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Title: Longitudinal Physiological Data from a Wearable Device Identifies SARS-CoV-2 Infection and Symptoms and Predicts COVID-19 Diagnosis

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ABSTRACT:

Background: Changes in autonomic nervous system function, characterized by heart rate variability (HRV), have been associated with and observed prior to the clinical identification of infection. We performed an evaluation of this metric collected by wearable devices, to identify and predict Coronavirus disease 2019 (COVID-19) and its related symptoms.

Methods: Health care workers in the Mount Sinai Health System were prospectively followed in an ongoing observational study using the custom Warrior Watch Study App which was downloaded to their smartphones. Participants wore an Apple Watch for the duration of the study measuring HRV throughout the follow up period. Survey's assessing infection and symptom related questions were obtained daily.

Findings: Using a mixed-effect COSINOR model the mean amplitude of the circadian pattern of the standard deviation of the interbeat interval of normal sinus beats (SDNN), a HRV metric, differed between subjects with and without COVID-19 (p=0.006). The mean amplitude of this circadian pattern differed between individuals during the 7 days before and the 7 days after a COVID-19 diagnosis compared to this metric during uninfected time periods (p=0.01). Significant changes in the mean MESOR and amplitude of the circadian pattern of the SDNN was observed between the first day of reporting a COVID-19 related symptom compared to all other symptom free days (p=0.01).

Interpretation: Longitudinally collected HRV metrics from a commonly worn commercial wearable device (Apple Watch) can identify the diagnosis of COVID-19 and COVID-19 related symptoms. Prior to the diagnosis of COVID-19 by nasal PCR, significant changes in HRV were observed demonstrating its predictive ability to identify COVID-19 infection.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) has resulted in over 41 million infections and more than 1.1 million deaths.[1] A prolonged incubation period and variable symptomatology has facilitated disease spread, with approximately 30-45% of individuals having asymptomatic SARS-CoV-2 infections, and testing generally limited to only symptomatic individuals.[2-4] Health care workers (HCWs), characterized as any type of worker in a health care system, represent a vulnerable population with a threefold increased risk of infection compared to the general population.[5] This increased risk of transmission is important in healthcare settings, where asymptomatic or pre-symptomatic HCWs can shed the virus contributing to transmission within healthcare facilities and their households.[6]

Digital health technology offers an opportunity to address the limitations of traditional public health strategies aimed at curbing COVID-19 spread.[7] Smart phone Apps are effective in using symptoms to identify those possibly infected with SARS-CoV-2, but they rely on ongoing participant compliance and self-reported symptoms.[8] Wearable devices are commonly used for remote sensing and provide a means to objectively quantify physiological parameters including heart rate, sleep, activity and measures of autonomic nervous system (ANS) function (e.g., heart rate variability [HRV]).[9] The addition of physiological data from wearable devices to symptom tracking Apps has been shown to increase the ability to identify those infected with SARS-CoV-2.[10]

HRV is a physiological metric providing insight into the interplay between the parasympathetic and sympathetic nervous system which modulate cardiac contractility and cause variability in the beat-to-beat intervals.[11] It exhibits a 24 hour circadian pattern with relative sympathetic tone during the day and parasympathetic activity at night.[12-14] Changes in this circadian pattern can be leveraged to identify different physiological states. Several studies have demonstrated that lower HRV, indicating increased sympathetic balance, is a reliable predictor of infection onset.[15,16] However, HRV and its dynamic changes over time have not been evaluated as a marker or

predictor of COVID-19. In response to the COVID-19 pandemic we launched The
Warrior Watch Study™, employing a novel smartphone App to remotely enroll and
monitor HCWs throughout the Mount Sinai Health System in New York City, a site of
initial case surge. This digital platform enables remote survey delivery to Apple iPhones
and passive collection of Apple Watch data, including HRV. The aim of this study is to
determine if SARS-CoV-2 infections can be identified and predicted prior to a positive
test result using the longitudinal changes in HRV metrics derived from the Apple Watch.

METHODS

Study Design

The primary aim of the study was to determine whether changes in HRV can
differentiate participants infected or not infected with SARS-CoV-2. The secondary aim
was to see if changes in HRV can predict the development of a SARS-CoV-2 infection
prior to diagnosis by a SARS-CoV-2 nasal PCR. Exploratory aims were (1) to determine
whether changes in HRV can identify the presence of COVID-19 related symptoms; (2)
to determine whether changes in HRV can predict the development of COVID-19
related symptoms; and (3) to evaluate how HRV changed throughout the infection and
symptom period.

HCWs in the Mount Sinai Health System were enrolled in an ongoing prospective
observational cohort study. Eligible participants were ≥18 years of age, current
employees in the Mount Sinai Health System, had an iPhone Series 6 or higher, and
had or were willing to wear an Apple Watch Series 4 or higher. Participants were
excluded if they had an underlying autoimmune disease or were on medications known
to interfere with ANS function. A positive COVID-19 diagnosis was defined as a positive
SARS-CoV-2 nasal PCR swab reported by the participant. Daily symptoms were
collected including fevers/chills, tired/weak, body aches, dry cough, sneezing, runny
nose, diarrhea, sore throat, headache, shortness of breath, loss of smell or taste, itchy

eyes, none, or other. This study was approved by the Institutional Review Board at The
Icahn School of Medicine at Mount Sinai.

Study Procedures

Participants downloaded the custom Warrior Watch App to complete eligibility
questionnaires and sign an electronic consent form. Participants completed an App-
based baseline assessment collecting demographic information, prior COVID-19
diagnosis history, occupation, and medical history and were then followed prospectively
through the App. Daily survey questionnaires captured COVID-19 related symptoms,
symptom severity, SARS-CoV-2 nasal PCR results, serum SARS-CoV-2 antibody test
results, and daily patient care related exposure (**Supplementary Table 1**). Participants
carried out their normal activities throughout the study and were instructed to wear the
Apple Watch for a minimum duration of 8 hours per day.

Wearable Monitoring Device and Autonomic Nervous System Assessment

HRV was measured via the Apple Watch Series 4 or 5, which are commercially
available wearable devices. Participants wore the device on the wrist and connected it
via Bluetooth to their iPhone. The Watch is equipped with an enhanced
photoplethysmogram (PPG) optical heart sensor that combines a green LED light paired
with a light sensitive photodiode generating time series peaks that correlate with the
magnitude of change in the green light generated from each heartbeat.[17] Data are
filtered for ectopic beats and artifact. The time difference between heartbeats is
classified as the Interbeat Interval (IBI) from which HRV is calculated. The Apple Watch
and the Apple Health app automatically calculate HRV using the standard deviation of
the IBI of normal sinus beats (SDNN), measured in milliseconds (ms). This time domain
index reflects both sympathetic and parasympathetic nervous system activity and is
calculated by the Apple Watch during ultra-short-term recording periods of
approximately 60 seconds.[11] The Apple Watch generates several HRV measurements
throughout a 24-hour period. HRV metrics are stored in a locally encrypted database

accessible through the iPhone Health app which is retrieved through our custom Warrior
Watch App. Data is transferred from the iPhone and Apple Watch upon completion of
the e-consent and any survey in the App. Wearable data is stored locally allowing
retrieval during the days when surveys are not completed by participants.

