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Physiologic Response to the COVID-19 Vaccine Measured Using Wearable Devices

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Abstract

Background: The Pfizer COVID-19 Vaccine employs a novel technology which utilizes messenger Ribonucleic Acid (mRNA) to deliver viral proteins to the host and elicit a protective immune response, but the short-term physiologic response to the vaccine has yet to be studied using wearable devices.

Objective: Using wearable devices, we aim to characterize physiologic changes in response to COVID-19 vaccination in a small cohort of subjects.

Methods: In this prospective observational study, physiologic data from 19 internal medicine residents at a single institution who received both doses of the Pfizer COVID-19 vaccine were collected using the WHOOP strap 3.0 to determine participant baseline resting heart rate (RHR), heart rate variability (HRV), respiratory rate (RR), and sleep duration. Primary outcomes included change from baseline in HRV, RHR, RR, and sleep duration. Percent change and standard deviation from baseline (defined as the 30 days of wear prior to vaccination) were calculated for six days after the first and second dose of the Pfizer COVID-19 for all participants who met inclusion and exclusion criteria. Symptom type, severity, and duration were reported as secondary outcomes.

Results: In 19 individuals, mean age 28.8 (+/- 2.2), 53% female, percent change in HRV was decreased on day 1 (-13.44% +/- 13.62%) following administration of the first vaccine dose, and this response was blunted following dose 2 (-9.25% +/- 22.6%). RHR had a slight initial increase (+2.73% +/- 5.50%, +4.20% +/- 9.42%) after each dose and normalized after one day and RR showed no change compared to baseline after either vaccine dose. Sleep duration was increased up to 6 days post vaccine and peaked on day 3. Increased sleep duration prior to vaccine also demonstrated a more significant change in HRV compared to those who were sleep deprived (as determined by Pearson correlations). A more robust response in terms of symptom severity and duration was seen following dose 2. Arm soreness was the most reported symptom for both doses.

Conclusions: This represents the first observational study of the physiologic response in humans to any of the novel COVID-19 vaccines, as measured using wearable devices. We provide evidence that HRV decreases in response to both vaccine doses, with no consequent changes in RHR or RR. Sleep duration initially decreased following each dose and subsequently increased thereafter. Future studies with a larger cohort and comparison to other inflammatory and immune biomarkers, such as antibody response, will be needed to determine the true utility of this type of continuous wearable monitoring in regards to vaccine responses. Our data raises the possibility that increased sleep prior to vaccination may impact physiologic response, which could be used to track immune response to vaccination. Clinical Trial: NCT04304703: https://www.clinicaltrials.gov/ct2/show/NCT04304703

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Disclosures: none

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Introduction:

The development and administration of vaccines have been significant contributions to the advancement of public health over the last century and are responsible for a large reduction in mortality from infectious diseases and slowed the impact of pandemics in years past [1]. Despite this successful history, the rate of vaccination over recent years has been stagnant. This is in large part due to concern over the safety of vaccines, potential long-term side effects and society's lack of direct experience of prior pandemics and eradicated diseases [2]. Given the recent application of a newer vaccine technology, there has been an increased level of caution and concern towards the recently developed SARS-CoV-2 vaccine.

Mechanistically, vaccines leverage the human body's natural immune response to attain immunity to a viral infection. Therefore, it is reasonable to conclude that other physiologic parameters will be also influenced in conjunction with the immune system. A newer modality of vaccines utilize messenger Ribonucleic Acid (mRNA) delivered to the host cell, which in turn uses host cell machinery to synthesize viral proteins that are trafficked to the cell surface. Antibodies are then formed against this viral protein to protect the host from subsequent viral infection [3]. This technology was recently used to develop two novel COVID-19 mRNA vaccines encoding the spike protein of the SARS-CoV-2 virus [4]. This is different from previous vaccines using a live or attenuated viral vaccine to inoculate a host to garner immunity, as it carries no risk of creating a systemic viral infection, yet it does create a host immune response.

Despite sound scientific data showing the safety of vaccines in randomized controlled trials, there remains a high level of public concern, specifically regarding the frequency, severity and duration of both long-term and short-term symptoms. Short-term side effects are often described as symptoms related to an acute illness, when in actuality, they are merely physiologic manifestations of the innate immune response [5]. For example, the seasonal influenza vaccine commonly produces minor symptoms including body aches and fever, which are short-term and usually self-limiting [6]. Overall, it is important for the public to understand that such inflammatory responses are not complications of the vaccine but instead are quintessential for adaptive immunity and protection from the detrimental effects of a subsequent virus.

