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Long-term cardiovascular health status and physical functioning of nonhospitalized patients with COVID-19 compared with non-COVID-19 controls

Long-term cardiovascular health status and physical functioning of non-hospitalized COVID-19 patients compared to non-COVID-19 controls

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Running head: Long-term cardiovascular outcomes after COVID-19 at home

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Abstract

Coronavirus disease 2019 (COVID-19) is reported to have long-term effects on cardiovascular health and physical functioning, even in the non-hospitalized population. The physiological mechanisms underlying these long-term consequences are however less well-described. We compared cardiovascular risk factors, arterial stiffness and physical functioning in non-hospitalized COVID-19 patients, at a median of six months post-infection, *versus* age- and sex-matched controls. Cardiovascular risk was assessed using blood pressure and biomarker concentrations (amino-terminal pro-B-type-natriuretic-peptide, high-sensitive cardiac troponin I, C-reactive protein) and arterial stiffness was assessed using carotid-femoral pulse wave velocity. Physical functioning was evaluated using accelerometry, handgrip strength, gait speed and questionnaires on fatigue, perception of general health status and health-related quality of life (hrQoL). We included 101 former COVID-19 patients (age 59 [55-65] years, 58% male) and 101 controls. At 175 [126-235] days post-infection, 32% of the COVID-19 group reported residual symptoms, notably fatigue, and 7% required post-COVID-19 care. We found no differences in blood pressure, biomarker concentrations or arterial stiffness between both groups. Former COVID-19 patients showed a higher handgrip strength (43 [33-52] *versus* 38 [30-48] kg, p=0.004), less sleeping time (8.8 [7.7-9.4] *versus* 9.8 [8.9-10.3] hours/day, p<0.001) and reported fatigue more often than controls. Accelerometry-based habitual physical activity levels, gait speed, perception of general health status and hrQoL were not different between groups. In conclusion, one in three non-hospitalized COVID-19 patients reports residual symptoms at a median of six months post-infection, but we were unable to relate these symptoms to increases in cardiovascular risk factors, arterial stiffness or physical dysfunction.

New & Noteworthy

We examined cardiovascular and physical functioning outcomes in non-hospitalized COVID-19 patients, at a median of six months post-infection. Compared to matched controls, minor differences in physical functioning were found, but objective measures of cardiovascular risk and arterial stiffness did not differ between groups. However, one in three former COVID-19 patients reported residual symptoms, notably fatigue. Follow-up studies should investigate the origins of residual symptoms and their long-term consequences in former, non-hospitalized COVID-19 patients.

Keywords: COVID-19, non-hospitalized, long-term effects, cardiovascular health, physical functioning

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causing coronavirus disease 2019 (COVID-19) has led to a global pandemic. As of November 2022, the World Health Organization reports totals of over 600 million cases and 6.5 million deaths (1). Besides respiratory involvement, COVID-19 can exhibit systemic effects in the acute phase, including affecting the cardiovascular system. Angiotensin-converting enzyme 2-mediated SARS-CoV-2 entry of myocardial and endothelial cells may result in myocardial injury and endothelial dysfunction (2-4). This may result in myocarditis, arrhythmias, acute coronary syndrome, stroke, venous thromboembolism or heart failure (2-4).

These signs of cardiovascular involvement may persist and lead to long-term symptoms and syndromes including chest pain, shortness of breath, palpitations, myocardial and vascular inflammation, arrhythmias and thromboembolism (5-9). Post-acute effects on physical functioning have also been reported, demonstrating that patients may suffer from fatigue, joint pain, muscle weakness and a decreased health-related quality of life (hrQoL) months after the infection (5, 6, 8, 10-12). These long-term effects have mostly been investigated in hospitalized populations, whilst the majority of COVID-19 patients recover at home (13-15). Nonetheless, post-acute cardiovascular events, such as dysrhythmias, ischemic heart disease and heart failure have also been described in patients who were not hospitalized (9).