Statistical Analysis

Heart Rate Variability Modelling

The HRV data collected through the Apple Watch was characterized by a circadian
pattern, a sparse sampling over a 24-hour period, and a non-uniform timing across days
and participants. These characteristics bias easily derived features including mean,
maximum and minimum creating the need to derive methods that model the circadian
rhythm of HRV. A COSINOR model was used to model daily circadian rhythm over a 24
hour period with the non-linear function $Y(t) = M + A\cos(2\pi t/\tau + \phi) + e_i(t)$ [equation 1],
where τ is the period ($\tau = 24h$), M is the Midline Statistic of Rhythm (MESOR), a rhythm-
adjusted mean, A is the amplitude, a measure of half the extent of variation within a day
and Φ is the Acrophase, a measure of the time of overall high values recurring in each
day (**Supplementary Figure 1**). This non-linear model with 3 parameters has the
advantage of being easily transformed into a linear model by recoding time (t) into two
new variables x and z as $x = \sin(2\pi t/\tau),\ z = \sin(2\pi t/\tau)$. HRV can then be written as
$Y(t) = M + \beta x_t + \gamma z_t + e_i(t)$ [equation 2], where the linear coefficients $\beta,\ \gamma$ of the linear
model in equation 2 are related to the non-linear parameters of the non-linear model in
equation 1 by $\beta = A\cos(\phi)\ \ \gamma = -A\sin(\phi)$. One can estimate the linear parameters $\beta,\ \gamma$
and then obtain the A and ϕ as:

$$\widehat{A} = \left(\widehat{\beta}^2 + \widehat{\gamma}^2\right)^{1/2}$$
$$\widehat{\phi} = \arctan\left(-\widehat{\gamma}/\widehat{\beta}\right) + K\pi$$

We took advantage of the longitudinal structure of the data to identify a participant
specific daily pattern and then measured departures from this pattern as a function of
COVID-19 diagnosis or other relevant covariates. In order to do so we used a mixed-

effect COSINOR model, where the HRV measure of participant i at time t can be written as $HRV_{it} = (M + \beta.x_{it} + \gamma.z_{it}) + W_{it}.\theta_i + e_i(t)$, $e_i(t) \sim N(0,s)$, and where M, β and γ are the population parameters (fixed-effects) and θ_i is a vector of random effects and assumed to follow a multivariate normal distribution $\theta_i \sim N(0,\Sigma)$. In this context the introduction of random effects intrinsically model the correlation due to the longitudinal sampling. To measure the impact of any covariate C on the participants' daily curve, we can introduce such covariates as fixed-effects as its interactions with x and z: $HRV_{it} = M + a_0 C_i + (\beta + a_2 C_i).x_{it} + (\gamma + a_3 C_i.)z_{it} + W_{it}.\theta_i + e_i(t)$ [equation 3]. Model parameters and the standard errors of equation 3 can be estimated via maximum likelihood or reweighted least squares (REWL) and hypothesis testing can be carried out for any comparison that can be written as a linear function of $a's, \beta$ and γ parameters.

However, to test if the COSINOR curve, defined by the non-linear parameters M, A and ϕ in equation 1 differs between the populations defined by the covariate C, we proposed the following bootstrapping procedure where for each resampling iteration we: (1) Fit a linear mixed-effect model using REWL; (2) Estimated the marginal means obtaining the linear parameters for each group defined by covariate C; (3) Used the inverse relationship to estimate marginal means M, A and ϕ for each group defined by C; and (4) Defined the bootstrapping statistics as the pairwise differences of M, A and ϕ between groups defined by C. For such iterations, the confidence intervals for the non-linear parameter was defined using standard bootstrap techniques, as well deriving the p-values for the differences of each non-linear parameter between groups defined by Ci. Age and sex were included as a covariate in HRV analyses and admitted invariant and time-variant covariates.

Association and Prediction of COVID-19 Diagnosis and Symptoms

The relationship between a COVID-19 diagnosis and change in HRV curves were evaluated. To test this association, we defined the time variant covariate C_{it} for participant i at time t as:

$$C_{it} = \begin{cases} 1 & t \in [t_o, t_o + 14] \\ 0 & otheriwise \end{cases}.$$

HRV metrics for the 14 days following the time of first positive SARS-CoV-2 nasal PCR test were used to define the positive SARS-CoV-2 infection window. To evaluate the predictive ability of changes in HRV prior to a COVID-19 diagnosis and to explore its changes during the infection period, the time variant covariate was used to characterize the following 4 groups: healthy uninfected individuals [$t < t_0 - 7$], 7 days before COVID-19 diagnosis [$t \geq t_0 - 7$, $t < t_0$], the first 7 days post COVID-19 diagnosis [$t_0 \leq t < t_0 + 7$] and the 7-14 days post diagnosis [$t_0 + 7 \leq t < t_0 + 14$].

To determine the association between COVID-19 symptoms and changes in HRV metrics, we defined being symptomatic as the 1st day of a reported symptom and compared this to all other days. To evaluate the predictive ability of HRV to identify upcoming symptom days and to explore its changes over time the time variant covariate was used to characterize the following 4 groups: healthy asymptomatic individuals for $t < t_0 - 1$, one day before COVID-19 symptoms [$t \geq t_0 - 1$, $t < t_0$], the first day of COVID-19 symptoms [$t_0 \leq t < t_0 + 1$] and one day post COVID-19 symptom development [$t_0 + 1 \leq t < t_0 + 2$].

Role of the Funding Source

The study sponsors played no role in the study design, data collection, analysis, writing or decision for publication.

RESULTS

Two hundred and ninety-seven participants were enrolled between April 29th and September 29th, 2020, when data was censored for analysis (**Table 1**). The median age at enrollment was 36 years with 69% of participants being women. Twenty participants reported having a positive SARS-CoV-2 nasal PCR test prior to enrollment, while 28 participants reported having a positive blood antibody test prior to joining the study. The median duration of follow up was 42 days (range 0-152 days). A median of 28 HRV

samples (range 1-129) were obtained per participant. Study compliance over the follow up period, defined as participants answering over 50% of daily surveys, was 70.4%.

Identification and Prediction of COVID-19 Diagnosis

Thirteen participants reported a positive SARS-CoV-2 nasal PCR during the follow up period. The mean MESOR, acrophase and amplitude of the circadian SDNN pattern in participants diagnosed with and without COVID-19 are described in **Table 2**. A significant difference in the circadian pattern of SDNN was observed in participants diagnosed with COVID-19 compared to those without COVID-19. There was a significant difference (p=0.006) between the mean amplitude of SDNNs circadian pattern in those with (1.23 ms, 95% CI -1.94- 3.11) and without COVID-19 (5.30 ms, 95% CI 4.97-5.65). No difference was observed between the MESOR (p=0.46) or acrophase (p=0.80) in these two infection states (**Figure 1a-c**).

