**
Model 2[§] (fully adjusted)	1.0 (ref)	NA	0.71 (0.34 to 1.41)	**0.26 (0.07 to 0.99)**
Model 3[‖] (selected confounders by DAGs)	1.0 (ref)	NA	0.71 (0.34 to 1.40)	**0.24 (0.06 to 0.99)**

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease; DAGs, directed acyclic graphs; RR, relative risk; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[*] Model 1: adjusted for age (20−39, 40−59, and ≥60 years) and sex.

[§] Model 2: adjusted for the age; sex; region of residence (Seoul Capital Area, Daegu/Gyeongbuk area, and other areas); Charlson comorbidity index (0, 1, and ≥2); history of diabetes mellitus, tuberculosis, stroke, and cardiovascular disease; body mass index (continuous; using the cubic spline function); systolic blood pressure (continuous; using the restricted cubic spline function); diastolic blood pressure (continuous); fasting blood glucose (continuous); serum total cholesterol (continuous); glomerular filtration rate (≥90, 60−89, and ≤59 ml/min); household income (low, middle, and high); smoking (never, ex-, and current); alcoholic drinks (<1, 1−2, 3−4, ≥5 days per week);

medication for hypertension, diabetes mellitus, and cardiovascular disease.

|| Model 3: adjusted for potential confounders selected by DAGs (age; sex; region of residence; household income; smoking; and alcoholic

drinks).

‡ Severe COVID-19 consisted of requirement of oxygen therapy, admission to the intensive care unit, invasive ventilation, or death.

Numbers in bold indicate significant differences ($P < 0.05$).

Table 3. Subgroup analysis of the association of SARS-CoV-2 infection and severe COVID-19 outcomes associated with study patients who engaged in physical activities according to exercise guideline. Values are adjusted relative risks[*] (95% confidence intervals; Cohort A)

| Subgroups | Event | Types of physical activity | | | |
		Insufficient aerobic and muscle strengthening	Muscle strengthening only	Aerobic only	Aerobic and muscle strengthening
Age groups (years)					
20-39	COVID-19	1.0 (ref)	1.43 (0.63 to 3.17)	1.13 (0.55 to 2.27)	0.99 (0.51 to 1.99)
40-59	COVID-19	1.0 (ref)	1.04 (0.66 to 1.64)	0.98 (0.76 to 1.27)	**0.85 (0.70 to 0.99)**
≥ 60	COVID-19	1.0 (ref)	0.83 (0.44 to 1.52)	0.82 (0.61 to 1.10)	0.77 (0.51 to 1.19)
Sex					
Male	COVID-19	1.0 (ref)	1.02 (0.67 to 1.54)	0.97 (0.73 to 1.29)	**0.81 (0.64 to 0.98)**
Female	COVID-19	1.0 (ref)	1.06 (0.62 to 1.79)	0.90 (0.71 to 1.15)	0.90 (0.66 to 1.28)
Smoking					
Never smoker	COVID-19	1.0 (ref)	1.02 (0.67 to 1.54)	0.97 (0.73 to 1.29)	**0.79 (0.64 to 0.99)**

Ex-smoker	COVID-19	1.0 (ref)	0.91 (0.45 to 1.84)	0.92 (0.57 to 1.51)	0.75 (0.45 to 1.31)
Current smoker	COVID-19	1.0 (ref)	0.90 (0.27 to 2.93)	1.28 (0.64 to 2.48)	1.33 (0.58 to 3.00)
Charlson comorbidity index					
0	COVID-19	1.0 (ref)	1.09 (0.72 to 1.61)	0.99 (0.78 to 1.30)	**0.74 (0.58 to 0.94)**
1	COVID-19	1.0 (ref)	0.83 (0.34 to 2.03)	1.16 (0.74 to 1.79)	0.53 (0.16 to 1.09)
≥2	COVID-19	1.0 (ref)	0.95 (0.54 to 1.11)	0.78 (0.54 to 1.12)	1.48 (0.94 to 2.31)
Age groups (years)					
20-39	Severe COVID-19[§]	1.0 (ref)	1.03 (0.62 to 1.76)	0.66 (0.50 to 1.05)	0.58 (0.25 to 1.30)
40-59	Severe COVID-19[§]	1.0 (ref)	1.09 (0.61 to 2.02)	0.67 (0.43 to 1.19)	0.48 (0.15 to 1.24)
≥ 60	Severe COVID-19[§]	1.0 (ref)	0.79 (0.26 to 3.05)	0.58 (0.18 to 1.75)	**0.16 (0.02 to 0.96)**
Sex					
Male	Severe COVID-19[§]	1.0 (ref)	0.97 (0.60 to 1.60)	0.79 (0.56 to 1.27)	0.45 (0.18 to 1.07)
Female	Severe COVID-19[§]	1.0 (ref)	1.14 (0.64 to 2.09)	**0.57 (0.41 to 0.95)**	0.48 (0.15 to 1.26)