The underlying mechanisms of post-acute effects in non-hospitalized COVID-19 patients remain incompletely understood. Physiological measurements may help us understand the origin of these effects. To our knowledge, literature on this subject is limited. For example, post-acute cardiac biomarker concentrations were reported once, demonstrating an increase of cardiac troponin I. However, the sample size of this study was small and follow-up duration was limited to one month (16). Studies on the long-term effects on arterial stiffness mostly showed an increase after COVID-19 (17-23). However, findings were discrepant across studies and not all study samples were representative of the general, non-hospitalized population (17-21). Furthermore, physical functioning

after COVID-19 in non-hospitalized patients was reported to be decreased, but these findings were based exclusively on patients suffering from long COVID (24-26). Moreover, an integrative approach is lacking as most studies focused on a specific outcome. Thus, COVID-19 seems to have long-term effects on cardiovascular health and physical functioning as measured by physiological parameters, but the results are not yet conclusive for the general, non-hospitalized population.

Therefore, we aimed to create a comprehensive overview of physiological parameters describing cardiovascular health and physical functioning in post-acute COVID-19 patients who recovered at home. Given the current literature on post-acute cardiovascular events, physical dysfunction symptoms and physiological parameters, we hypothesized to measure minor decreases in cardiovascular health and physical functioning in non-hospitalized, post-acute COVID-19 patients, in comparison to age- and sex-matched controls.

Methods

Study design and population

In this cross-sectional study, male and female adult volunteers were recruited from the Nijmegen Exercise Study, a cohort consisting of participants of Dutch mass-participation exercise events (International Nijmegen Four Days Marches and the Seven Hills Run) and their family members and friends (27, 28). An inclusion criterion for the COVID-19 group was evidence of a positive polymerase chain reaction (PCR) test for SARS-CoV-2; whereas an exclusion criterion was hospitalization due to the SARS-CoV-2 infection. We aimed to include participants approximately six months after SARS-CoV-2 infection. An age- and sex-matched control group was recruited from the same cohort. Controls were only included if they had never had signs, symptoms or suspicions of a SARS-CoV-2 infection, nor a lifetime positive test of any sort for SARS-CoV-2 prior to study participation. Dutch language proficiency and residency was an inclusion criterion for both groups. Randomization was not applicable for the current study design. Primary outcome assessors were not blinded for the participant group.

Recruitment of both the COVID-19 and control group took place in May 2021. Participants from both groups were invited for a single visit to our research center at the Radboud University Medical Center (Radboudumc, Nijmegen, the Netherlands) between May and September 2021. Thereafter, a personalized link was sent to every participant for completion of various online questionnaires. Attrition was not applicable to our study due to the cross-sectional study design without follow-up period. The local Medical Research Ethics Committee provided approval (NL36743.091.11) and the study was conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent.

Measurements

COVID-19 characteristics. The COVID-19 group was asked to report the date of onset and duration of their illness, their vaccination status and vaccination dates and the symptoms they experienced at the time of infection and at the time of inclusion. Furthermore, they were asked whether they required post-COVID-19 care of physiotherapist, general practitioner, psychologist, occupational therapist or medical specialist.

Cardiovascular risk factors. Height [m] and weight [kg] (measured with Seca GmbH & Co. KG, Hamburg, Germany) were assessed and body mass index (BMI, [kg/m^2]) was calculated. Non-invasive left brachial blood pressure [mmHg] and heart rate [beats/min] were measured twice after five minutes of rest in supine position (M3, OMRON Healthcare Europe B.V., Hoofddorp, the Netherlands). The average values of the two measurements were used for analysis. Venous blood was drawn from the antecubital vein (8.5 mL, BD Vacutainer® SST™ II Advance) and coagulated for 45 to 60 minutes before being centrifuged at 3,000 revolutions per minute for 10 minutes at 4 °C. Serum was then transferred to 2 mL microtubes and stored at -80 °C until analysis. The following biomarkers were analyzed: full cholesterol profile (total cholesterol, high-density-lipoprotein (HDL) cholesterol, low-density-lipoprotein (LDL) cholesterol, triglycerides, all in [mmol/L]), glucose hexokinase [mmol/L], insulin [µIU/mL], creatinine [µmol/L], high-sensitive cardiac troponin I (hs-cTnI) [ng/L], amino-terminal pro-B-