The mean MESOR, acrophase and amplitude of the circadian SDNN pattern for those without COVID-19, those during the 7 days prior to a COVID-19 diagnosis, participants during the 7 days after a COVID-19 diagnosis and those during the 7-14 days after a COVID-19 diagnosis are described in **Table 3**. Significant changes in the circadian pattern of SDNN were observed in participants during the 7 days prior and the 7 days after a diagnosis of COVID-19 when compared to uninfected participants. There was a significant difference between the amplitude of the SDNN circadian rhythm between uninfected participants (5.31 ms, 95% CI 4.95-5.67) compared to individuals during the 7 day period prior to a COVID-19 diagnosis (0.29 ms, 95% CI -4.68-1.73; p=0.01) and participants during the 7 days after a COVID-19 diagnosis (1.22 ms, 95% CI -2.60-3.25; p=0.01). There were no other significant differences between the MESOR, amplitude, and acrophase of SDNNs circadian rhythm observed between healthy individuals, individuals 7 days before a COVID-19 diagnosis, individuals 7 days after a COVID-19 diagnosis, and individuals 7-14 days after infection (**Figure 1d-e**).

Identification and Prediction of COVID-19 Symptoms

Symptoms were frequently reported during the follow up period with the greatest number of participants reporting feeling tired or weak (n=87), followed by headaches (n= 82) and sore throat (n=60) (**Table 4**). Evaluating the days when participants experienced symptoms, we found that loss of smell or taste were reported the most with a mean of 138 days. This was followed by feeling tired or weak, reported a mean of 25 days and runny nose, reported a mean of 19.5 days (**Figure 2**). The mean MESOR, acrophase and amplitude observed in the circadian SDNN pattern in participants on the first day a symptom and on all other days of follow up are reported in **Table 5.** There was a significant difference in the circadian SDNN pattern between participants on the first day a symptom was reported compared to all other days of follow up. Specifically, there was a significant difference (p=0.01) between the mean MESOR of SDNNs circadian pattern on the first day of symptoms (46.01 ms, 95% CI 43.37-48.77) compared to all other days (43.48 ms, 95% CI 41.77-45.27). Similarly, there was a significant difference (p=0.01) between the mean amplitude of SDNNs circadian pattern on the first day of symptoms (2.58 ms, 95% CI 0.26-5.00) compared to all other days (5.30 ms, 95% CI 4.95-5.66) (**Figure 3a-c**).

The mean MESOR, acrophase and amplitude observed in the circadian SDNN pattern in participants on the day before symptoms develop, on the first day of the symptom, on the day following the first day of the symptom and on all other days are reported in **Table 6**. Significant changes in the circadian pattern of SDNN were observed, specifically in the mean amplitude (p=0.04) when comparing participants on the first day of the symptom (3.07 ms, 95% CI 0.88-5.22) to all other days (5.32 ms, 95% CI 4.99-5.66). Excluded from this analysis was the day prior and day after the first symptomatic day. Changes in SDNN characteristics trended toward significance prior to the development of symptoms. Specifically, the differences in the mean amplitude of SDNNs circadian pattern trended toward significance when comparing the day prior to symptom development (2.92 ms, 95% CI 0.50-5.33) with all other days (5.32, 95% CI 4.99-5.66; p=0.056). Again, excluded from the analysis was the first day of the symptom and the day after the first symptomatic day. Additionally, there was trend toward

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significance when comparing the amplitude of the SDNN circadian pattern between participants during the first day of the symptom (3.07 ms, 95% CI 0.88-5.22) with the one day after the first symptom was reported (5.47 ms, 95% CI 3.16-7.76; p=0.56). Excluded from the analysis was the day prior to symptom development and all other days. There were no other significant differences between the MESOR, amplitude, and acrophase of SDNNs circadian rhythm when comparing participants on the day before symptoms develop, on the first day of the symptom, on the day following the first day of the symptom and on all other days (**Figure 3d-e**).

DISCUSSION

In this prospective study, longitudinally evaluated HRV metrics were found to be associated with a positive SARS-CoV-2 diagnosis and COVID-19 symptoms. Significant changes in these metrics were observed 7 days prior to the diagnosis of COVID-19. To the best of our knowledge this is the first study to demonstrate that physiological metrics derived from a commonly worn wearable device (Apple Watch) can identify and predict SARS-CoV-2 infection prior to diagnosis with a SARS-CoV-2 nasal PCR swab. These preliminary results identify a novel easily measured physiological metric which may aid in the tracking and identification of SARS-CoV-2 infections.

Current means to control COVID-19 spread rely on case isolation and contact tracing, which have played a major role in the successful containment of prior infectious disease outbreaks.[18-20] However, the variable incubation period, high percentage of asymptomatic carriers, and infectivity during the pre-symptomatic period of COVID-19 have made containment challenging.[21] This has further limited the utility of systematic screening technologies reliant on vital sign assessment or self-reporting of symptoms.[7] Advances in digital health provide a unique opportunity to enhance disease containment. Wearable devices are commonly used and well accepted for health monitoring.[9,22] Commercially available devices are able to continually collect several physiological parameters. Unlike App-based platforms, wearable devices have the advantage of not requiring users to actively participate aside from regular use of the

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device. Prior to the COVID-19 pandemic, population level data from the Fitbit wearable device demonstrated effectiveness at real-time geographic surveillance of influenza-like illnesses through the assessment of physiological parameters.[23] This concept was recently expanded during the COVID-19 pandemic by Quer and colleagues who demonstrated that the combination of symptom-based data with resting heart rate and sleep data from wearable devices was superior to relying on symptom-based data alone to identify COVID-19 infections.[10]

HRV has been shown to be altered during illnesses with several small studies demonstrating changes in HRV associated with and predictive of the development of infection.[24] Ahmad and colleagues followed 21 subjects undergoing bone marrow transplant finding a significant reduction in root mean square successive difference metrics prior to the clinical diagnosis of infection. Furthermore, wavelet HRV was noted to decrease by 25% on average 35 hours prior to a diagnosis of sepsis in 14 patients.[16] In another study in 100 infants, significant HRV changes were noted 3-4 days preceding sepsis or systemic inflammatory response syndrome with the largest increase being seen 24 hours prior to development.[15] Building on these observations demonstrating that ANS changes accompany or precede infection, our team launched the Warrior Watch Study.