An estimated 21% of US adults report using wearables that objectively measure various physiologic parameters [7]. Although marketed for personal use, the widespread nature of these devices allow healthcare professionals to monitor physiologic changes in real-time in larger cohorts [8]. Previous studies have evaluated patients' inflammatory responses to the influenza vaccine in the context of cardiac autonomic function measured via resting heart rate (RHR) and heart rate variability (HRV), as a surrogate for an overall immunologic response. These studies demonstrated a decreased HRV correlated to an appropriate inflammatory/immunologic response, as measured by serum C-Reactive Protein (CRP) in the first two days following influenza vaccination [9-12]. Recent studies have shown the Pfizer-BioNTech COVID-19 vaccine to be 95% effective in protection against COVID-19 infection [4]. Eight weeks following vaccination, subjects showed high levels of IgM, and IgG anti-SARS-CoV-2 spike protein and receptor binding domain binding titers [13].

HRV is a direct measure of the interplay between the sympathetic and parasympathetic nervous system due to their effects on chronotropy (heart rate, HR) and is determined by the subtle variation in time between successive heart beats (R-R intervals). Decreases in HRV have been shown to predict the onset of sepsis in bone marrow transplant patients, who are highly susceptible to infection, and HRV decreases have been associated with increased mortality in sepsis patients treated in the intensive care unit [14-16]. These studies support the use of HRV changes as a clinical tool for remote monitoring of other infectious and inflammatory conditions [17]. This underscores the potential utility of surrogate measures, such as HRV, to monitor post-vaccination immune and inflammatory response [18].

The use of wearable devices allows for passive, real-time, and continuous assessment of HRV and RHR and thus has come into favor for use in the outpatient setting for various chronic diseases [19]. A recent study using the WHOOP wearable device was able to track physiologic changes, specifically an increase in

nocturnal RR and decrease in HRV, in individuals who reported COVID-19 infection. These changes were noted 2 days before symptom onset in 20% of subjects and 80% of the cohort after symptom onset [20]. Other studies have used HRV and other physiologic metrics measured by wearable devices to prospectively and retrospectively predict and identify COVID-19 infection (confirmed by positive testing) [12, 21, 22]. Therefore, we postulated that it would be possible to track an array of physiologic responses following COVID-19 vaccination as an indicator of the body's immune response.

Methods:

Study Design

The primary objective of this study is to determine the physiologic changes, as measured by HRV, RR, RHR, and duration of total, rapid eye movement (REM) and deep sleep, following the first and second doses of the Pfizer-BioNTech COVID-19 vaccine. The secondary objective will evaluate the symptomatic response in participants to each dose, in terms of type, severity, duration, as well as prophylactic analgesic use.

Study Procedures

Thirty-eight internal medicine residents were enrolled in a 12-month prospective observational study where subjects were given a WHOOP Strap 3.0 to wear in order to measure various physiologic parameters. Eligible participants were surveyed to disclose their vaccination dates for the novel Pfizer-BioNTech COVID-19 vaccine administered at Penn State Hershey Medical Center, along with type, severity, and duration of symptoms following each vaccines dose (spread mean 19.6 +/- 2.8 days apart).

Inclusion criteria included subjects concurrently enrolled in a clinical trial (NCT04304703) using the WHOOP device, transmitted at least 80% of physiologic data during the study period including at least 24 of 45 days prior to dose one (to establish baseline metrics), and all data for the 6 days following vaccine dose one, dose two, or both. These data cutoffs were chosen based on published data using the WHOOP device for establishing a change from baseline in RR [23]. Subjects were excluded if they did not or were unable to disclose the dates of vaccination. Of the 38 participants, 18 (47.4%) individuals met inclusion and exclusion criteria to be included in the analysis of dose one and 13 (34.2%) participants met criteria to be included in analysis of the second dose. Data were blinded to study investigators for analysis. Recorded demographics included age, gender, and year of residency training. Primary outcomes were: percent change from baseline in HRV, RHR, RR, total sleep duration, REM sleep duration, deep sleep duration, total sleep cycles, and sleep disturbances. Secondary outcomes were: symptoms (type, severity, duration) following each dose, and prophylactic analgesic use.

Data collection was approved by the Institutional Board Review at Penn State Hershey Medical Center (STUDY14522).

Physiologic Metrics

The WHOOP Strap is a wearable, waterproof, and rechargeable device containing a photoplethysmogram, accelerometer, capacitive touch sensor, and gyroscope that can be worn 24-hours per day, usually on the wrist, lasts 5 days between charges, and wirelessly transfers data to mobile devices running the associated WHOOP application.

The WHOOP strap 3.0 has been externally validated for tracking of HRV, RHR, RR and sleep stage duration [24]. Heart rate variability (HRV), a measure of autonomic tone, or the balance of the effects of the sympathetic and parasympathetic nervous system on the cardiovascular system, is measured by root mean square standard deviation (RMSSD) of successive heart beats (R-R interval difference) during the last 5 minutes of the last cycle of deep sleep [25]. This has been shown to be a standardized and reproducible time frame for measurement that minimizes intrinsic and extrinsic stimuli that can influence and distort HRV

readings [26].