type-natriuretic-peptide (NT-proBNP) [pmol/L] and C-reactive protein (CRP) [mg/L]. Analyses were performed batchwise on Atellica™ (and IMMULITE® 2000 for insulin) analyzers (Siemens Healthcare Diagnostics Inc., Tarrytown, NY, USA) in the Gelderse Vallei Hospital, Ede, the Netherlands. Smoking behavior and history of cardiovascular disease (CVD) and cardiovascular risk factors including hypertension, hypercholesterolemia, diabetes mellitus, myocardial infarction, stroke, thrombosis, heart failure and resuscitation were inquired via questionnaires.

Arterial stiffness. Arterial stiffness was assessed by non-invasive, image-free ultrasound technology with the ARTSENS® Plus (Healthcare Technology Innovation Centre, Indian Institute of Technology Madras, Chennai, India) (29-32). Simultaneous recording of carotid artery distensibility and cuff-based femoral artery blood pressure facilitated assessment of carotid-femoral pulse wave velocity (cf-PWV) [m/s], a parameter of central stiffness (33). Furthermore, local carotid artery stiffness was quantified using the dimensionless stiffness index Beta and pressure strain elasticity Epsilon [kPa] (34).

Physical functioning. Eight-day 24-hour ambulant physical activity monitoring was performed with an activPAL3 micro accelerometer (PAL Technologies Ltd., Glasgow, UK) (35, 36). During this period, participants were requested to keep a sleep/wake diary to enable automated analysis. Data were extracted via PALbatch (PAL Software Suite version 8, PAL Technologies Ltd.) and analyzed using a modified version of the script by Winkler et al. (37, 38) in SAS (Statistical Analysis System, RRID:SCR_008567, version 9.4; SAS Institute Inc., Cary, NC, USA) to compute daily light intensity (LIPA) and moderate-to-vigorous physical activity (MVPA) duration [minutes/day], sleeping and sitting time [hours/day] and step count [steps/day]. Peak handgrip strength [kg] of the non-dominant hand was measured three times separated by one-minute intervals using the Jamar® Hydraulic Hand Dynamometer, following the method described by Webb et al. (39). The single highest value was used in the analysis. Gait speed [km/hour] was assessed twice over a four-meter stretch with two-meter acceleration and deceleration zones on either side to ensure a stable pace. The fastest try was used in the analysis. This method follows the four-meter gait speed protocol as described in the short physical

performance battery (40). Questionnaires were used to assess fatigue (Fatigue Severity Scale, high score indicating more fatigue), general health status (Short Form 12, SF-12, high score indicating a high level of general health status) and hrQoL (EQ-5D-5L, high score indicating a low hrQoL) (41-43).

Statistical analysis

No power analysis was conducted as all Nijmegen Exercise Study participants with a positive PCR test were eligible for study participation. Biomarker concentrations were log-transformed. Outlier analysis was performed by visual inspection using boxplots. No outliers were excluded. All parameters were tested for normality using the Shapiro-Wilk test. Normally distributed continuous variables were reported as mean (standard deviation) and compared between the COVID-19 and control group using independent sample t-tests, whereas non-Gaussian distributed continuous variables were reported as median [Q1-Q3] and compared between groups using the Mann-Whitney U test. Categorical variables were reported as number (%) and compared using Fisher's Exact test. A subgroup analysis was performed among COVID-19 patients with residual symptoms *versus* their age- and sex-matched controls. P-values <0.05 were considered significant. Statistical analyses were performed in RStudio (RRID:SCR_000432, version 4.1.2) and figures were created using packages *ggplot2* and *cowplot*.