We demonstrated that significant changes in the circadian pattern of HRV, specifically SDNN's amplitude, was associated with a positive COVID-19 diagnosis. Interestingly, when we compared these changes over the seven days preceding the diagnosis of COVID-19 we continued to see significant alterations in amplitude when compared to individuals without COVID-19. This demonstrates the predictive ability of this metric to identify infection. Interestingly when we follow individuals 7-14 days after diagnosis with COVID-19, we find that the circadian HRV pattern starts to normalize and is no longer statistically different from an uninfected pattern. As an exploratory analysis we evaluated how HRV was impacted by symptoms associated with a COVID-19 diagnosis, since individuals may not be tested despite symptoms. We found significant changes in the amplitude of the circadian HRV pattern on the first day of symptoms,

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with a trend toward statistical significance on the day before and after symptoms are reported. Taken together, these findings highlight the possible use of HRV collected via wearable devices to identify and predict COVID-19 infections.

There are several limitations to our study. First, there was a small number of participants who were diagnosed with COVID-19 in our cohort limiting our ability to determine how predictive HRV can be of infection. However, these preliminary findings support the further evaluation of HRV as a metric to identify and predict COVID-19 and warrant further study. An additional limitation is the sporadic collection of HRV by the Apple Watch. While our statistical modelling was able to account for this a denser dataset would allow for expanded evaluation of the relationship between this metric and infections/symptoms. The Apple Watch also only provides HRV in one time-domain (SDNN), limiting assessment of the relationship between other HRV parameters with COVID-19 outcomes. Lastly, an additional limitation is that we relied on self-reported data in this study, precluding independent verification of COVID-19 diagnosis.

In summary, we demonstrated a relationship between longitudinally collected HRV acquired from a commonly used wearable device and SARS-CoV-2 infection. These preliminary results support the further evaluation of HRV as a biomarker of SARS-CoV-2 infection by remote sensing means. While further study is needed, this may allow for the identification of SARS-CoV-2 infection during the pre-symptomatic period, in asymptomatic carriers and prior to diagnosis by a SARS-CoV-2 nasal PCR tests. These findings warrant further evaluation of this approach to track and identify COVID-19 infections and possibly other type of infections.

References

1.   Johns Hopkins University & Medicine: Coronavirus Resource Center. https://coronavirus.jhu.edu/ (accessed October 22, 2020.

2.   Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; **395**(10223): 497-506.

3.   He X, Lau EHY, Wu P, et al. Temporal dynamics in viral shedding and transmissibility of COVID-19. *Nat Med* 2020; **26**(5): 672-5.

4.   Oran DP, Topol EJ. Prevalence of Asymptomatic SARS-CoV-2 Infection : A Narrative Review. *Ann Intern Med* 2020; **173**(5): 362-7.

5.   Nguyen LH, Drew DA, Graham MS, et al. Risk of COVID-19 among front-line health-care workers and the general community: a prospective cohort study. *Lancet Public Health* 2020; **5**(9): e475-e83.

6.   Shah ASV, Wood R, Gribben C, et al. Risk of hospital admission with coronavirus disease 2019 in healthcare workers and their households: nationwide linkage cohort study. *BMJ* 2020; **371**: m3582.

7.   Whitelaw S, Mamas MA, Topol E, Van Spall HGC. Applications of digital technology in COVID-19 pandemic planning and response. *Lancet Digit Health* 2020; **2**(8): e435-e40.

8.   Menni C, Valdes AM, Freidin MB, et al. Real-time tracking of self-reported symptoms to predict potential COVID-19. *Nat Med* 2020; **26**(7): 1037-40.

9.   Vogels EA. About one-in-five Americans use a smart watch or fitness tracker. https://www.pewresearch.org/fact-tank/2020/01/09/about-one-in-five-americans-use-a-smart-watch-or-fitness-tracker/.

10.   Quer G, Radin JM, Gadaleta M, et al. Wearable sensor data and self-reported symptoms for COVID-19 detection. *Nat Med* 2020.

11.   Shaffer F, Ginsberg JP. An Overview of Heart Rate Variability Metrics and Norms. *Front Public Health* 2017; **5**: 258.

12.   Boudreau P, Yeh WH, Dumont GA, Boivin DB. A circadian rhythm in heart rate variability contributes to the increased cardiac sympathovagal response to awakening in the morning. *Chronobiol Int* 2012; **29**(6): 757-68.

13.   Buijs RM, la Fleur SE, Wortel J, et al. The suprachiasmatic nucleus balances sympathetic and parasympathetic output to peripheral organs through separate preautonomic neurons. *J Comp Neurol* 2003; **464**(1): 36-48.

14.   Nonell A, Bodenseh S, Lederbogen F, et al. Chronic but not acute hydrocortisone treatment shifts the response to an orthostatic challenge towards parasympathetic activity. *Neuroendocrinology* 2005; **81**(1): 63-8.

15.   Kovatchev BP, Farhy LS, Cao H, Griffin MP, Lake DE, Moorman JR. Sample asymmetry analysis of heart rate characteristics with application to neonatal sepsis and systemic inflammatory response syndrome. *Pediatr Res* 2003; **54**(6): 892-8.

16.   Ahmad S, Ramsay T, Huebsch L, et al. Continuous multi-parameter heart rate variability analysis heralds onset of sepsis in adults. *PLoS One* 2009; **4**(8): e6642.

17.   Monitor your heart rate with Apple Watch. https://support.apple.com/en-us/HT204666 (accessed October 22nd, 2020.

18.   Glasser JW, Hupert N, McCauley MM, Hatchett R. Modeling and public health emergency responses: lessons from SARS. *Epidemics* 2011; **3**(1): 32-7.

19.   Swanson KC, Altare C, Wesseh CS, et al. Contact tracing performance during the Ebola epidemic in Liberia, 2014-2015. *PLoS Negl Trop Dis* 2018; **12**(9): e0006762.
20.   Kang M, Song T, Zhong H, et al. Contact Tracing for Imported Case of Middle East Respiratory Syndrome, China, 2015. *Emerg Infect Dis* 2016; **22**(9): 1644-6.
21.   Hellewell J, Abbott S, Gimma A, et al. Feasibility of controlling COVID-19 outbreaks by isolation of cases and contacts. *Lancet Glob Health* 2020; **8**(4): e488-e96.
22.   Hirten RP, Stanley S, Danieletto M, et al. Wearable Devices Are Well Accepted by Patients in the Study and Management of Inflammatory Bowel Disease: A Survey Study. *Dig Dis Sci* 2020.
23.   Radin J, Wineinger NE, Topol EJ, Steinhubl SR. Harnessing wearable device data to improve state-level
real-time surveillance of influenza-like illness in the USA:
a population-based study. *Lancet Digital Health* 2020; **2**: e85–93.
24.   Ahmad S, Tejuja A, Newman KD, Zarychanski R, Seely AJ. Clinical review: a review and analysis of heart rate variability and the diagnosis and prognosis of infection. *Crit Care* 2009; **13**(6): 232.

Table 1. Baseline demographics of participants at enrollment.