Resting heart rate (RHR) is defined as the measure of average heart beats per minute during complete rest, and is also measured during the last 5 minutes of the last cycle of deep sleep. Respiratory Rate (RR) is defined as the median value of respirations per minute and is derived each night during the main sleep period via photoplethysmography. This is based on respiratory sinus arrhythmia, or the variability in heart rate in synchrony with respiration, by which the R-R interval on an ECG is shortened during inspiration and prolonged during expiration [27].

Sleep is characterized by generalized cardiovascular activation and baroreflex sensitivity [28]. Sleep stages including rapid eye movement (REM) and non-REM phases, the latter of which can be broken down further to deep (also referred to as slow wave sleep; SWS) or light sleep. Both REM and deep sleep are considered restorative sleep, in which the autonomic nervous system dictates both sympathetic and parasympathetic nerve activity to allow for physical and mental recovery [26]. REM sleep exhibits high muscle and lumbar sympathetic nerve activity, sometimes exceeding sympathetic nerve activity seen during wakefulness with burst of elevated blood pressure and heart rate. Conversely, deep sleep is more stable with reduced blood pressure variability, constant autonomic activity, lower cardiac output and regular minute ventilation (respiratory rate x tidal volume), offering a highly standardized condition for reproducible HRV assessment [28]. Measuring HRV during deep sleep has been identified as the most reliable measurement period, devoid of both external (environmental) and internal (emotional) factors that can affect autonomic tone, and therefore HRV [26]. The WHOOP device samples the entirety of sleep duration in individuals to determine sleep stages based on HR and HRV changes, and has been shown to accurately predict sleep stages when tested against the gold standard of polysomnography and continuous electrocardiogram [24].

Statistical Analysis

Due to small sample size, we did not perform formal statistical testing for significance, therefore no *P*-values are presented. Instead, we defined a significant change from baseline to be greater than 5% a priori. This cutoff was set based on recent findings in two studies: (1) changes in RR and other physiologic parameters in COVID-19 positive individuals, which were used to develop a predictive algorithm for COVID-19 infection risk stratification [23], and (2) precision measurements of HR, RR, HRV, and REM sleep stage duration using the WHOOP device were found to have less than 10% error [24].

Baseline metrics were calculated from all participants who met inclusion criteria (total n=19; 18 participants with data post dose 1 and 13 participants with data post dose 2). The percent change of each metric for each participant in the dataset was averaged together for the overall percent change of that metric for each day, d (Equation 1). In Equation 1, b_n is given as the average of the metric from the baseline period for participant n and x_n is the value of the metric on the day, d, being calculated post vaccine dose.

Equation 1

$$\left(Mean\ Percent\ Change\right)_d = \frac{\sum_{i=0}^{n} \left(\frac{b_n - x_{nd}}{b_n} \times 100\,\%\right)}{n}, b_n = \frac{\sum i_{n_0}}{n_o}$$

In order to determine the effect of sleep for the week (7 days) leading up to the vaccine on the physiological effects of the vaccine, we computed Pearson correlations between hours of sleep in the 7 days prior to vaccine Dose 1 and the percent changes of the physiological measurements post vaccine Dose 1 [29].

Symptoms were aggregated and the density of the self-reported duration of symptoms was calculated [30].

Results:

Physiologic Response to COVID-19 Vaccination, by Dose

Of the 19 subjects included in the final analysis, 53% were female, with an age range of 26-35 years; mean and median age of 28.8 (+/- 2.2) and 29 years, respectively. Baseline metrics were collected for all participants up to 45 days prior to vaccination Dose 1 (**Table 1, Supplementary Figure 1**). Subjects included in analysis had mean baseline RHR of 63.09 +/- 6.36 beats per minute (bpm), HRV of 52.09 +/- 21.58 milliseconds (ms), RR of 16.27 +/- 1.23 respirations per minute (rpm). During the baseline assessment period, subjects slept, on average, 6 hours and 43 minutes per might (+/- 35 minutes), of which 21.99% (1 hour and 28 minutes) was REM sleep and 19.1% (1 hour and 17 minutes) was deep sleep. Although interindividual variability in metrics had a wider range, intraindividual variability was much lower, most notably in nocturnal RR, with an intraindividual standard deviation of 0.37 +/- 0.12 rpm Percent change in HRV, RHR, RR were calculated for the 6 days following vaccine Dose 1 and Dose 2.

For Dose 1 (n=18), there was a reduction in HRV on day 1 (-13.44 +/- 13.62%) and slight decrease on day 2 (-3.74 +/- 34.63%) post-vaccination. HRV returned to baseline on Day 3 and remained at baseline thereafter (**Figure 1A, blue; Table 2**). There was no significant change in RHR and RR compared to baseline in the 6 days following vaccination (**Figure 1B, C, blue; Table 2**). RHR change from baseline following Dose 1 ranged from +2.73% (+/- 5.5%) on Day 1 to -2.23% (+/- 7.31%) on Day 3. RR changes from baseline showed an even narrower range: +1.34% (+/- 1.98%) on Day 2 to -1.73% (+/- 2.56%) on Day 4. Notably, overall RR changes on Day 1 were minimal, at +0.16% (+/- 1.95%).