Results

Study population

In total, 6,220 participants of the Nijmegen Exercise Study were invited to participate. From a group of 1,406 interested individuals, all participants (N=101) with a PCR-proven SARS-CoV-2 infection who were not hospitalized because of their infection were included. From the remaining group of interested individuals, we used one-to-one matching to select N=101 age- and sex-matched controls without signs, symptoms or suspicions of a SARS-CoV-2 infection, nor a lifetime positive test of any sort for

SARS-CoV-2. This led to a total of N=202 participants to be included in this study. Participants were 58 [54-65] years old, 118 (58%) were male and 84 (42%) were female.

COVID-19 characteristics. The median time between infection and inclusion was 175 [126-235] days (**Supplemental Figure 1**, https://figshare.com/s/ea3383ca0857151150ab). Five participants (7%) had been vaccinated once prior to becoming infected; none of the participants had completed the primary vaccination series before infection. The majority of the COVID-19 group (76%) was infected before February 2021, when the original SARS-CoV-2 variant was dominant in the Netherlands (44). Out of the 96 participants in the COVID-19 group who completed the questionnaires, 75 participants (78%) had been vaccinated at least once prior to inclusion. Ninety-four (98%) participants experienced symptoms at the time of infection, of which fatigue (80%), muscle pain (65%), dry cough (64%), headache (61%) and fever (58%) were most commonly reported. Most symptoms were of minor severity (**Supplemental Table 1**, https://figshare.com/s/dc1abca43e0afd33e3eb). Thirty-one (32%) participants reported residual symptoms at the time of inclusion of which fatigue, dysosmia/dysgeusia, concentration issues, feeling of weakness and headache were most commonly reported (**Supplemental Figure 2,** https://figshare.com/s/8bbe91e399c8bdae6a30). Seven participants (7%) required post-COVID-19 care of a physiotherapist (N=5), general practitioner (N=4), psychologist (N=3), medical specialist (N=2) or occupational therapist (N=2).

Cardiovascular risk factors. History of CVD and smoking behavior were not different between groups (**Table 1**). BMI (24.2 [22.3-25.6] *versus* 24.7 [22.9-26.5] kg/m^2, p=0.17), systolic blood pressure (134 [124-148] *versus* 134 [124-146] mmHg, p=0.82), diastolic blood pressure (83 (10) *versus* 81 (9) mmHg, p=0.10) and heart rate (58 [52-64] *versus* 58 [53-64] beats/min, p=0.49) were not different between the COVID-19 and control group. Similarly, serum concentrations of lipid levels, glucose, insulin and creatinine were not different between groups (**Table 1)**. Concentrations of hs-cTnI, NT-proBNP and CRP, but also the prevalence for these biomarkers exceeding the assay-specific upper reference limit, were not different between the COVID-19 and control group (**Figure 1**).

Arterial stiffness. As time constraints restricted us to perform these measurements in the full cohort, arterial stiffness was successfully assessed in 87 former COVID-19 patients and 49 controls. Participant characteristics differed neither between participants with *versus* without arterial stiffness measurements in the COVID-19 and control group, nor between COVID-19 patients and controls with an arterial stiffness measurement (data not presented). No differences in cf-PWV or local arterial stiffness (Beta, Epsilon) were found between the COVID-19 and control group (**Figure 2**).

