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Clinical Research Study

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ABSTRACT

Introduction: Data on the associations of pre-pandemic physical activity and sedentary behavior with SARS-CoV-2 infection and Coronavirus Disease 2019 (COVID-19) severity, particularly milder illness, have been limited.

Methods: We used data from 43,913 participants within the Nurses' Health Study II and Health Professionals Follow-Up Study who responded to periodic COVID-related surveys from May 2020 through March 2021. History of physical activity from the pre-pandemic period was assessed as the metabolic equivalents of task (MET)-hours/week of various activities of different intensity and sedentary behavior assessed from reports of time spent sitting from questionnaires completed 2016-2017. Multivariable logistic regression models were fitted to calculate the odds ratios (ORs) and 95% confidence intervals (CIs) for risk of SARS-CoV-2 infection and COVID-19 severity, as well as predicted COVID-19 defined using a validated symptom-based algorithm.

Results: Higher levels of pre-pandemic physical activity were associated with a lower risk for SARS-CoV-2 infection. Compared to participants with <3 MET-hours/week, the multivariable-adjusted OR

was 0.86 (95% CI:0.74, 0.99; P-trend=0.07) for those with ≥27 MET-hours/week. Higher physical activity levels were also associated with lower risk of symptomatic SARS-CoV-2 infection (OR:0.84; 95% CI:0.72, 0.99; P-trend=0.05) and predicted COVID-19 (OR:0.87; 95% CI:0.78, 0.97; P-trend=0.01). Longer time sitting at home watching TV (OR:0.85; 95% CI:0.73, 0.97) or for other tasks (OR:0.78; 95% CI:0.66, 0.92) was associated with a lower risk of SARS-CoV-2 infection.

Conclusions: Our findings support a protective association between pre-pandemic physical activity and lower risk and severity of COVID-19.

Keywords: Physical activity; sedentary behavior; COVID-19; SARS-CoV-2 infection

INTRODUCTION

Since the emergence of the novel SARS-CoV-2, the Coronavirus Disease 2019 (COVID-19) pandemic has swept the globe. Worldwide, there have been more than 646 million confirmed cases of COVID-19, including over 6.6 million deaths as of December 2022[1]. Despite efforts to reduce viral transmission and infection with strategies such as social distancing, mask wearing, vaccination, and antibody therapies, variants of SARS-CoV-2 have emerged that will remain a challenge for the foreseeable future[2].

A growing body of evidence suggests that risk factors for COVID-19 severe disease (symptomatic, hospitalization, or ventilated) is a function of the host-pathogen-environment interaction. To date, the most prominent risk factors for severe COVID-19 include advanced age, male sex, and the presence of underlying chronic conditions including obesity, diabetes, hypertension, cardiovascular disease, and cancer[3]. Importantly, the metabolic risk factors associated with complications and increased mortality due to COVID-19 may have modifiable components, such as physical activity. Previous investigations have demonstrated that a lack of physical activity is consistently associated with increased risk of major non-communicable diseases[4-7]. The benefits of increased physical activity are well-

established, including improved insulin sensitivity, blood lipids, and respiratory and immune function, while decreasing inflammation and visceral adiposity[8].

Initial evidence suggested that there is a relationship between history of physical activity and COVID-19 severity[9-11]. A recent CDC systematic review of 25 studies concluded that people who were inactive had a higher risk of adverse outcomes[10]. However, to date, there is still limited evidence on the effects of an individual's history of physical activity and sedentary behavior on COVID-19 with milder presentations. Therefore, we examined associations between pre-pandemic physical activity and sedentary behavior in relation to SARS-CoV-2 infection and COVID-19 severity within large nationwide cohorts of health professionals in the U.S.

METHODS

Study Population

We used data from the pre-pandemic period on physical activity as well as periodic surveys on participants' experiences during the COVID-19 pandemic within the large, longitudinal cohorts of the Nurses' Health Study II (NHS II) and the Health Professionals Follow-Up Study (HPFS). The NHS II is an ongoing prospective cohort of 116,429 female nurses residing in 14 U.S. states aged 25 to 42 years at study enrollment in 1989. The HPFS is an ongoing cohort of 51,529 U.S. male health professionals from all 50 states aged 40-75 years at study enrollment in 1986. Participants from both studies completed questionnaires that captured information on demographics, medical conditions, and lifestyle behaviors at baseline and biennially, with follow-up rates exceeding 90% in each 2-year cycle. The study was approved by the Institutional Review Board at Brigham and Women's Hospital and the Human Subjects Committee at the Harvard T.H. Chan School of Public Health, and all participants were assumed to provide consent through return of the questionnaires.

In May 2020, we invited NHS II participants who were known to be alive and had returned the most recent main cohort questionnaire to complete a supplementary COVID-19 online survey querying COVID-19 related symptoms, testing results, and health-related behaviors[12, 13]. Of 55,925 invited participants, 39,564 (70.7%) completed the baseline COVID-19 survey. Non-frontline healthcare workers completed monthly surveys and those who identified as frontline healthcare workers (who physically worked or volunteered at a worksite providing clinical care) completed weekly surveys. In August 2020, the scheduling of the surveys was changed to quarterly for non-frontline healthcare workers and monthly for frontline healthcare workers. The end of follow-up for the current analysis was March 23, 2021.

Similarly, in September 2020, we invited HPFS participants who were known to be alive and had returned the most recent main cohort questionnaire to complete a supplementary COVID-19 online survey. Of the 8,900 invited participants, 4,349 (48.8%) completed the baseline COVID-19 survey. In 2021, we administered the first follow-up survey.

The final analytic cohort included 43,913 participants (**Supplemental Figure 1**), among whom 20,356 reported having been tested at least once for SARS-CoV-2.