	Cohort (n=297)
Age, mean (SD)	36.3 (9.8)
Body Mass Index, mean (SD)	25.6 (5.7)
Female Gender (%)	204 (69.4)
Race (%)	
Asian	73 (24.6)
Black	29 (9.8)
Other	43 (14.5)
White	108 (36.4)
Ethnicity (%)	
Hispanic	44 (14.8)
Baseline Positive SARS-CoV-2 nasal PCR (%)	20 (6.7)
Baseline Positive SARS-CoV-2 serum antibody (%)	28 (9.4)
Occupation* (%)	
Clinical non-Trainee	198 (68.0)
Clinical Trainee	36 (12.4)
Non-clinical Staff	57 (19.6)
Baseline Smoking Status (%)	
Current/Past smoker	35 (11.9)
Never/Rarely smoker	259 (88.1)
Baseline Immune Suppressing Medication (%)	4 (1.4)

PCR, polymerase chain reaction; SD, standard deviation
*Clinical trainee defined as a resident or fellow; clinical non-trainee defined as HCWs reporting at least one patient facing day during follow up, exclusive of resident and fellows; non-clinical staff defined as a HCW who did not report a patient facing day during follow up.

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Table 2. HRV parameters in participants with and without COVID-19 diagnosed based on SARS-CoV-2 nasal PCR swabs.

Parameter	Parameter Mean, ms (95% CI) COVID-19 Negative	Parameter Mean, ms (95% CI) COVID-19 Positive	Difference (95% CI)	p-value
MESOR	43.57 (41.40-45.40)	42.46 (38.90-45.79)	-1.12 (-4.22- 1.73)	0.46
Amplitude	5.30 (4.97-5.65)	1.23 (-1.94- 3.11)	-4.07 (-7.29- -2.07)	**0.006**
Acrophase	-2.44 (-2.49- -2.39)	-2.23 (-2.22- -4.24)	0.22 (-1.74- 2.43)	0.80

Table 3. Comparison of HRV parameters based on the time period before and after diagnosis.

Parameter	Period Around COVID-19 Diagnosis	Mean, ms (95% CI)	Period Around COVID-19 Diagnosis	Mean, ms (95% CI)	Difference (95% CI)	p-value
MESOR						
	7 Days Before	40.56 (35.98-45.46)	Uninfected	43.58 (41.88-45.37)	-3.03 (-6.98-1.02)	0.13
	7 Days After	40.77 (36.44-45.42)	Uninfected	43.58 (41.88-45.37)	-2.81 (-6.73-1.10)	0.17
	7-14 Days After	43.80 (40.01-47.65)	Uninfected	43.58 (41.88-45.37)	0.22 (-3.39- 3.73)	0.89
	7 Days Before	40.56 (35.98-45.46)	7-14 Days After	43.80 (40.01-47.65)	-3.24 (-9.63-3.33)	0.32
	7 Days After	40.77 (36.44-45.42)	7-14 Days After	43.80 (40.01-47.65)	-3.03 (-6.98-1.02)	0.13
	7 Days After	40.77 (36.44-45.42)	7 Days Before	40.56 (35.98-45.46)	0.217 (-3.39-3.73)	0.89
Amplitude						
	7 Days Before	0.29 (-4.68-1.73)	Uninfected	5.31 (4.95-5.67)	-5.02 (-10.14- -3.58)	**0.01**
	7 Days After	1.22 (-2.60-3.25)	Uninfected	5.31 (4.95-5.67)	-4.09 (-7.87- -1.93)	**0.01**
	7-14 Days After	3.80 (-0.64-7.88)	Uninfected	5.31 (4.95-5.67)	-1.51 (-5.79-2.35)	0.48
	7 Days Before	0.29 (-4.68-1.73)	7-14 Days After	3.80 (-0.64-7.88)	-3.51 (-10.50-0.22)	0.20
	7 Days After	1.22 (-2.60-3.25)	7-14 Days After	3.80 (-0.64-7.88)	-2.58 (-8.44-2.08)	0.34
	7 Days After	1.22 (-2.60-3.25)	7 Days Before	0.29 (-4.68-1.73)	0.93 (-1.92- 5.83)	0.58
Acrophase						
	7 Days Before	-1.67 (-3.78-1.19)	Uninfected	-2.44 (-2.49- -2.39)	0.78 (-1.4- 3.62)	0.45
	7 Days After	-0.53 (-2.39-5.89)	Uninfected	-2.44 (-2.49- -2.39)	1.92 (0.03-8.13)	0.48
	7-14 Days After	-2.63 (-3.95-1.19)	Uninfected	-2.44 (-2.49- -2.39)	-0.19 (-1.39-1.16)	0.70
	7 Days Before	-1.67 (-3.78-1.19)	7-14 Days After	-2.63 (-3.95-1.19)	0.96 (-1.85-4.32)	0.55
	7 Days After	-0.53 (-2.39-5.89)	7-14 Days After	-2.63 (-3.95-1.19)	2.10 (0.10-8.29)	0.35
	7 Days After	-0.53 (-2.39-5.89)	7 Days Before	-1.67 (-3.78-1.19)	1.14 (-1.34- 7.27)	0.58

Table 4. Number of participants reporting each symptom.

Symptom	Number of Participants (%)*
Fever or chills	11 (3.7)
Tired or weak	87 (29.3)
Body aches	47 (15.8)
Dry cough	32 (10.8)
Sneezing	52 (17.5)
Runny nose	43 (14.4)
Diarrhea	33 (11.1)
Sore throat	60 (20.2)
Headache	82 (27.6)
Shortness of breath	11 (3.7)
Loss of smell or taste	5 (1.7)
Itchy eyes	53 (17.8)
Other	26 (8.8)

* Precents add to greater than 100% as participants can report one or more symptom

Table 5. HRV parameters on the first day of reported symptoms compared to all other symptom free days.

Parameter	Parameter Mean, ms (95% CI) First Day of Symptoms	Parameter Mean, ms (95% CI) All Other Days	Difference (95% CI)	p-value
MESOR	46.01 (43.37-48.77)	43.48 (41.77-45.27)	2.53 (0.82-4.36)	**0.01**
Amplitude	2.58 (0.26-5.00)	5.30 (4.95-5.66)	-2.73 (-5.16- 0.31)	**0.01**
Acrophase	-2.21 (-2.83- -1.58)	-2.44 (-2.49- -2.39)	0.24 (-0.38- 0.88)	0.44

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Table 6. Comparison of HRV parameters based on symptom state and the time-period before and after the first day of reported symptoms.