For Dose 2 (n=13), HRV decreased on Day 1 (- 9.25 +/- 22.69%) but quickly normalized to baseline by Day 6 and did not show substantial deviation from baseline through Day 6 (**Figure 1A, magenta; Table 3**). Similar to Dose 1, there was no significant change in RHR and RR in response to Dose 2, with both metrics remaining at baseline from Day 1 to Day 6 (**Table 3**).

Post-Vaccination Changes in Sleep

Total, REM, and deep sleep duration (in hours) were measured for all subjects for 6 days following vaccine administration. Total sleep duration followed the same overall pattern for both vaccine doses: an initial decrease was observed on Day 1 (Dose 1: -8.41% +/- 22.96%, Dose 2: -2.1% +/- 26.8%) followed by an increase (above baseline) on Days 2, 3 and 4, with subsequent return to baseline on Day 5-6 (**Figure 2A; Table 2, 3**). The sleep duration change following Dose 1 peaked on Day 3 at +9.41% (+/- 21.6%), and this peak occurred on Day 4 at +9.22% (+/- 28.37%) following Dose 2. Total sleep duration was proportional to time in bed, and thus showed similar trends in response to vaccine Dose 1 and Dose 2, thus did not influence sleep duration.

Patterns of change in REM and deep sleep did not follow the same pattern as total sleep duration. REM sleep remained slightly under baseline for Dose 1 from Day 1-6 (range: -2.7% +/- 31.1% on Day 5 to -16.98% +/- 29.41% on Day 6). REM sleep was far more variable following Dose 2, showing increases on Day 1 (+13.79% +/- 45.88%), 3 (+12.67% +/- 36.41%, and 5 (+6.12% +/- 32.02%) and decreases on Day 2 (-8.73% +/- 39.57%) and Day 6 (-8.35% +/- 43.06%) (**Figure 2B; Table 2, 3**).

The percent change of deep sleep increased on Day 1 following Dose 1 (+9.64% +/- 26.30%) and then remained near baseline for Dose 1 aside from a mild decease on Day 5 (-6.05% +/- 19.58%). Deep sleep percentage was steady following Dose 2 until Day 6, where a moderate decrease was observed (-11.37% +/- 24.40%). Minimal changes in deep sleep following the second dose were observed (**Figure 2C; Table 2, 3)**.

Sleep impact on HRV

Given the known effect of sleep duration and sleep deprivation on immunologic responses with other vaccines, specifically Hepatitis B, we were interested in assessing whether sleep prior to vaccination had an overall effect on physiologic response, measured by change in HRV [31, 32]. Sleep duration was evaluated 7 days preceding vaccine administration. Higher hours of sleep the week (7 days) prior to receiving the first

dose of the vaccine is moderately correlated with higher percent change in HRV on the two days following vaccine Dose 1 (Pearson R = 0.570 day 1, 0.494 day 2).

Symptom Type, Severity, and Duration

An array of symptoms was reported by participants ranging from arm soreness to fatigue and body aches. A greater frequency and duration of symptoms were reported following Dose 2 (**Figure 3A, B**). Arm soreness was reported in greater than 60% of subjects for both doses. The majority symptoms subsided by hour 60 post-vaccination (**Figure 3A**). The mean symptom duration following Dose 1 was 49.7 +/- 49.2 hours and for Dose 2 this decreased to 34.1 +/- 13.3 hours. The most frequent symptom duration after Dose 1 and Dose 2 was 24 hours. Overall, post-vaccination symptoms would be classified as mild to moderate, as no severe adverse reactions such as angioedema/other allergic reactions requiring urgent treatment were reported.

Analgesic effects on HRV, sleep, symptoms

Interestingly, 0 of 19 subjects pre-medicated with anti-analgesic medications (ibuprofen or acetaminophen) prior to Dose 1, but this number increased to 7 of 13 (54%) that pre-medicated prior to Dose 2.

While we are not adequately powered to do a statistical analysis between the participants who self-medicated with an anti-analgesic medication prior to Dose 2 and the participants who took no medication prior to Dose 2, we provide an observational analysis in Supplementary Figures 1 and 2. Overall changes in HRV were the same amongst both groups (pre-medication versus no pre-medication) (**Supplementary Figure 2A**). Those who did not pre-medicate had a greater response (increase) in RR on Day 1 and Day 2; overall RR was unaffected when both groups were analyzed together) (**Supplementary Figure 2B**). RHR had a slightly greater increase on Day 1 for those who did pre-medicate) (**Supplementary Figure 2C**). The group that pre-medicated had both a greater initial decrease and compensatory increase in total sleep duration) (**Supplementary Figure 3A**). This group also had higher percentage of REM and deep sleep in the days after receiving dose 2, which were most prominent on Day 1 both (**Supplementary Figure 3B, 3C**).