Assessment of Pre-pandemic Physical Activity and Sedentary behavior

Pre-pandemic physical activity and sedentary behaviors were assessed from the 2017 questionnaire in the NHSII and from the 2016 questionnaire in the HPFS. These physical activity assessments have been validated elsewhere[14]. Participants were asked to rate their average time per week in the following activities: walking for exercise or transportation, running or jogging, bicycling (at low, medium, or high intensity), tennis or squash or racquetball, lap swimming (at low, medium, or high intensity), other aerobic activities (such as dance, ski or stair machine), lower intensity exercise (yoga or stretching), other vigorous activities (lawn mowing), and weight training or resistance exercise. The time frame

selections ranged from zero to eleven or more hours per week. Weekly energy expenditure was estimated by multiplying the typical intensity expressed in Metabolic Equivalent of Task (MET, the ratio of metabolic rate during the activity to metabolic rate at rest) by the reported hours spent per week. The weekly MET-hour scores were summed to derive the primary exposure (total weekly physical activity in units of MET-hours/week). A three MET-hour is equivalent to about one hour of brisk walking.

Participants were also asked to provide their average time per week standing or walking at work or at home, sitting at work or home or while driving, sitting at home watching TV, or sitting at home engaged in other activities such as eating or reading[15].

Ascertainment of COVID-19 Outcomes

The primary outcome of this analysis was self-reported SARS-CoV-2 infection (positive test for infection or antibody) and COVID-19 severity. For severity, we considered the following outcomes according to WHO clinical progression scale[16] including asymptomatic and not infected; tested positive and asymptomatic; tested positive and symptomatic; and tested positive and hospitalized. We also derived a predicted COVID-19 outcome using a validated symptom-based algorithm[17], which has demonstrated similar estimates of COVID-19 prevalence and incidence as those reported from the Office for National Statistics Community Infection Survey[18].

Statistical Analysis

We restricted the analysis to 20,356 participants who reported having been tested for SARS-CoV-2 for analyses of SARS-CoV-2 infection and COVID-19 severity. For the analysis of predicted COVID-19, we included the entire cohort of 43,913 participants.

We employed multivariable logistic regression models to examine the risk of COVID-19 outcomes by categories of physical activity and sedentary behavior. We adjusted for potential

confounding factors including age, sex, lifestyle, behaviors, and comorbidities. We examined the possibly non-linear relation non-parametrically with restricted cubic splines[19]. We also conducted subgroup analyses according to age, sex, BMI, being a frontline healthcare worker, and time of sitting. Furthermore, we evaluated physical activity by type (aerobic vs. resistance training). In a sensitivity analysis, to account for the probability of receiving a SARS-CoV-2 test, we used inverse probability weighting (IPW) with stabilized weights as a function of age, sex, race, being a frontline healthcare worker, COVID-19 related symptoms, 2010 census tract median income, and total physical activity level. Analyses were conducted using SAS 9.4 (SAS Institute, Cary, N.C.); p-values <0.05 were considered statistically significant.

Data Statement

Data described in the manuscript, code book, and analytic code will be made available upon request pending application and approval. Further information including the procedures to obtain and access data is described at https://www.nurseshealthstudy.org/researchers and https://sites.sph.harvard.edu/hpfs/for-collaborators/.

RESULTS

Descriptive characteristics of the 20,356 participants who had been tested for SARS-CoV-2 according to categories of total pre-pandemic physical activity are shown in **Table 1**. Participants with higher level of physical activity (≥27.0 MET-hours/week) had the highest median income, dietary quality, alcohol intake and the lowest BMI. They were also less likely to be current smokers and have chronic comorbidities as compared to those in the lower level. Participants who responded to the COVID-19 online survey tended to be more physically active than those who did not. Other socio-demographic and clinical characteristics were similar (**Supplemental Table 1**).

Pre-pandemic Physical Activity and SARS-CoV-2 infection

A total of 2,721 (13.4%) participants reported a positive test for SARS-CoV-2 infection. Higher amounts of total pre-pandemic physical activity were associated with a lower risk of SARS-CoV-2 infection (**Table 2**). Compared to the participants with low physical activity (<3 MET-hours/week), the age- and sex-adjusted odds ratio (OR) and 95% confidence interval (95% CI) was 0.66 (0.58, 0.75; P-trend<0.001) for those with ≥27 MET-hours/week. This association was slightly attenuated but remained significant in the multivariable-adjusted model (OR, 0.86; 95% CI: 0.74, 0.99; P-trend=0.07).

Pre-pandemic Physical Activity and COVID-19 Severity

Associations between physical activity and COVID-19 severity are shown in **Figure 1**. In age- and sex-adjusted analyses, higher levels of physical activity were associated with a lower risk of symptomatic SARS-CoV-2 infection (OR top quintile, 0.66; 95% CI: 0.57, 0.76; P-trend<0.001) and hospitalization (OR top quintile, 0.48; 95% CI: 0.30, 0.77; P-trend=0.03), whereas the association with asymptomatic SARS-CoV-2 infection was not statistically significant (OR top quintile, 0.77; 95% CI: 0.53, 1.12; P-trend=0.05). In the multivariable-adjusted models, only the association with symptomatic SARS-CoV-2 infection remained statistically significant (OR top quintile, 0.84; 95% CI: 0.72, 0.99; P-trend=0.05).

When evaluating physical activity by type, higher levels of aerobic exercise were associated with a lower risk of symptomatic SARS-CoV-2 infection (**Supplemental Table 2**). After adjustment for lifestyle and comorbidities, compared to participants with low aerobic exercise (<3 MET-hours/week), the multivariable-adjusted OR was 0.83 (95% CI: 0.70, 0.98; P-trend=0.04) for those with ≥27 MET-hours/week. In contrast, resistance training was not significantly associated with symptomatic SARS-CoV-2 infection.