| Parameter	Symptom State	Mean, ms (95% CI)	Symptom State	Mean, ms (95% CI)	Difference (95% CI)	p-value
MESOR						
	One day after 1st symptom day	44.52 (42.05-46.94)	Asymptomatic	43.49 (41.74-45.21)	1.03 (-0.64-2.67)	0.21
	One day before 1st symptom day	43.84 (41.41-46.15)	Asymptomatic	43.49 (41.74-45.21)	0.34 (-1.46-2.23)	0.73
	1st day of symptom	44.87 (42.42-47.18)	Asymptomatic	45.49 (41.74-45.21)	1.37 (-0.24-3.04)	0.11
	One day before 1st symptom day	43.84 (41.41-46.15)	One day after 1st symptom day	44.52 (42.05-46.94)	-0.69 (-3.72-2.47)	0.66
	1st day of symptom	44.87 (42.42-47.18)	One day after 1st symptom day	44.52 (42.05-46.94)	0.34 (-1.46-2.23)	0.73
	1st day of symptom	44.87 (42.42-47.18)	One day before 1st symptom day	43.84 (41.41-46.15)	1.03 (-0.64-2.67)	0.21
Amplitude						
	One day after 1st symptom day	5.47 (3.16-7.76)	Asymptomatic	5.32 (4.99-5.66)	0.15 (-2.21-2.37)	0.91
	One day before 1st symptom day	2.92 (0.50-5.33)	Asymptomatic	5.32 (4.99-5.66)	-2.40 (-4.75- -0.07)	0.056
	1st day of symptom	3.07 (0.88-5.22)	Asymptomatic	5.32 (4.99-5.66)	-2.25 (-4.38- -0.27)	**0.04**
	One day before 1st symptom day	2.92 (0.50-5.33)	One day after 1st symptom day	5.47 (3.16-7.76)	-2.55 (-6.64- 1.65)	0.25
	1st day of symptom	3.07 (0.88-5.22)	One day after 1st symptom day	5.47 (3.16-7.76)	-2.40 (-4.75- -0.06)	0.056
	1st day of symptom	3.07 (0.88-5.22)	One day before 1st symptom day	2.92 (0.50-5.33)	0.15 (-2.20- 2.37)	0.91
Acrophase						
	One day after 1st symptom day	-2.30 (-2.60- -2.00)	Asymptomatic	-2.45 (-2.50- -2.39)	0.14 (-0.15- 0.44)	0.33
	One day before 1st symptom day	-2.52 (-3.31- -1.71)	Asymptomatic	-2.45 (-2.50- -2.39)	-0.08 (-0.79-0.66)	0.86
	1st day of symptom	-2.26 (-2.73- - 1.79)	Asymptomatic	-2.45 (-2.50- -2.39)	0.19 (-0.24- 0.63)	0.36
	One day before 1st symptom day	-2.52 (-3.31- -1.71)	One day after 1st symptom day	-2.30 (-2.60- -2.00)	-0.22 (-1.11-0.70)	0.63
	1st day of symptom	-2.26 (-2.73- - 1.79)	One day after 1st symptom day	-2.30 (-2.60- -2.00)	0.04 (-0.36-0.46)	0.86
	1st day of symptom	-2.26 (-2.73- - 1.79)	One day before 1st symptom day	-2.52 (-3.31- -1.71)	0.26 (-0.40-0.92)	0.41
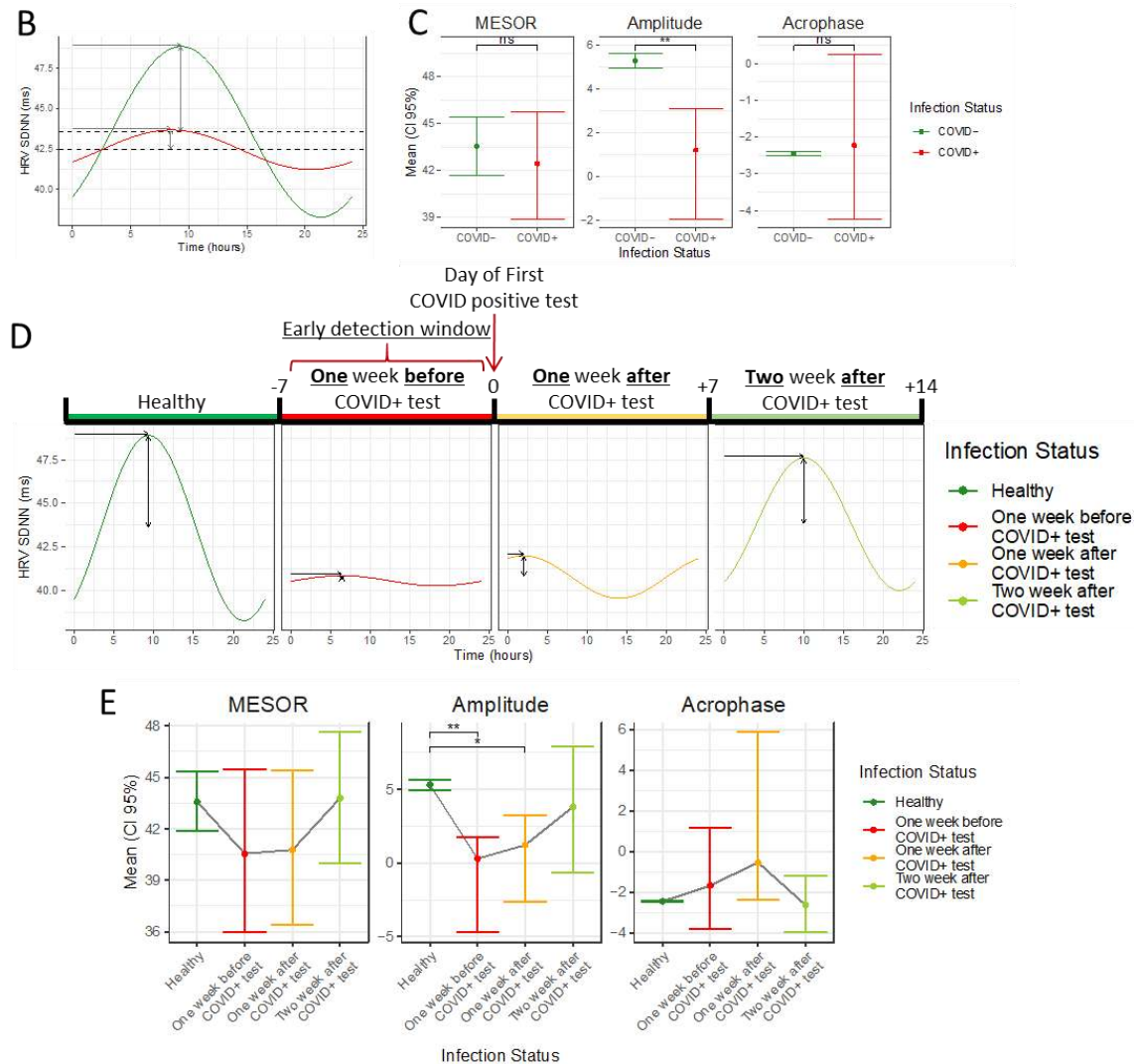
Figure 1: Relationship between HRV circadian rhythm and COVID-19 status.
Timeline (A) illustrates HRV measures from the time of COVID-19 diagnosis via nasal
PCR and during the following 2 weeks where subjects were deemed to be COVID-19+
(red), and were compared with measurements outside this window, where subjects
were deemed COVID- (green). Daily HRV rhythm (B) during days with COVID+ (red)
and COVID- (green) diagnosis, time (hours) is indicated by the x-axis while SDNN (ms)
is indicated by the y-axis. Plots (C) showing Mean and 95%CI for the parameters
defining the circadian rhythm: Acrophase, Amplitude and MESOR in COVID+ (red) and
COVID- (green) days. Daily HRV pattern (D) for days were subjects were healthy
(green), 7 days before COVID-19+ test (red), 7 days after COVID-19+ test (orange) and
7-14 days after COVID-19+ test (light green), time (hours) is indicated by the x-axis
while HRV (ms) is indicated by the y-axis. Mean and 95% CI for the Acrophase,
Amplitude and MESOR of the HRV measured on days were participants were Healthy
(green), 7 days before COVID-19+ test (red), 7 days after COVID-19+ test (orange) and
7-14 days after COVID-19+ test (light green).
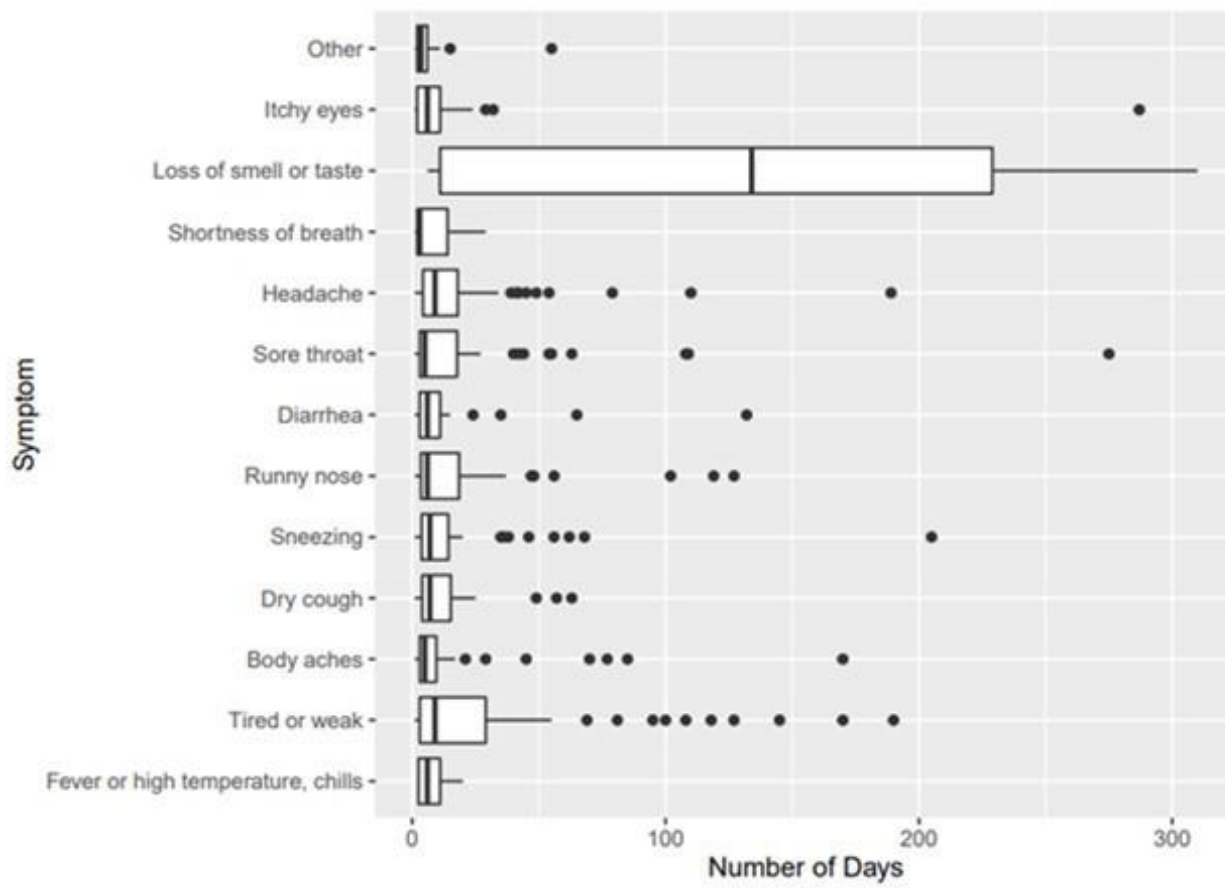**+**p<0.1;*p<0.05; **p<0.01; ***p<0.001; ns, not significant