Physical functioning. Habitual physical activity characteristics were not different between groups, except for sleeping time (1.0 hour/day lower in the COVID-19 *versus* control group (**Figure 3**)). Step count was not different between the COVID-19 and control group (13,266 [10,600-16,131] *versus* 14,024 [11,393-17,197] steps/day, p=0.42). The COVID-19 group had a higher handgrip strength compared to the control group (43 [33-52] *versus* 38 [30-48] kg, p=0.007), while gait speed did not differ between groups (5.5 [5.1-6.2] *versus* 5.6 [5.3-6.2] km/hour, p=0.26). Self-reported level of fatigue was higher in the COVID-19 group, whereas the perceived general health status was lower in the COVID-19 versus control group but did not reach statistical significance (p=0.07, **Figure 4**). HrQoL did not differ between groups (**Figure 4**).

Impact of residual symptoms. Subgroup analyses among COVID-19 patients with residual symptoms (N=31) *versus* their age- and sex-matched controls (N=31) largely confirmed our primary findings, in that no differences were observed in biomarker concentrations and physical functioning outcomes between groups. A lower cf-PWV and perceived general health status were found in the COVID-19 patients with residual symptoms (**Supplemental Table 2**, https://figshare.com/s/b1fcd503ecc55ab09038).

Discussion

The purpose of this study was to examine the long-term effects of COVID-19 on physiological parameters of cardiovascular health and physical functioning in individuals who recovered at home.

We observed no significant differences in traditional cardiovascular risk factors (e.g., BMI, blood pressure), cardiovascular biomarkers (e.g., hs-cTnI, NT-proBNP, CRP) or arterial stiffness between groups. Objective measures of habitual physical activity characteristics were mostly comparable between groups, but the COVID-19 group showed a higher handgrip strength, lower sleeping time and a higher level of fatigue than the control group. These findings suggest that objective outcomes such as cardiovascular risk factors, biomarker concentrations and physical activity characteristics are not different between non-hospitalized COVID-19 patients at a median of six months following infection compared to their age- and sex-matched non-infected peers, despite a high prevalence of residual symptoms and poorer subjective outcomes in the COVID-19 *versus* control group.

In contrast to our hypothesis, traditional cardiovascular risk factors and cardiovascular biomarker concentrations were comparable between the COVID-19 and control group. To our knowledge, literature on cardiac biomarker concentrations in post-acute, non-hospitalized COVID-19 patients is limited to one study, that reported elevated cardiac troponin I levels in 21% of the participants at 28 days after the infection (16). Notably, this study also reported a decline in biomarker concentrations between day 1 and day 28. This decline over the course of one month may explain why we did not find elevated hs-cTnI levels in our COVID-19 group, as previously elevated levels could have normalized over a median follow-up of six months.

Similarly, indicators of central and local arterial stiffness were comparable between our COVID-19 and control group. As these arterial stiffness parameters are established and independent predictors for future cardiovascular morbidity and mortality (45-48), our data suggest no indication of increased cardiovascular risk within our COVID-19 cohort of relatively healthy non-hospitalized individuals. Furthermore, the subgroup analysis between COVID-19 participants with residual symptoms and their matched controls showed a lower cf-PWV in the COVID-19 group, opposite of what was expected. However, these results were based on N=28 COVID-19 and N=15 control participants and should therefore be interpreted with caution. Follow-up studies with a larger sample

size are warranted to further investigate this. Our findings of no differences in arterial stiffness in COVID-19 *versus* control participants is in line with some (18), but in contrast with other studies (19-21). The main differences between these studies and our study are that our study had a longer median follow-up duration, included participants of all ages in contrast to young individuals only, and included approximately four times as many participants. Two other studies using the same study population of non-hospitalized individuals reported increased arterial stiffness at four and twelve months post-COVID-19 respectively (22, 23). Their study sample resembled our cohort in terms of age, sample size and follow-up duration, yet showed results conflicting with our findings. A possible explanation for this could be that they included patients visiting a dedicated post-COVID-19 outpatient clinic. This suggests that these patients were affected more strongly by the disease than our general group of non-hospitalized COVID-19 participants. Moreover, three of these studies suggest a transient increase in arterial stiffness after COVID-19 that declines with time (17, 20, 22). Our finding that arterial stiffness was not different between COVID-19 and control participants may therefore also be due to a normalization of values over the median follow-up of six months.