Pre-pandemic Physical Activity and Risk of Predicted COVID-19

We confirmed a protective association between higher levels of physical activity and lower risk of COVID-19 using the symptom-based algorithm (**Table 3**). Participants who had ≥27.0 MET-hours/week of physical activity had a 13% lower risk of getting predicted COVID-19 (95% CI: 3%, 22%; P-trend=0.01) in the multivariable-adjusted model, compared to those with less than 3 MET-hours/week.

Pre-pandemic Sedentary Behavior and Risk of SARS-CoV-2 infection

Sitting at home watching TV and sitting at home (tasks other than TV) were associated with a lower risk of SARS-CoV-2 infection (**Table 4**). Compared to those with the lowest amount of sitting (0-5 hours/week), the OR and 95% CI was 0.85 (0.73, 0.97) for those who sat the most (≥21 hours/week) at home, and 0.78 (0.66, 0.92) for those who sat at home other than watching TV. In contrast, sitting in the car or at work was not statistically significantly associated with infection (OR, 0.96; 95% CI: 0.84, 1.08). When combining the three sitting variables, total time of sitting was statistically significantly associated with a lower risk of infection, with a multivariable OR of 0.83 (95% CI: 0.72, 0.95) comparing participants in the highest quintile to those in the lowest (**Supplemental Table 3**).

Subgroup/Sensitivity Analyses

The inverse association between physical activity and risk of SARS-CoV-2 infection was stronger among participants who had a BMI <25 kg/m^2 (OR comparing the MET-hours/week ≥27 to <3: 0.62; 95% CI: 0.46, 0.83) compared to those with a BMI >25 kg/m^2 (OR: 0.92; 95% CI: 0.78, 1.08; P-interaction=0.02; **Figure 2**). Other factors including age, sex, being a frontline healthcare worker, and time sitting did not statistically significantly modify the association between physical activity and SARS-CoV-2 infection.

Restricted spline analysis did not show non-linear relationships of total physical activity with symptomatic SARS-CoV-2 infection (P-linearity=0.10) and predicted COVID-19 (P-linearity=0.04;

Supplemental Figure 2). When we used IPW to account for the possibility of receiving a test for COVID-19, the association between total physical activity and SARS-CoV-2 infection remained largely similar (data not shown). In addition, mutual adjustment for physical activity and time sitting did not change the associations.

DISCUSSION

Using data from pre-pandemic questionnaires and periodic surveys administered from May 2020 to March 2021 within two cohorts of 43,913 health professionals, higher levels of pre-pandemic physical activity (≥27 MET-hours/week) were associated with lower risk of SARS-CoV-2 infection and COVID-19 severity. This association was independent of age, sex, BMI, interaction with others, mask wearing, and chronic comorbidities. In addition, longer sitting at home was associated with a lower risk of SARS-CoV-2 infection.

In our study, we assessed the history of physical activity during pre-pandemic periods to examine whether it was protective for SARS-CoV-2 infection, including asymptomatic infection and symptomatic COVID-19. A portion of data thus far have assessed physical activity as it relates to changes in physical activity due to lockdown measures[15]. Prior reports of physical activity and COVID-19 have yielded compelling results, but data have been limited primarily to more severe cases. CDC systematically reviewed 25 studies and concluded that people who were physically inactive had a higher risk of hospitalization and death and a potential higher risk of admission to intensive care unit and ventilation compared to those who were physically active[10]. A sedentary lifestyle was associated with an over five-fold higher risk of mortality among 552 hospitalized patients with COVID-19[20]. Our findings contribute to the literature by demonstrating that being physically active is also protective for milder presentations of COVID-19.

The benefits of increased physical activity are well-established, including improved insulin sensitivity, blood lipids, and respiratory and immune function, while decreasing inflammation and visceral adiposity[8]. Specifically, physical activity improves insulin sensitivity by increasing the energy demands of the cell via metabolic work as well as building more lean tissue, which is highly sensitive to glucose uptake[21]. Physical activity also promotes decreased visceral adiposity[22]. Increased fat mass leads to insulin resistance, systemic inflammation, and reduced β-cell function, which have been shown to impair host immune responses to infection[23]. Additionally, physical activity has been shown to improve lung function in healthy adults as well as those with respiratory disease[24, 25]. Higher levels of cardiorespiratory fitness have been shown to be strong independent predictive factors for the development of adverse clinical outcomes, even after controlling for intermediate cardiovascular risk factors[26]. These mechanisms demonstrate that the benefits of physical activity on COVID-19 span cardiorespiratory, metabolic, and immunologic pathways. Finally, it is also possible that individuals who are more physical active may be more likely to take necessary precautions against exposure from COVID-19.

The findings in the present study are in alignment with the known benefits of physical activity. However, we also found a protective association between sitting at home watching TV and sitting at home (tasks other than TV) and risk of infection. This may be explained by the trend that those who sat at home more pre-pandemic may have also been more likely to stay at home during COVID-19 lockdowns, which resulted in less potential exposure to the virus. This may be due to circumstances such as they already were in the remote workforce, or had pre-existing conditions that made them more likely to remain home, or that they did not leave the house to get tested and therefore had fewer positive test results. Of note, when we adjusted for interaction with other variables in the model, the association did not change significantly.

There are several strengths of the study including the large sample size and the availability of detailed assessment of physical activity history (total and according to type) and comprehensive information on lifestyle factors and comorbidity conditions. Our study also has limitations. First, despite adjustment for several potential confounders, the possibility of residual confounding cannot be eliminated as in other observational studies. Second, with the majority of COVID-19 cases in our study being mild in severity, and especially our inability to ascertain deaths rapidly, the impact of history of physical activity on more severe COVID-19 risk remains to be investigated. Third, we did not collect detailed information on physical activity during the pandemic period. However, we were focused on the longer-term effects of physical activity on host physiology that would potentially influence risk of COVID-19. Fourth, our outcome of SARS-CoV-2 infection and symptoms were based on self-report. However, the responses are considered to be accurate since our population comprised of health professionals. Additionally, to what extent results from our study population restricted to mainly White health professionals can be generalized to other educational or racial/ethnic backgrounds would need further study.