Smoking					
Never smoker	Severe COVID-19[§]	1.0 (ref)	1.25 (0.81 to 1.96)	**0.59 (0.45 to 0.94)**	**0.44 (0.23 to 0.99)**
Ex-smoker	Severe COVID-19[§]	1.0 (ref)	0.67 (0.32 to 1.56)	0.81 (0.46 to 1.55)	0.54 (0.14 to 1.45)
Current smoker	Severe COVID-19[§]	1.0 (ref)	0.60 (0.17 to 3.85)	1.19 (0.48 to 2.94)	0.28 (0.06 to 2.15)
Charlson comorbidity index					
0	Severe COVID-19[§]	1.0 (ref)	0.89 (0.51 to 1.63)	**0.52 (0.33 to 0.96)**	**0.23 (0.09 to 0.80)**
1	Severe COVID-19[§]	1.0 (ref)	1.00 (0.41 to 2.65)	0.56 (0.26 to 1.27)	0.81 (0.31 to 2.41)
≥2	Severe COVID-19[§]	1.0 (ref)	1.09 (0.63 to 1.95)	0.81 (0.59 to 1.28)	0.57 (0.32 to 1.34)

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[*] Regression models were adjusted for age (20-39, 40-59, and ≥60 years); sex; region of residence (Seoul Capital Area, Daegu/Gyeongbuk area, and other area); Charlson comorbidity index (0, 1, and ≥2); history of diabetes mellitus, tuberculosis, stroke, and cardiovascular disease; body mass index (continuous; using the restricted cubic spline function); systolic blood pressure (continuous); diastolic blood pressure (continuous); fasting blood glucose (continuous); serum total cholesterol (continuous); glomerular filtration rate (≥90, 60−89, and ≤

59 ml/min); household income (low, middle, and high); smoking (never, ex-, and current); alcoholic drinks (<1, 1−2, 3−4, ≥5 days per week);

medication for hypertension, diabetes mellitus, and cardiovascular disease.

§ Severe COVID-19 consisted of requirement of oxygen therapy, admission to the intensive care unit, invasive ventilation, or death.

Numbers in bold indicate significant differences ($P < 0.05$).

Table 4. Sensitivity and additional analysis of the association of SARS-CoV-2 infection, severe COVID-19 outcomes, and COVID-19 related

death associated with study patients who engaged in physical activities according to exercise guideline or MET score.

Events	Cohort	N (%)	Exposure	Adjusted RR (95% CI)
COVID-19	Table S2; Propensity score matched cohort A	95/2649 (3.6)	Insufficient aerobic and muscle strengthening	1.0 (ref) [§]
		69/2649 (2.6)	Aerobic and muscle strengthening	**0.73 (0.54 to 0.99)**
COVID-19	Table S5; Cohort C	1087/33,263 (3.3)	Inactive (MET, 0)	1.0 (ref) [**]
		344/12,650 (2.7)	Insufficiently active (MET, 1 to <500)	0.91 (0.79 to 1.04)
		249/9689 (2.6)	Active (MET, 500 to <1000)	**0.78 (0.66 to 0.92)**
		615/20,793 (3.0)	Highly Active (MET, ≥ 1000)	0.94 (0.85 to 1.05)
COVID-19	Table S6; Propensity score matched cohort C	991/29,993 (3.3)	Low physical activity (MET, 0 to 500)	1.0 (ref) [**]
		852/29,993 (2.8)	High physical activity (MET, ≥ 500)	**0.90 (0.83 to 0.99)**
COVID-19	Table S8; Cohort D	803/22,811 (3.5)	Inactive (MET, 0)	1.0 (ref) [**]
		1641/50,052 (3.3)	Insufficiently active (MET, 1 to <500)	**0.89 (0.82 to 0.97)**
		816/25,932 (3.2)	Active (MET, 500 to <1000)	**0.85 (0.75 to 0.96)**
		622/19,973 (3.1)	Highly Active (MET, ≥ 1000)	**0.85 (0.74 to 0.99)**