These findings, suggesting no increased cardiovascular risk, are contradictory to observations in a large American cohort study (N=153,760), in which COVID-19 survivors had an increased incidence of cerebrovascular and thrombotic disorders, dysrhythmias and inflammatory or ischemic heart disease during twelve months of follow-up (9). There are several explanations for these discrepant outcomes. First, baseline characteristics were different across studies as participants in the American cohort were older, more often smokers, male, black or obese and more often had diabetes, hypertension or hyperlipidemia compared to our Dutch cohort. The higher prevalence of cardiovascular risk factors in the American cohort may have contributed to the increased CVD risk during follow-up, even after correction for confounding factors, as COVID-19 may have acted as a catalyst to express and deteriorate underlying disease. Second, participants in our study were highly physically active, demonstrated by the high daily step count (13,499 [10,924-16,854] steps/day) and a weekly exercise volume (729 [589-904] minutes) that well exceeds the international guidelines on

physical activity (49, 50). Physical activity is known to reduce the risk of cardiovascular and chronic diseases (49-51), and previous studies have demonstrated a protective effect of a physically active lifestyle on COVID-19-related outcomes (52). Our study sample might therefore not be representative of the general population, underestimating the long-term consequences of COVID-19 in those who were not hospitalized. Finally, it may be possible that the impact of different SARS-CoV-2 variants on health outcomes was assessed (53), although the similar timelines of both studies make this explanation less likely.

Habitual physical activity characteristics, such as time spent sedentary, LIPA and MVPA, were not different between the COVID-19 and control group. These findings are contradictory to some, (24-26, 54) studies assessing physical activity levels of former, non-hospitalized COVID-19 patients. It is important to note that studies demonstrating a decline in physical activity patterns included participants who explicitly suffered from long COVID or post-COVID-19 syndrome (24-26) or used subjective measures for physical activity (54). In contrast, the majority (68%) of our sample did not experience long-term symptoms and is therefore more likely to represent the general, non-hospitalized population. Subgroup analysis among individuals with residual symptoms further confirmed our observation that activity patterns were not different between the COVID-19 and control group.

We found a small but significantly higher handgrip strength in the COVID-19 group compared to the control group. This finding is in contrast with previous observations of muscle weakness being a prevalent long-term consequence of COVID-19 in both hospitalized and non-hospitalized patients (6, 12, 55). Nonetheless, handgrip strength of both groups was within the normal range (39) and not associated with differences in physical function (e.g. gait speed). Moreover, clinical significance of handgrip strength is primarily described in frail, elderly individuals, whilst we examined a relatively younger population.

A lower sleeping time and higher level of fatigue were found in the COVID-19 *versus* control group. These findings align with literature, as sleeping disturbances and fatigue have been previously reported as long-term consequences of COVID-19 in multiple studies (5, 6, 12). Fatigue was also the most frequently reported symptom among participants with residual symptoms in our study.

An important finding of our study is the discrepancy between objective cardiovascular and physical functioning measurements and subjective outcomes. The long-term effects of COVID-19 on cardiovascular health and physical functioning may be limited in physically active patients who recovered at home, whereas residual symptoms are reported by one out of three participants, with fatigue being most often mentioned. Noteworthy is that this subgroup with residual symptoms reports a lower perceived general health status, which suggests that these participants are truly affected in their daily life. Follow-up studies are needed to investigate the origin of these residual symptoms, which may be caused by persistent infections, pulmonary injury, diaphragm dysfunction or other pathophysiological pathways that we did not assess in the current study. Investigating how residual symptoms evolve across the years after COVID-19 and/or following renewed infection(s) will contribute to a more thorough understanding of the long-term consequences of COVID-19 and the corresponding healthcare needs.