In this study, we observed a protective association of higher levels of pre-pandemic physical activity with SARS-COV-2 infection and COVID-19 severity. People with physical activity levels equivalent to 9 hours of brisk walking per week had 16% lower odds of having a symptomatic SARS-CoV-2 infection. This evidence that physical activity is a modifiable risk factor for COVID-19 further supports the necessity to educate the population about the benefits of physical activity related to adverse COVID-19 outcomes and to systematically promote regular physical activity during the pandemic and beyond. These findings, along with the growing body of evidence demonstrating that physical activity is a modifiable risk factor for not only all-cause mortality, but for severe health risks as in a global

pandemic, solidify the need for the CDC and other national and international agencies to consider adding physical inactivity as a risk factor for COVID-19.

Clinical significance

- Higher levels of pre-pandemic physical activity were associated with a lower risk for SARS-CoV-2 infection and severity of COVID-19.
- Our data support a protective association between pre-pandemic physical activity and lower risk and severity of COVID-19, solidifying the need for the CDC and other national and international agencies to consider adding physical inactivity as a risk factor for COVID-19.

Declaration of Competing Interest

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

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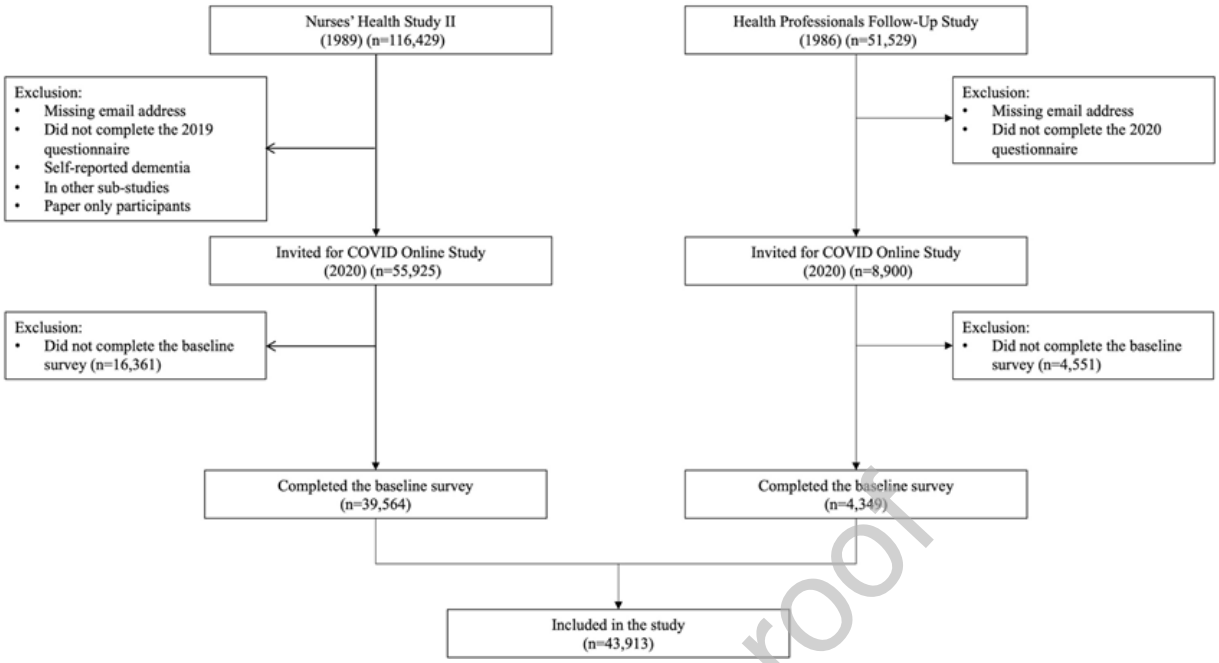
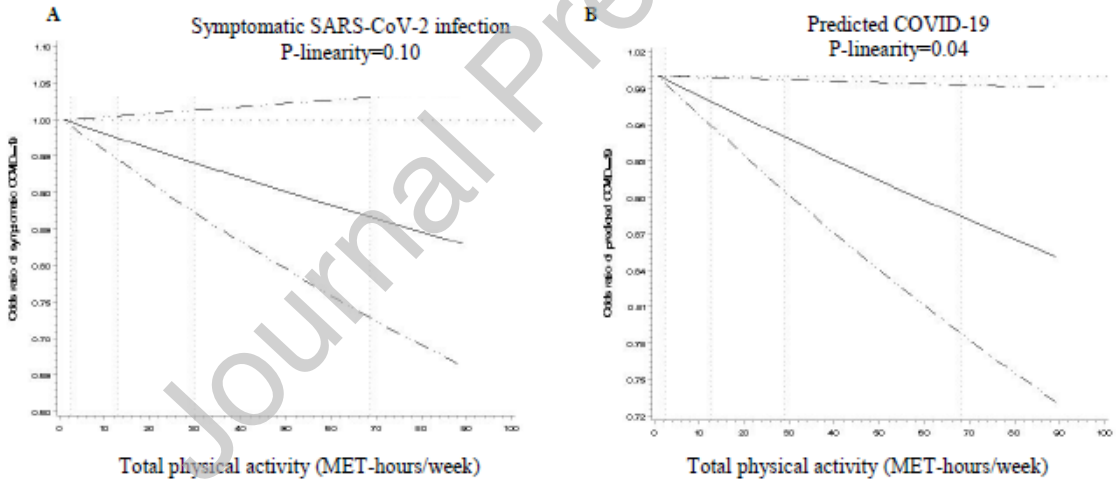