The duration of all reported symptoms between the groups were similar: participants without medication experienced symptoms of a duration 30.0 +/- 13.4 hours and participants who self-medicated prior to Dose 2 experienced symptoms of a duration 37.7 +/- 10.0 hours. There was no significant difference in symptom severity amongst the two groups, suggesting that pre-medication may not prevent a worse symptomatic response.

Discussion:

In this small, prospective, observational study of vaccination effects measured by the WHOOP wearable device, decreases from baseline in HRV were most pronounced on Day 1 and 2 for vaccine Dose 1 and Day 1 only for vaccine Dose 2, whereas RR and RHR were overall unaffected. Sleep duration had similar trends for both vaccine doses: an initial decreased on Day 1, followed by a compensatory increase from Day 2-4, and subsequent return to baseline. Sleep deprivation was associated with a blunted HRV response, which could be a marker of decreased inflammatory or immune response, and pre-medication was associated with less change in RR and increases in REM and deep sleep percentages. Vaccine-related symptoms were of mild to moderate severity, with arm soreness being the most reported symptom.

We hypothesized HRV, a surrogate marker of autonomic tone, would change in response to vaccination as it has been shown to correlate with clinical outcomes, such as ICU mortality in sepsis [14-16]. HRV change from baseline was the most prominent signal in our study population, as the presumed immune response would alter autonomic tone with differential effects on intrinsic sympathetic and parasympathetic outflow. In this case, a more robust response (greater magnitude decrease and duration) was seen following Dose 1 than Dose 2 (**Figure 4**). Return to baseline was seen by Day 3 for Dose 1 and Day 2 for Dose 2, indicating a relatively fast return to baseline, but with a noticeable effect immediately following vaccination. These

changes in HRV may be of clinical significance. The potentiation of HRV changes with sleep deprivation, and could be explored in future studies to correlate the possible relation with an immune response.

Sleep duration is a modifiable factor that may improve immune response due to physiologic stress [33]. Sleep deprivation leads to chronic up-regulation of pro-inflammatory cytokines, resulting in greater physiologic stress on the human body [34]. When an additional stressor, such as a vaccine, is introduced, the magnitude of the immune response may be dampened [35]. Previous studies have shown increased sleep was associated with a greater short-term antibody response for various vaccines such as H1N1, hepatitis A, hepatitis B and influenza [31, 36-38]. Based on these studies, we propose a higher percent change in HRV equates to a more robust immune response, which may be more protective against infection. This would require further investigation but could be a potential surrogate marker for immune system activation from vaccination (**Figure 5**) [18]. The overall decrease in HRV is important to note as this is likely due to an increased parasympathetic tone as the body generates an immune response to the vaccine itself. This demonstrates sleep can potentially impact the immune response to the COVID-19 vaccine and can possibly be used to potentiate the effectiveness of vaccination.

There was relatively no change in both RR and RHR in response to vaccination (**Figure 1B, 1C**). This is of particular interest given spikes in RR and decreased HRV have been suggested to be clinically relevant in prediction of COVID-19 infection [12, 21-23]. Often individuals who have symptoms following vaccination for other infections, such as influenza, avoid vaccination in the future because they feel they have similar symptoms to having the infection itself. This provides objective evidence there is distinct difference, namely in RR and RHR, between COVID-19 vaccination and contracting the infection. Although we did not directly collect data on oxygen saturation or rates of hypoxia, we propose that this finding is present only with true COVID-19 infection, and not with mRNA vaccination against COVID-19. Symptom duration and severity is slightly greater in our study as compared to published reports of the adverse effects of the Pfizer-BioNTech COVID-19 vaccine, and notably did not include any severe reactions to the vaccine [39]. This could be explained by the much smaller sample size, age and demographic of the participants.

While no subjects reported use of analgesics before Dose 1, just over half of subjects pre-medicated prior to the second vaccine dose. This was likely due to early reports and social media activity regarding a perception of an increased severity of symptoms following vaccine Dose 2. Our data showed no difference in HRV amongst those who pre-medicated versus those who did not. Medication was associated with less nocturnal RR changes, and more prominent changes in sleep and REM/deep sleep durations. This may suggest analgesics allow for better restorative sleep (REM and deep sleep stages) and may be associated with less fluctuation in RR, although they do not greatly affect heart rate parameters (HRV and RHR) (**Supplementary Figures 2, 3**). Interestingly, symptom duration and severity were no different between the groups, but this was likely limited by the size of the study, and a larger cohort may have detected less symptom duration and severity with pre-medication. There are some concerns these medications can actually lessen an individual's physiologic response when taken prior to vaccination, although larger scale studies are needed to validate these findings [40].