Figure 2. Number of symptom days per participant when evaluating days when participants reported symptoms
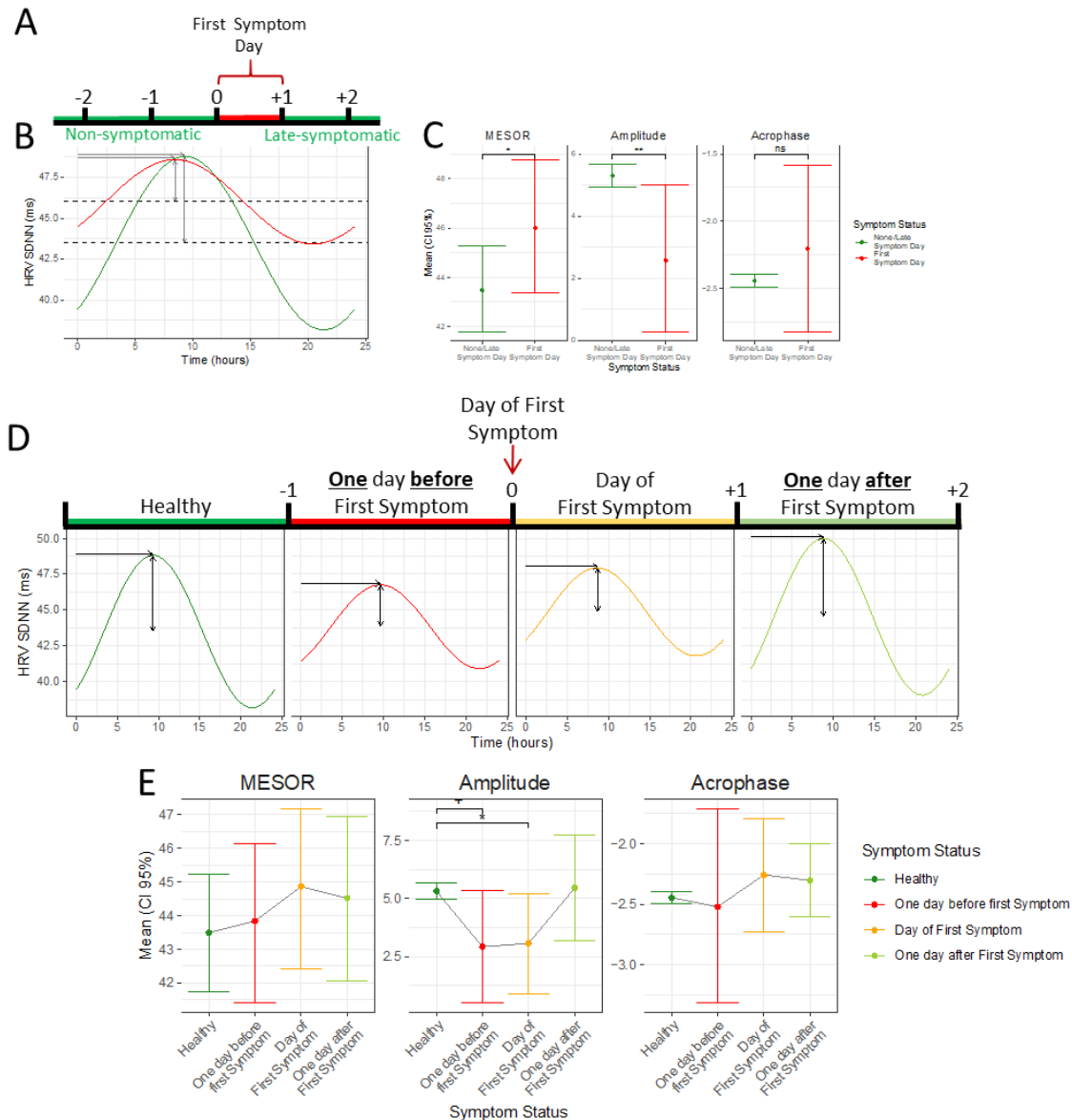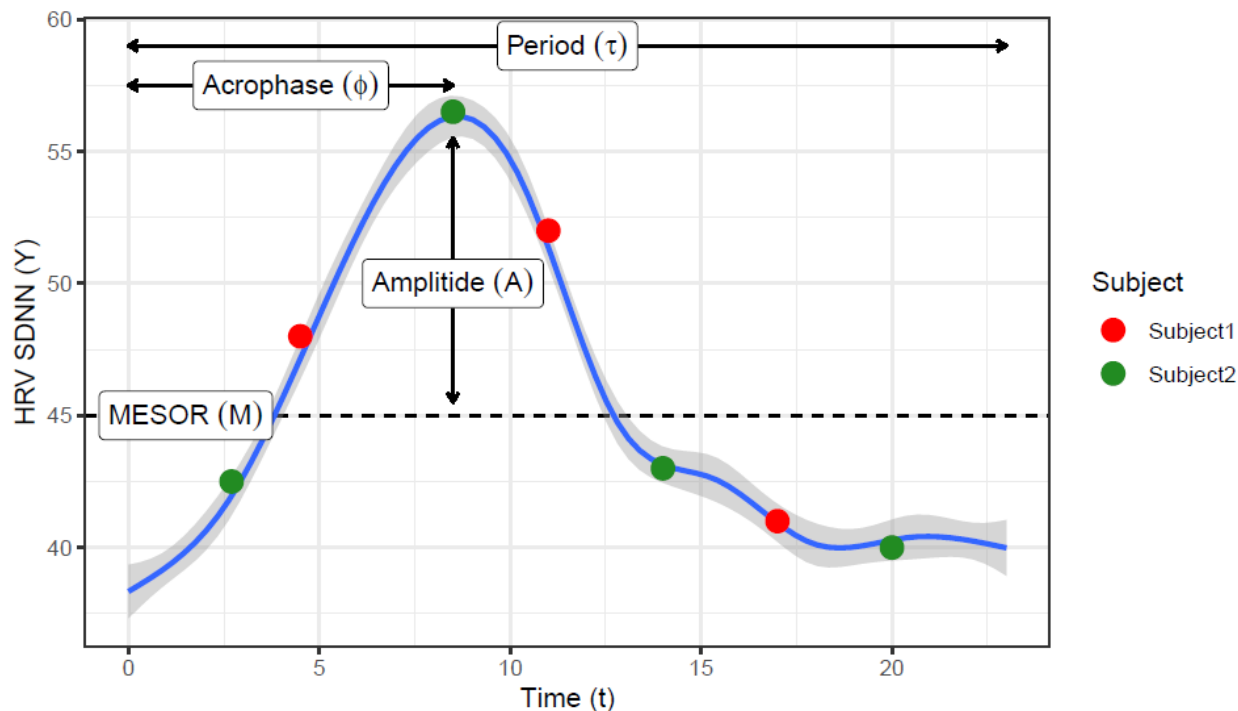
Figure 3: Relationship between HRV circadian rhythm and symptom onset. Timeline (A) illustrates timing of symptom onset, HRV profiles of the first-symptom day (red) were compared to all other days (green). Daily HRV rhythm (B) on day of first symptom (red) and non/late-symptom (green) days, time (hours) is indicated by the x-axis and HRV (ms) is indicated by the y-axis. Plots (C) showing Mean and 95%CI for the parameters defining the circadian rhythm: Acrophase, Amplitude and MESOR on first symptom (red) and non/late-symptom (green) days. Daily HRV pattern (D) for non/late-symptomatic days (green), the day before first symptom (red), day of first symptom (orange) and day after first symptom (light green), time (hours) is indicated by the x-axis while HRV (ms) is indicated by the y-axis. Mean and 95% CI for the Acrophase, Amplitude and MESOR of the HRV measured on non/late-symptomatic days (green), the day before first symptom (red), day of first symptom (orange) and day after first symptom (light green),