Supplemental Figure 1. Flowchart of the study



Supplemental Figure 2. Restricted cubic spline of total physical activity and risk of symptomatic SARS-CoV-2 infection (A) and predicted COVID-19 (B). Models were adjusted for age, sex, white race, smoking pack-years (0, 0.1-10.0, 10.1-20.0, >20.0), the Alternate Healthy Eating Index (quintiles), body mass index (<22.5, 22.5-24.9, 25.0-27.4, 27.5-29.9, 30-34.9, ≥35.0 kg/m^2), alcohol intake (0, 0.1-5.0, 5.1-10.0, >10 g/d), 2010 census tract median income (quintiles), being a frontline healthcare worker, interaction with people with documented/presumed COVID-19 (no, interaction with people with presumed COVID-19, interaction with people

with documented COVID-19), receipt of a COVID-19 vaccine, use of N95 masks at work (always, sometimes, never, not applicable), use of surgical masks at work (always, sometimes, never, not applicable), hypertension, hypercholesterolemia, diabetes, heart disease, and cancer. There is no evidence for non-linearity (P for non-linearity > 0.05 for each).

Supplemental Table 1. Characteristics of participants within the Nurses' Health Study II and the Health Professionals Follow-Up Study according to the inclusion of the COVID-19 online survey

	Nurses' Health Study II		**Health Professionals Follow-Up Study**	
	Inclusion of the COVID-19 survey		Inclusion of the COVID-19 survey	
	Yes	No	Yes	No
Age, years	62.8 (4.5)	62.0 (4.7)	73.9 (10.1)	73.9 (14.9)
White, %	94.2	92.5	93.6	91.8
Current postmenopausal hormone use, %	17.3	20.3	NA	NA
2010 census tract median income, dollars	83631 (32365)	82255 (31471)	90686 (25229)	89072 (25013)
Body mass index, kg/m^2	27.7 (6.3)	27.8 (6.4)	25.1 (4.0)	24.8 (4.5)
Alcohol intake, g/d	7.7 (11.4)	7.1 (10.9)	14.8 (10.9)	13.7 (10.2)
Alternate Healthy Eating Index	62.1 (12.2)	60.5 (12.4)	59.5 (7.3)	59.3 (7.3)
Past smoker, %	31.9	31.3	43.0	42.9
Current smoker, %	3.2	4.1	1.2	1.1
Smoking, pack-years	5.0 (10.3)	5.2 (10.8)	7.6 (8.4)	7.4 (8.4)
Hypertension, %	25.2	23.2	37.8	39.2
Hypercholesterolemia, %	27.7	24.2	31.6	31.6
Diabetes, %	6.4	6.1	7.6	7.9
Heart disease, %	0.3	0.4	2.1	2.7
Cancer, %	4.2	4.1	9.1	12.4
Physical activity, MET-hours/week	28.3 (31.8)	26.1 (31.9)	37.2 (22.6)	34.5 (22.7)
Vigorous activity	12.6 (19.9)	11.6 (19.8)	19.0 (18.0)	16.9 (15.8)
Moderate/low-intensity activity	16.1 (17.3)	15.0 (17.1)	18.3 (12.9)	16.5 (12.2)
Time of sitting at home while watching TV (hours/week)	10.8 (7.9)	10.7 (8.0)	11.3 (5.1)	10.9 (5.1)
Time of sitting at work or away from home or while driving (hours/week)	10.6 (8.5)	10.5 (8.6)	7.5 (4.7)	7.4 (4.6)
Other sitting at home (hours/week)	9.2 (7.2)	8.9 (7.3)	9.3 (4.7)	8.8 (4.7)

Values are means(SD) or percentages standardized to the distribution of age, with the exception of age itself.

Abbreviations: MET, metabolic equivalent of task.

Supplemental Table 2. Associations between physical activity types (aerobic and resistance training) and risk of symptomatic SARS-CoV-2 infection

	Physical activity (MET-hours/week)					
	0-2.9	3.0-8.9	9.0-17.9	18.0-26.9	≥27.0	P-trend
Aerobic						
Median	1.45	6.0	13.2	22.4	45.0	
Cases/Non-cases	306/1807	425/2931	405/3202	318/2307	637/5733	
MV model 1	1 (ref)	0.85 (0.73, 1.00)	0.73 (0.62, 0.86)	0.80 (0.67, 0.95)	0.64 (0.55, 0.74)	<0.001
MV model 2	1 (ref)	0.94 (0.79, 1.11)	0.86 (0.73, 1.03)	0.98 (0.82, 1.18)	0.83 (0.70, 0.98)	0.04
Resistance training						
Median	0	5.4	10.0	20.0		
Cases/Non-cases	1603/11831	278/2486	117/1186	101/724		
MV model 1	1 (ref)	0.84 (0.73, 0.96)	0.79 (0.65, 0.96)	1.03 (0.83, 1.28)		0.15
MV model 2	1 (ref)	0.98 (0.85, 1.13)	0.96 (0.78, 1.19)	1.16 (0.92, 1.47)		0.41

Logistic regression models were used in the analysis. The number of participants included in the analysis was 18,019, and the number of participants who were symptomatic and tested positive was 2,087.

Model 1 was adjusted for age and sex.

Model 2 was further adjusted for white race, smoking pack-years (0, 0.1-10.0, 10.1-20.0, >20.0), the Alternate Healthy Eating Index (quintiles), body mass index (<22.5, 22.5-24.9, 25.0-27.4, 27.5-29.9, 30-34.9, ≥35.0 kg/m^2), alcohol intake (0, 0.1-5.0, 5.1-10.0, >10 g/d), 2010 census tract median income (quintiles), being a frontline healthcare worker, and interaction with people with documented/presumed COVID-19 (no, interaction with people with presumed COVID-19, interaction with people with documented COVID-19), receipt of a COVID-19 vaccine, use of N95 masks at work (always, sometimes, never, not applicable), use of surgical masks at work (always, sometimes, never, not applicable), hypertension, hypercholesterolemia, diabetes, heart disease, and cancer.