Limitations and Future Studies

Our study involved a small cohort (n=19) of relatively healthy, young adults within a single medical center. A larger study population for a similarly designed study may validate this initial work and be adequately powered, for formal statistical analysis, to detect more subtle physiologic changes in response to vaccination. A more diverse set of subjects with a larger age range may show different results. Current vaccination recommendations from the Centers from Disease Control and Prevention are focused on people above 65 years old with significant comorbidities, in addition to frontline healthcare workers. Thus it would be important to study this population as well. Stratifying vaccine response by baseline comorbidities, medications, and other demographics would also help discern which parameters are the most important to monitor. A larger study cohort would also allow for determination of vaccine effects amongst different ethnicities as minority groups are unequally affected by the consequences of COVID-19 [41]. This study

cohort may have selected for a group that may be sleep deprived at baseline, which is common in medical trainees and known to be associated with physiologic changes, therefore would need further validation in non-medical residents [42].

As outlined in Figure 5, correlating changes in HRV, RHR, and RR with serum levels of inflammatory or immunologic markers such as CRP and antibody titers in further studies would help determine the potential utility to track overall response to vaccine. Although similar, and likely related, there is a clear difference between physiologic changes as measured by HRV, markers of inflammation or inflammatory response (such as CRP measures), and innate immune response leading to antibody development and eventual host immunity. We report a cumulative perturbation in physiologic homeostasis due to vaccination using wearable device measured HRV. Previous studies have linked changes in HRV to changes in CRP levels and antibody titers, therefore we hypothesize that our observations could be clinically relevant to easily and conveniently track important responses to vaccination, such as immune response. Further studies using collected serum samples to detect inflammatory markers as well as serial measurement of antibody titers post vaccination could help delineate this connection and possibly validate HRV as an easily measurable surrogate to detect a clinically meaningful immune response (**Figure 5**).

Conclusion:

We present the first observational study on the physiologic response in humans to the COVID-19 vaccine measured using wearable devices. We provide evidence HRV decreases in response to both vaccine doses, with no consequent changes in RHR or RR. Sleep duration initially decreased following each dose and subsequently increased thereafter. Future studies with a larger cohort and comparison to other inflammatory and immune biomarkers, such as antibody response, will be needed to determine the true utility of this type of continuous wearable monitoring in regards to vaccine responses. Our data raises the possibility that increased sleep prior to vaccination may impact physiologic response, which could be used to track immune response to vaccination.

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Tables and Figures:

Table 1. Baseline physiological and sleep metrics intraindividual Mean and Standard Deviation.

	Intraindividual Mean (Mean +/- SD)	Intraindividual Standard Deviation (Mean +/- SD)
Heart Rate Variability (ms)	52.09 +/- 21.58	13.16 +/- 6.94
Resting Heart Rate (bpm)	63.09 +/- 6.36	4.95 +/- 1.50
Respiratory Rate (rpm)	16.27 +/- 1.23	0.37 +/- 0.12
Hours of Sleep (hours)	6.71 +/- 0.58	1.48 +/- 0.39
Percent of REM sleep (%)	21.99 +/- 6.71	6.49 +/- 1.23
Percent of Deep sleep (%)	19.10 +/- 2.15	3.81 +/- 0.66

Table 2. Percent Changes from Baseline in physiological and sleep metrics for 6 days post-vaccine dose #1 (n=18)

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
Heart Rate Variability	-13.44 +/- 13.62 %	-3.74 +/- 34.63 %	+4.21 +/- 27.23 %	-1.32 +/- 30.39 %	-4.35 +/- 26.79 %	-2.80 +/- 27.46 %
Resting Heart Rate	+2.73 +/- 5.50 %	-1.10 +/- 6.93 %	-2.23 +/- 7.31 %	+0.72 +/- 8.80 %	+0.26 +/- 8.68 %	+2.02 +/- 11.48 %
Respiratory Rate	+0.16 +/- 1.95 %	+1.34 +/- 1.98 %	-0.23 +/- 2.70 %	+0.02 +/- 3.81 %	-1.73 +/- 2.56 %	-1.04 +/- 2.29 %
Hours of Sleep	-8.41 +/- 22.96 %	+5.00 +/- 18.27 %	+9.41 +/- 21.60 %	+7.74 +/- 17.81 %	3.21 +/- 24.38 %	-3.21 +/- 27.54 %
Percent of REM sleep	-4.94 +/- 37.65 %	-6.53 +/- 30.06 %	-5.13 +/- 33.34 %	-6.70 +/- 19.62 %	-2.70 +/- 31.10 %	-16.98 +/- 29.41 %
Percent of Deep sleep	+9.64 +/- 26.30 %	+3.08 +/- 23.00 %	+4.11 +/- 12.66 %	+4.58 +/- 15.28 %	-6.05 +/- 19.58 %	-2.38 +/- 17.53 %

Table 3. Percent Changes from Baseline in physiological and sleep metrics for 6 days post-vaccine dose #2 (n=13)