Outcome	Source	Events/Total (%)	Category	Estimate (95% CI)
COVID-19	Table S9; Propensity score matched cohort D	429/11,930 (3.6)	Low physical activity (MET, 0 to 500)	1.0 (ref) [**]
		372/11,930 (3.1)	High physical activity (MET, ≥ 500)	**0.87 (0.76 to 0.99)**
Severe COVID-19[*]	Table S2; Propensity score matched cohort A	21/2649 (0.79)	Insufficient aerobic and muscle strengthening	1.0 (ref) [§]
		9/2649 (0.34)	Aerobic and muscle strengthening	**0.43 (0.20 to 0.95)**
Severe COVID-19[*]	Table S3; Cohort B	273/1293 (21.1)	Insufficient aerobic and muscle strengthening	1.0 (ref) [§]
		25/150 (16.7)	Muscle strengthening only	0.87 (0.58 to 1.26)
		109/561 (19.4)	Aerobic only	0.90 (0.72 to 1.10)
		39/291 (13.4)	Aerobic and muscle strengthening	**0.66 (0.47 to 0.90)**
Severe COVID-19[*]	Table S5; Cohort C	239/33,263 (0.72)	Inactive (MET, 0)	1.0 (ref) [**]
		58/12,650 (0.46)	Insufficiently active (MET, 1 to <500)	0.78 (0.53 to 1.12)
		39/9689 (0.40)	Active (MET, 500 to <1000)	**0.62 (0.43 to 0.90)**
		110/20,793 (0.53)	Highly Active (MET, ≥ 1000)	0.79 (0.61 to 1.03)
Severe COVID-19[*]	Table S6; Propensity score matched cohort C	209/29,993 (0.70)	Low physical activity (MET, 0 to 500)	1.0 (ref) [**]
		146/29,993 (0.49)	High physical activity (MET, ≥ 500)	**0.77 (0.63 to 0.95)**
Severe COVID-19[*]	Table S8; Cohort D	75/22,811 (0.33)	Inactive (MET, 0)	1.0 (ref) [**]
		109/50,052 (0.22)	Insufficiently active (MET, 1 to <500)	**0.65 (0.47 to 0.86)**

Outcome	Table; Cohort	n/N (%)	Physical activity category	Adjusted HR/OR (95% CI)
		49/25,932 (0.19)	Active (MET, 500 to <1000)	**0.54 (0.35 to 0.79)**
		44/19,973 (0.22)	Highly active (MET, ≥ 1000)	**0.66 (0.45 to 0.96)**
Severe COVID-19[*]	Table S9; Propensity score matched cohort D	40/11,930 (0.28)	Low physical activity (MET, 0 to 500)	1.0 (ref) [**]
		24/11,930 (0.20)	High physical activity (MET, ≥ 500)	**0.58 (0.35 to 0.99)**
Severe COVID-19[*]	Table S10; Cohort E	75/803 (9.3)	Inactive (MET, 0)	1.0 (ref) [**]
		109/1641 (6.6)	Insufficiently active (MET, 1 to <500)	**0.73 (0.53 to 0.99)**
		49/816 (6.0)	Active (MET, 500 to <1000)	**0.68 (0.44 to 0.98)**
		44/622 (7.1)	Highly active (MET, ≥ 1000)	0.74 (0.48 to 1.12)
COVID-19 related death	Table S2; Propensity score matched cohort A	3/2649 (0.11)	Insufficient aerobic and muscle strengthening	1.0 (ref)[§]
		1/2619 (0.04)	Aerobic and muscle strengthening	0.34 (0.04 to 3.20)
COVID-19 related death	Table S3; Cohort B	32/1293 (205)	Insufficient aerobic and muscle strengthening	1.0 (ref)[§]
		0/150 (0.0)	Muscle strengthening only	NA
		11/561 (2.0)	Aerobic only	0.71 (0.35 to 1.42)
		2/291 (0.7)	Aerobic and muscle strengthening	0.28 (0.06 to 1.20)
COVID-19 related death	Table S5; Cohort C	27/33,263 (0.07)	Inactive (MET, 0)	1.0 (ref) [**]
		5/12,650 (0.05)	Insufficiently active (MET, 1 to <500)	0.81 (0.22 to 2.42)