Supplemental Table 3. Associations between time of sitting and risk of SARS-CoV-2 infection

	Time of sitting (Quintiles)				
	1	2	3	4	5
Median	7.5	20.0	30.0	37.5	55.0
Cases/Non-cases	594/3456	429/2794	544/3469	467/3397	447/3082
MV model 1	1 (ref)	0.90 (0.78, 1.03)	0.93 (0.82, 1.05)	0.78 (0.69, 0.89)	0.85 (0.74, 0.97)
MV model 2	1 (ref)	0.88 (0.76, 1.01)	0.90 (0.79, 1.03)	0.75 (0.65, 0.86)	0.83 (0.72, 0.95)

Logistic regression models were used in the analysis. The number of participants included in the analysis was 18,679, and the number of participants who reported a positive test for SARS-CoV-2 infection was 2,481.

Model 1 was adjusted for age, sex, and total physical activity (0-2.9, 3.0-8.9, 9.0-17.9, 18.0-26.9, ≥27.0 MET-hours/week).

Model 2 was further adjusted for white race, smoking pack-years (0, 0.1-10.0, 10.1-20.0, >20.0), the Alternate Healthy Eating Index (quintiles), body mass index (<22.5, 22.5-24.9, 25.0-27.4, 27.5-29.9, 30-34.9, ≥35.0 kg/m^2), alcohol intake (0, 0.1-5.0, 5.1-10.0, >10 g/d), 2010 census tract median income (quintiles), being a frontline healthcare worker, and interaction with people with documented/presumed COVID-19 (no, interaction with people with presumed COVID-19, interaction with people with documented COVID-19), receipt of a COVID-19 vaccine, use of N95 masks at work (always, sometimes, never, not applicable), use of surgical masks at work (always, sometimes, never, not applicable), hypertension, hypercholesterolemia, diabetes, heart disease, and cancer.

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FIGURE LEGENDS

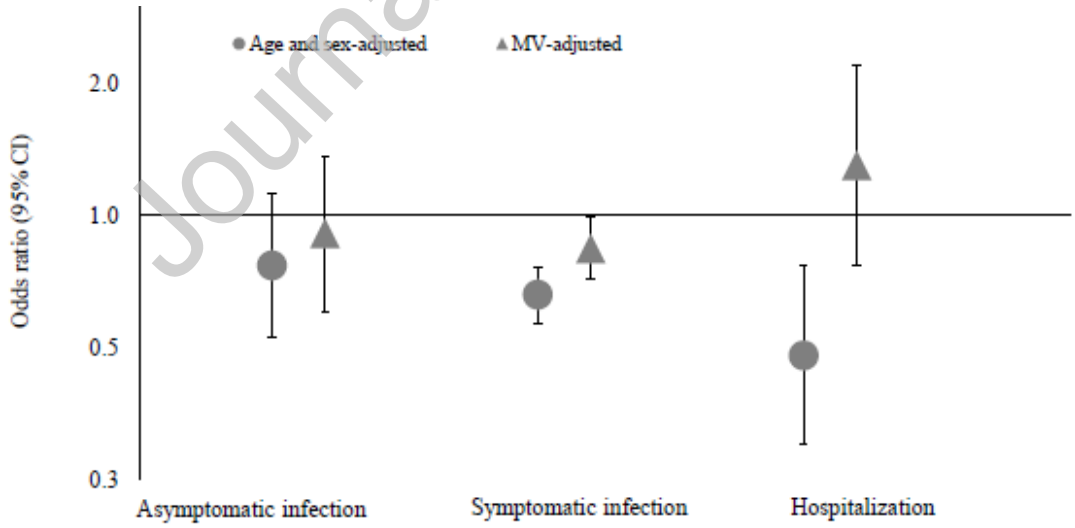

Figure 1. Total physical activity and risk of COVID-19 severity. Logistic regression models were used in the analysis. The number of participants was 17,390 for those who were asymptomatic and tested negative; 312 for asymptomatic SARS-CoV-2 infection; 2,259 for symptomatic SARS-CoV-2 infection; and 139 for hospitalization. MV models were adjusted for white race, smoking pack-years (0, 0.1-10.0, 10.1-20.0, >20.0), the Alternate Healthy Eating Index (quintiles), body mass index (<22.5, 22.5-24.9, 25.0-27.4, 27.5-29.9, 30-34.9, ≥35.0 kg/m^2), alcohol intake (0, 0.1-5.0, 5.1-10.0, >10 g/d), 2010 census tract median income (quintiles), being a frontline healthcare worker, interaction with people with documented/presumed COVID-19 (no, interaction with people with presumed COVID-19, interaction with people with documented COVID-19), receipt of a COVID-19 vaccine, use of N95 masks at work (always, sometimes, never, not applicable), use of surgical masks at work (always, sometimes, never, not applicable), hypertension, hypercholesterolemia, diabetes, heart disease, and cancer.