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
Heart Rate Variability	-9.25 +/- 22.69 %	+7.48 +/- 32.44 %	-1.30 +/- 19.44 %	-5.56 +/- 13.70 %	-7.76 +/- 13.12 %	+2.19 +/- 30.22 %
Resting Heart Rate	+4.20 +/- 9.42 %	+0.82 +/- 8.27 %	-0.15 +/- 5.15 %	+1.37 +/- 6.17 %	+4.63 +/- 10.38 %	+1.70 +/- 12.83 %
Respiratory Rate	+0.19 +/- 4.10 %	+1.07 +/- 6.44 %	-0.26 +/- 4.00 %	+0.15 +/- 3.22 %	-0.54 +/- 3.63 %	+0.13 +/- 3.06 %
Hours of Sleep	-2.10 +/- 26.18 %	+5.33 +/- 17.71	+6.06 +/- 23.84 %	+9.22 +/- 28.37 %	-4.58 +/- 20.45 %	+0.49 +/- 12.30 %
Percent of REM sleep	+13.79 +/- 45.88 %	-8.73 +/- 39.57	+12.67 +/- 36.41 %	+0.64 +/- 37.99 %	+6.12 +/- 32.02 %	-8.35 +/- 43.06 %
Percent of Deep sleep	4.00 +/- 25.02 %	-1.70 +/- 19.21	+3.56 +/- 20.31 %	-6.01 +/- 22.09 %	+3.42 +/- 21.31 %	-11.37 +/- 24.40 %

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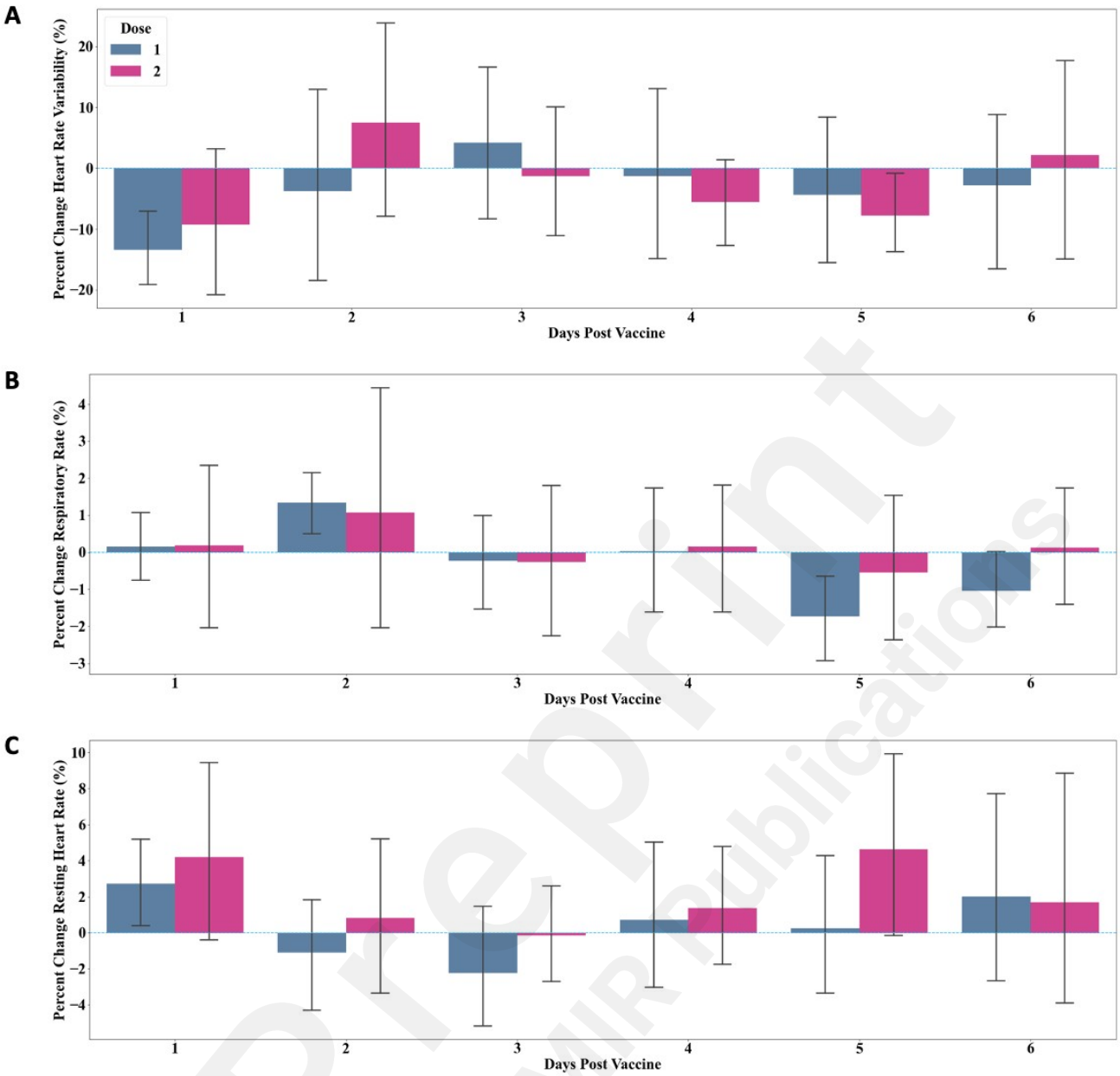

Figure 1: Percent change from baseline in (A) Heart Rate Variability, (B) Respiratory Rate, and (C) Resting Heart Rate, measured 6 days following COVID-19 Vaccine Dose 1 (blue) and 2 (magenta). Data is reported as mean +/- standard deviation.