Events	Cohort		Mean day (SD)	Exposure	Adjusted mean difference[§] (95% CI)
			1/9689 (0.01)	Active (MET, 500 to <1000)	**0.17 (0.07 to 0.98)**
			12/20,793 (0.06)	Highly Active (MET, ≥ 1000)	0.79 (0.42 to 1.59)
COVID-19 related death	Table S6; Propensity score matched cohort C		23/29,993 (0.07)	Low physical activity (MET, 0 to 500)	1.0 (ref) [**]
			11/29,993 (0.04)	High physical activity (MET, ≥ 500)	0.51 (0.26 to 1.01)
COVID-19 related death	Table S8; Cohort D		39/22,811 (0.17)	Inactive (MET, 0)	1.0 (ref) [**]
			53/50,052 (0.11)	Insufficiently active (MET, 1 to <500)	**0.60 (0.40 to 0.93)**
			17/25,932 (0.07)	Active (MET, 500 to <1000)	**0.35 (0.20 to 0.64)**
			13/19,973 (0.07)	Highly active (MET, ≥ 1000)	**0.37 (0.19 to 0.71)**
COVID-19 related death	Table S9; Propensity score matched cohort D		21/11,930 (0.18)	Low physical activity (MET, 0 to 500)	1.0 (ref) [*]
			9/11,930 (0.08)	High physical activity (MET, ≥ 500)	**0.46 (0.22 to 0.96)**
COVID-19 related death	Table S10; Cohort E		39/803 (4.9)	Inactive (MET, 0)	1.0 (ref) [**]
			53/1641 (3.2)	Insufficiently active (MET, 1 to <500)	0.74 (0.49 to 1.06)
			17/816 (2.1)	Active (MET, 500 to <1000)	**0.49 (0.27 to 0.82)**
			13/622 (2.1)	Highly active (MET, ≥ 1000)	**0.43 (0.22 to 0.83)**

Length of stay in hospital	Table S3; Cohort B	27.4 (15.3)	Insufficient aerobic and muscle strengthening	1.0 (ref) [§]
		26.3 (14.4)	Muscle strengthening only	-0.68 (3.28 to 1.89)
		26.7 (15.4)	Aerobic only	-0.57 (-2.06 to 0.92)
		25.0 (13.6)	Aerobic and muscle strengthening	**-2.08 (-4.04 to -0.14)**
Length of stay in hospital	Table S10; Cohort E	27.5 (16.5)	Inactive (MET, 0)	1.0 (ref) [**]
		27.3 (15.1)	Insufficiently active (MET, 1 to <500)	-0.18 (-1.47 to 1.11)
		24.8 (14.3)	Active (MET, 500 to <1000)	**-1.85 (-3.63 to -0.05)**
		26.1 (14.3)	Highly active (MET, ≥ 1000)	-0.68 (-3.19 to 1.82)

Abbreviations: COVID-19, coronavirus disease; MET, metabolic equivalent of task; RR, relative risk; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[*] Severe COVID-19 consisted of admission to the intensive care unit, invasive ventilation, or death.

[§] Regression models from cohort A were adjusted for the age; sex; region of residence (Seoul Capital Area, Daegu/Gyeongbuk area, and other areas); Charlson comorbidity index (0, 1, and ≥2); history of diabetes mellitus, tuberculosis, stroke, and cardiovascular disease; body mass index (continuous; using the restricted cubic spline function); systolic blood pressure (continuous); diastolic blood pressure (continuous); fasting blood glucose (continuous); serum total cholesterol (continuous); glomerular filtration rate (≥90, 60−89, and ≤59 ml/min); household income (low, middle, and high); smoking (never, ex-, and current); alcoholic drinks (<1, 1−2, 3−4, ≥5 days per week); medication for

hypertension, diabetes mellitus, and cardiovascular disease.

[**] Regression models from cohort B were adjusted for the age (20-59, 60-69, 70-79, and ≥ 80 years); sex; region of residence (rural and urban); Charlson comorbidity index (0, 1, and ≥2); history of diabetes mellitus, tuberculosis, stroke, and cardiovascular disease; body mass index (continuous; using the restricted cubic spline function); systolic blood pressure (continuous); diastolic blood pressure (continuous); fasting blood glucose (continuous); serum total cholesterol (continuous); glomerular filtration rate (≥90, 60−89, and ≤59 ml/min); household income (low, middle, and high); smoking (never, ex-, and current); alcoholic drinks (<1, 1−2, 3−4, ≥5 days per week); medication for hypertension, diabetes mellitus, and cardiovascular disease.

Numbers in bold indicate significant differences ($P < 0.05$).