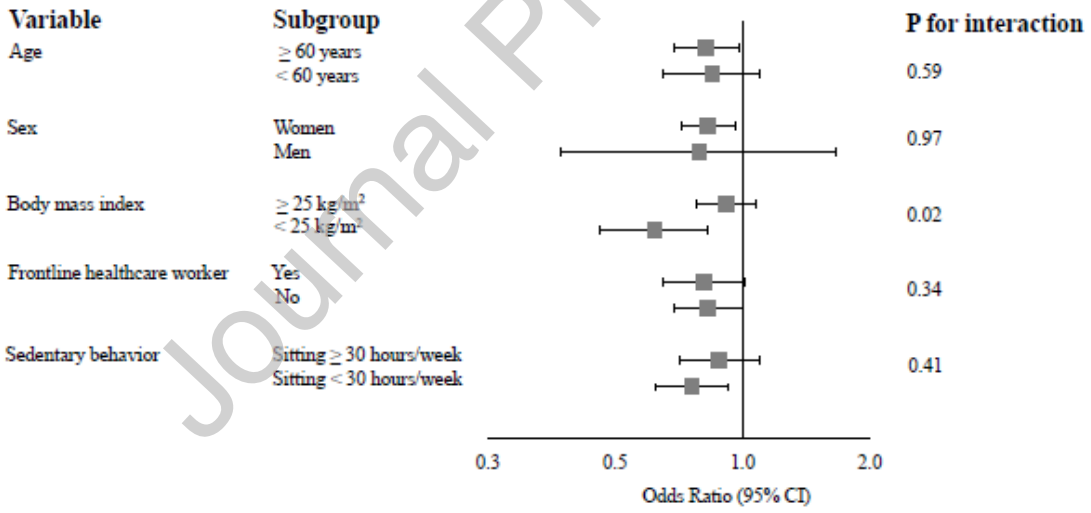

Figure 2. Total physical activity and risk of SARS-CoV-2 infection in subgroups. Logistic regression models were used in the analysis. Values represented the odds ratios of SARS-CoV-2 infection comparing participants with ≥27 MET-hours/week to those with <3 MET/hours/week. MV models were adjusted for white race, smoking pack-years (0, 0.1-10.0, 10.1-20.0, >20.0), the Alternate Healthy

Eating Index (quintiles), body mass index (<22.5, 22.5-24.9, 25.0-27.4, 27.5-29.9, 30-34.9, ≥35.0 kg/m2), alcohol intake (0, 0.1-5.0, 5.1-10.0, >10 g/d), 2010 census tract median income (quintiles), being a frontline healthcare worker, interaction with people with documented/presumed COVID-19 (no, interaction with people with presumed COVID-19, interaction with people with documented COVID-19), receipt of a COVID-19 vaccine, use of N95 masks at work (always, sometimes, never, not applicable), use of surgical masks at work (always, sometimes, never, not applicable), hypertension, hypercholesterolemia, diabetes, heart disease, and cancer.

Table 1. Characteristics of participants in the COVID-19 online survey within the Nurses' Health Study II and the Health Professionals Follow-Up Study

	Total physical activity (MET-hours/week)				
	0-2.9 (n=2270)	3.0-8.9 (n=3499)	9.0-17.9 (n=3717)	18.0-26.9 (n=2812)	≥27.0 (n=8058)
Age, years	63.4 (5.7)	63.5 (6)	63.4 (5.8)	63.6 (6.2)	63.7 (6.7)
Male, %	1.0 (0.2)	0.9 (0.2)	0.9 (0.3)	0.9 (0.3)	0.9 (0.3)
White, %	92.2	93.6	94.7	94.8	94.4
Current postmenopausal hormone use, %	14.7	16.6	17.8	18.4	19.9
2010 census tract median income, dollars	79551 (30393)	81980 (31435)	85148 (32133)	87864 (34505)	91609 (36617)
Body mass index, kg/m^2	31.4 (7.4)	29.2 (6.3)	27.8 (6.1)	26.7 (5.4)	25.5 (5.0)
Alcohol intake, g/d	6.9	7.3 (12.3)	8.3 (11.8)	9.0 (12)	10.0

	(13.1)				(12.7)
Alternate Healthy Eating Index	56.0 (11.6)	58.7 (11.8)	61.3 (11.7)	63.2 (11.5)	65.3 (11.8)
Past smoker, %	36.7	34.5	34.6	34.7	34.9
Current smoker, %	5.1	3.5	2.8	2.3	1.9
Smoking, pack-years	7.5 (13.3)	6.1 (11.9)	5.5 (10.5)	5 (9.7)	4.7 (9.3)
Hypertension, %	34.5	30.2	28.9	24.2	21.2
Hypercholesterolemia, %	31.5	30.6	31.0	28.6	25.0
Diabetes, %	11.9	9.2	7.1	5.6	3.8
Heart disease, %	0.8	0.5	0.6	0.3	0.5
Cancer, %	5.5	5.5	4.8	4.3	4.5
Frontline healthcare worker, %	32.8	32.1	31.9	30.2	31.1
Receipt of a COVID-19 vaccine, %*	90.2	92.0	92.6	93.5	93.6
Physical activity, MET-hours/week					
Vigorous activity	0.2 (0.4)	1.6 (2.1)	4.7 (3.9)	8.4 (6.6)	27.4 (26.7)
Moderate/low-intensity activity	1.1 (0.9)	4.2 (2.2)	8.6 (4.2)	14.0 (7.4)	30.2 (19.8)
Time of sitting at home while watching TV (hours/week)	10.7 (8.2)	11.4 (8.2)	10.8 (7.7)	10.8 (7.8)	10.2 (7.5)
Time of sitting at work or away from home or while driving (hours/week)	9.6 (8.4)	10.9 (8.7)	10.9 (8.7)	11.2 (8.6)	10.6 (8.3)

Other sitting at home (hours/week)	8.6 (7.5)	9.0 (7.2)	9.1 (7.1)	9.2 (7.2)	9.0 (7.0)

Values are means(SD) or percentages standardized to the distribution of age, with the exception of age itself. Abbreviations: MET, metabolic equivalent of task.

*Vaccine status was only assessed in women.

Table 2. Associations between total physical activity and risk of SARS-CoV-2 infection

	Total physical activity (MET-hours/week)					
	0-2.9	3.0-8.9	9.0-17.9	18.0-26.9	≥27.0	P-trend
Median	1.3	6.0	13.4	22.3	47.2	
Cases/Non-cases	385/1885	529/2970	478/3239	389/2423	940/7118	
MV model 1	1 (ref)	0.88 (0.76, 1.01)	0.73 (0.63, 0.84)	0.80 (0.69, 0.93)	0.66 (0.58, 0.75)	<0.001
MV model 2	1 (ref)	0.95 (0.82, 1.11)	0.84 (0.72, 0.98)	0.99 (0.84, 1.17)	0.86 (0.74, 0.99)	0.07

Logistic regression models were used in the analysis. The number of participants included in the analysis was 20,356. and the number of participants who reported a positive test for SARS-CoV-2 infection was 2,721.