+p<0.1;*p<0.05; **p<0.01; ***p<0.001; ns, not significant

Supplementary Table 1. Infection related survey questions.

Survey Question	Survey Responses
Have you had any of the following symptoms in the past 24 hours? Check all boxes that apply:	Fever or high temperature, chills, tired or weak, body aches, dry cough, sneezing, runny nose, diarrhea, sore throat, headache, shortness of breath, loss of smell or taste, itchy eyes, none, other [insert], None of these
On a scale of 1 - 10, how bad do your symptoms feel today, compared to colds or flu that you have had in the past?	1 [Extremely mild symptoms], 2, 3, 4, 5, 6, 7, 8, 9, 10 [The worst symptoms that you have ever had]
If you have been tested for the Coronavirus by nasal PCR since starting this study, what was the result of your test:	Positive / Negative / I have not been tested for Coronavirus/Prefer not to say
If you were tested for the Coronavirus by nasal PCR since starting the study, what is the date you were tested?	Date: _____
If you have been tested for the Coronavirus by blood antibody since starting this study, what was the result of your test:	Positive / Negative / I have not been tested for Coronavirus/Prefer not to say
If you were tested for the Coronavirus by blood antibody since starting the study, what is the date you were tested?	Date: _____

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Supplementary Figure 1. Locally estimated scatterplot smoothing (loess) curve showing a daily circadian pattern on HRV measures. Such pattern can be represented by the COSINOR model using 3 parameters: the rhythm-adjusted mean (MESOR), half the extent of variation within a day (Amplitude) and the time of overall high values recurring in each day (acrophase). Red and green dots represent hypothetical sampling times though the day from two subjects that have the same daily curve, showing that features like maximum, range, or CV will be easily biased by the sampling time.