Limitations. This study has some limitations. First, we did not perform cardiac imaging, so the long-term impact of COVID-19 on cardiac structure and function in non-hospitalized individuals requires further study. Second, arterial stiffness data were only available in a subset of our cohort. Nevertheless, participant characteristics of individuals with and without an arterial stiffness measurement were comparable, suggesting that these findings were likely unbiased, which was further reinforced by a similar distribution of the arterial stiffness parameters within the COVID-19 and control group. Third, we cannot exclude the possibility that controls were never infected with SARS-CoV-2 as we did not perform serological testing for antibodies. Some controls may have experienced an asymptomatic infection, but the impact of such misclassification on our findings is expected to be

minimal given our large sample size. Fourth, we aimed to include COVID-19 participants approximately six months after infection. However, the range of time between infection and inclusion was large, which may have impacted the study results.

Conclusion

No major differences in physiological parameters of cardiovascular health and physical functioning were found between non-hospitalized COVID-19 patients at a median of six months post-infection and age- and sex-matched controls. Nevertheless, a lower sleeping time and higher level of fatigue were found in former COVID-19 patients, in combination with a high prevalence of residual symptoms and a corresponding lower perception of general health status. Future research should focus on exploring the pathophysiological origins of residual symptoms to further unravel the long-term consequences of COVID-19 in those recovered at home.

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548 **Figure captions**

549 **Figure 1**: Biomarker concentrations of **A**) high-sensitive cardiac troponin I (hs-cTnI), **B**) amino-
550 terminal pro-B-type-natriuretic-peptide (NT-proBNP), and **C**) C-reactive protein (CRP) in the COVID-19
551 group (N=94) and control group (N=101). Each dot represents an individual datapoint, whereas the
552 boxplots represent group statistics (Q1, median, Q3; whiskers extending up to 1.5 times the
553 interquartile range). The dashed red lines indicate the upper reference limit (URL) and the limit of
554 detection (LOD). Statistical tests performed: Mann-Whitney U test.

555 **Figure 2**: Arterial stiffness parameters expressed as **A**) carotid-femoral pulse wave velocity (cf-PWV)
556 (m/s), **B**) stiffness index beta (dimensionless), and **C**) pressure strain elasticity epsilon (kPa) for the
557 COVID-19 group (N=87) and control group (N=49). Each dot represents an individual datapoint,
558 whereas boxplots represent group statistics (Q1, median, Q3; whiskers extending up to 1.5 times the
559 interquartile range). Statistical tests performed: Mann-Whitney U test.

560 **Figure 3**: Habitual physical activity patterns expressed as **A**) sleeping time, **B**) sitting time, **C**) time
561 spent light intensity physical activity (LIPA), and **D**) time spent moderate-to-vigorous physical activity
562 (MVPA) for the COVID-19 group (N=101) and control group (N=101). Each dot represents an
563 individual datapoint, whereas boxplots represent group statistics (Q1, median, Q3; whiskers
564 extending up to 1.5 times the interquartile range). Statistical tests performed for **A**), **C**) and **D**):
565 Mann-Whitney U test. Statistical test performed for **C**): independent sample t-test.

566 **Figure 4**: Self-reported outcomes of the COVID-19 group (N=96) and the control group (N=98): **A**)
567 level of fatigue (Fatigue Severity Scale, range 1-7, high score indicating a high level of fatigue), **B**)
568 general health status (pooled Short Form 12 (SF-12) score, range 0-100%, high score indicating a high
569 level of general health status), and **C**) health-related quality of life (hrQoL) (EQ-5D-5L, range 1-5, high
570 score indicating a low hrQoL). Each dot represents an individual datapoint, whereas the boxplot
571 represents group statistics (Q1, median, Q3; whiskers extending up to 1.5 times the interquartile

572 range). Statistical tests performed for **A**) and **C**): Fisher's Exact test. Statistical test performed for **B**):

573 Mann-Whitney U test.

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