Model 1 was adjusted for age and sex.

Model 2 was further adjusted for white race, smoking pack-years (0, 0.1-10.0, 10.1-20.0, >20.0), the Alternate Healthy Eating Index (quintiles), body mass index (<22.5, 22.5-24.9, 25.0-27.4, 27.5-29.9, 30-34.9, ≥35.0 kg/m^2), alcohol intake (0, 0.1-5.0, 5.1-10.0, >10 g/d), 2010 census tract median income (quintiles), being a frontline healthcare worker, interaction with people with documented/presumed

COVID-19 (no, interaction with people with presumed COVID-19, interaction with people with documented COVID-19), receipt of a COVID-19 vaccine, use of N95 masks at work (always, sometimes, never, not applicable), use of surgical masks at work (always, sometimes, never, not applicable), hypertension, hypercholesterolemia, diabetes, heart disease, and cancer.

P-trend was evaluated using the median value in each category as a continuous variable.

Table 3. Associations between total physical activity and risk of predicted COVID-19

	Total physical activity (MET-hours/week)					
	0-2.9	3.0-8.9	9.0-17.9	18.0-26.9	≥27.0	P-trend
Median	1.3	6.0	13.4	22.3	47.2	
Cases/Non-cases	622/4351	866/6774	862/7160	648/5503	1661/15466	
MV model 1	1 (ref)	0.90 (0.81, 1.00)	0.85 (0.76, 0.95)	0.84 (0.75, 0.94)	0.77 (0.70, 0.85)	<0.001
MV model 2	1 (ref)	0.95 (0.85, 1.06)	0.92 (0.82, 1.03)	0.93 (0.82, 1.05)	0.87 (0.78, 0.97)	0.01

Logistic regression models were used in the analysis. The number of participants included in the analysis was 43,913, and the number of participants with predicted COVID-19 was 4,659. Predicted covid cases were defined using -4.6167 +(0.0199*age) + (0.7311*fever) + (-1.0825*throat) + (0.5978*muscle) + (1.5348*taste) + (2.0717*smell) + (1.2952*other)

Model 1 was adjusted for age and sex.

Model 2 was further adjusted for white race, smoking pack-years (0, 0.1-10.0, 10.1-20.0, >20.0), the Alternate Healthy Eating Index (quintiles), body mass index (<22.5, 22.5-24.9, 25.0-27.4, 27.5-29.9, 30-34.9, ≥35.0 kg/m^2), alcohol intake (0, 0.1-5.0, 5.1-10.0, >10 g/d), 2010 census tract median income

(quintiles), being a frontline healthcare worker, and interaction with people with documented/presumed COVID-19 (no, interaction with people with presumed COVID-19, interaction with people with documented COVID-19), receipt of a COVID-19 vaccine, use of N95 masks at work (always, sometimes, never, not applicable), use of surgical masks at work (always, sometimes, never, not applicable), hypertension, hypercholesterolemia, diabetes, heart disease, and cancer.

P-trend was evaluated using the median value in each category as a continuous variable.

Table 4. Associations between time of sitting and risk of SAS-CoV-2 infection

	Time of sitting (hours/week)			
	0-5	6-10	11-20	≥21
Sitting at home while watching TV				
Cases/Non-cases	848/5031	706/4592	599/4280	365/2637
MV model 1	1 (ref)	0.92 (0.83, 1.03)	0.87 (0.78, 0.98)	0.87 (0.76, 1.00)
MV model 2	1 (ref)	0.92 (0.82, 1.03)	0.87 (0.77, 0.98)	0.85 (0.73, 0.97)
Sitting at work or away from home or while driving				
Cases/Non-cases	843/6006	628/3966	501/3078	534/3346
MV model 1	1 (ref)	1.07 (0.95, 1.19)	1.05 (0.93, 1.18)	0.98 (0.87, 1.11)
MV model 2	1 (ref)	1.03 (0.92, 1.16)	0.96 (0.85, 1.09)	0.96 (0.84, 1.08)
Other sitting at home				
Cases/Non-cases	1031/5980	803/5336	452/3388	228/1780
MV model 1	1 (ref)	0.90 (0.81, 0.99)	0.84 (0.74, 0.94)	0.80 (0.68, 0.93)
MV model 2	1 (ref)	0.90 (0.81, 1.00)	0.85 (0.75, 0.96)	0.78 (0.66, 0.92)

Logistic regression models were used in the analysis. The number of participants included in the analysis was 18,679, and the number of participants who reported a positive test for SARS-CoV-2 infection was 2,481.

Model 1 was adjusted for age, sex, and physical activity (<3.0, 3.0-8.9, 9.0-17.9, 18.0-26.9, ≥27.0 MET-hours/week).

Model 2 was further adjusted for white race, smoking pack-years (0, 0.1-10.0, 10.1-20.0, >20.0), the Alternate Healthy Eating Index (quintiles), body mass index (<22.5, 22.5-24.9, 25.0-27.4, 27.5-29.9, 30-34.9, ≥35.0 kg/m^2), alcohol intake (0, 0.1-5.0, 5.1-10.0, >10 g/d), 2010 census tract median income (quintiles), being a frontline healthcare worker, and interaction with people with documented/presumed COVID-19 (no, interaction with people with presumed COVID-19, interaction with people with documented COVID-19), receipt of a COVID-19 vaccine, use of N95 masks at work (always, sometimes, never, not applicable), use of surgical masks at work (always, sometimes, never, not applicable), hypertension, hypercholesterolemia, diabetes, heart disease, and cancer.