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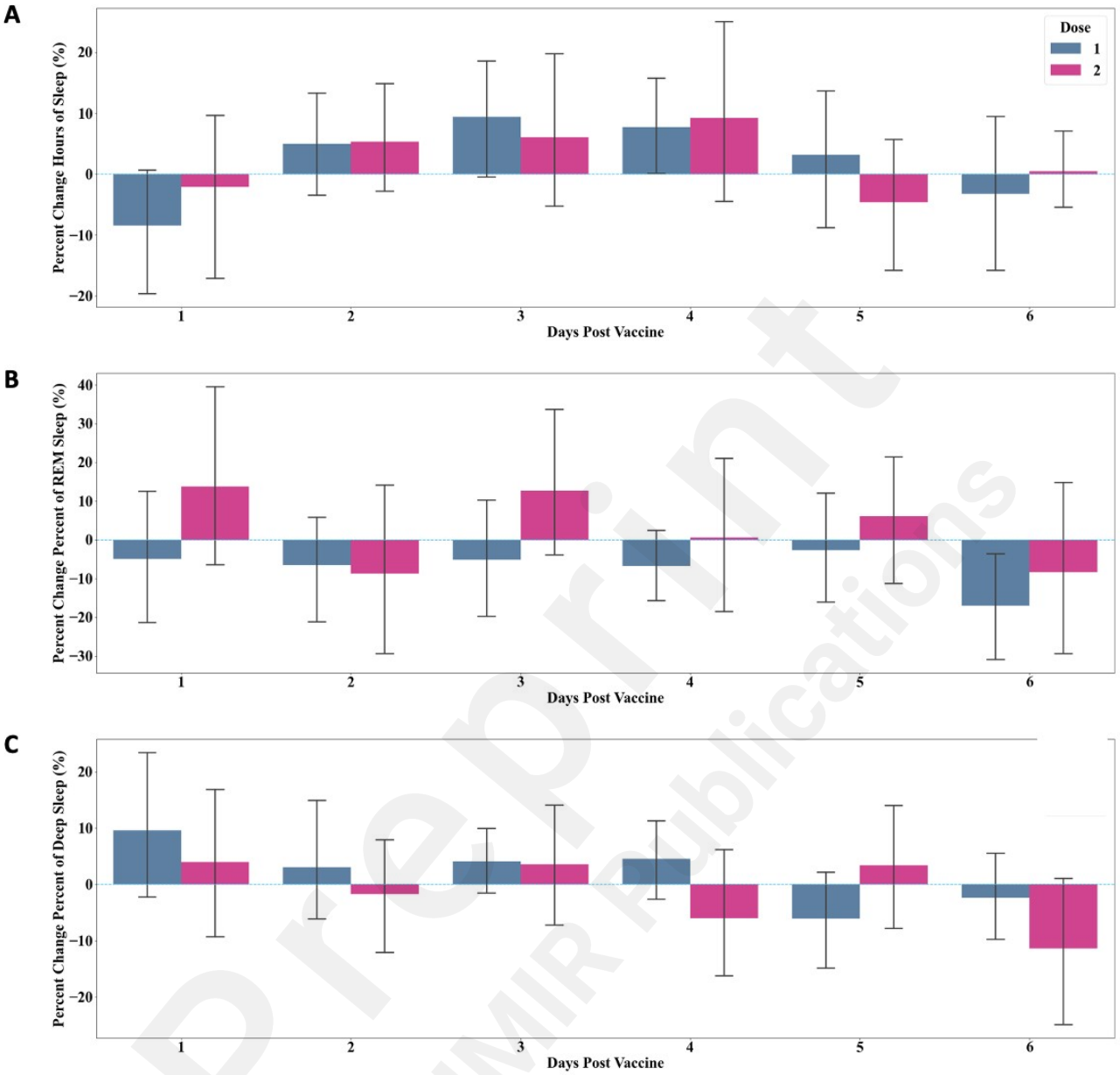

Figure 2: Percent change from baseline in (A) Total Sleep Duration, (B) REM Sleep Duration, and (C) Deep Sleep Duration, measured 6 days following COVID-19 Vaccine Dose 1 (blue) and 2 (magenta). Data is reported as mean +/- standard deviation.

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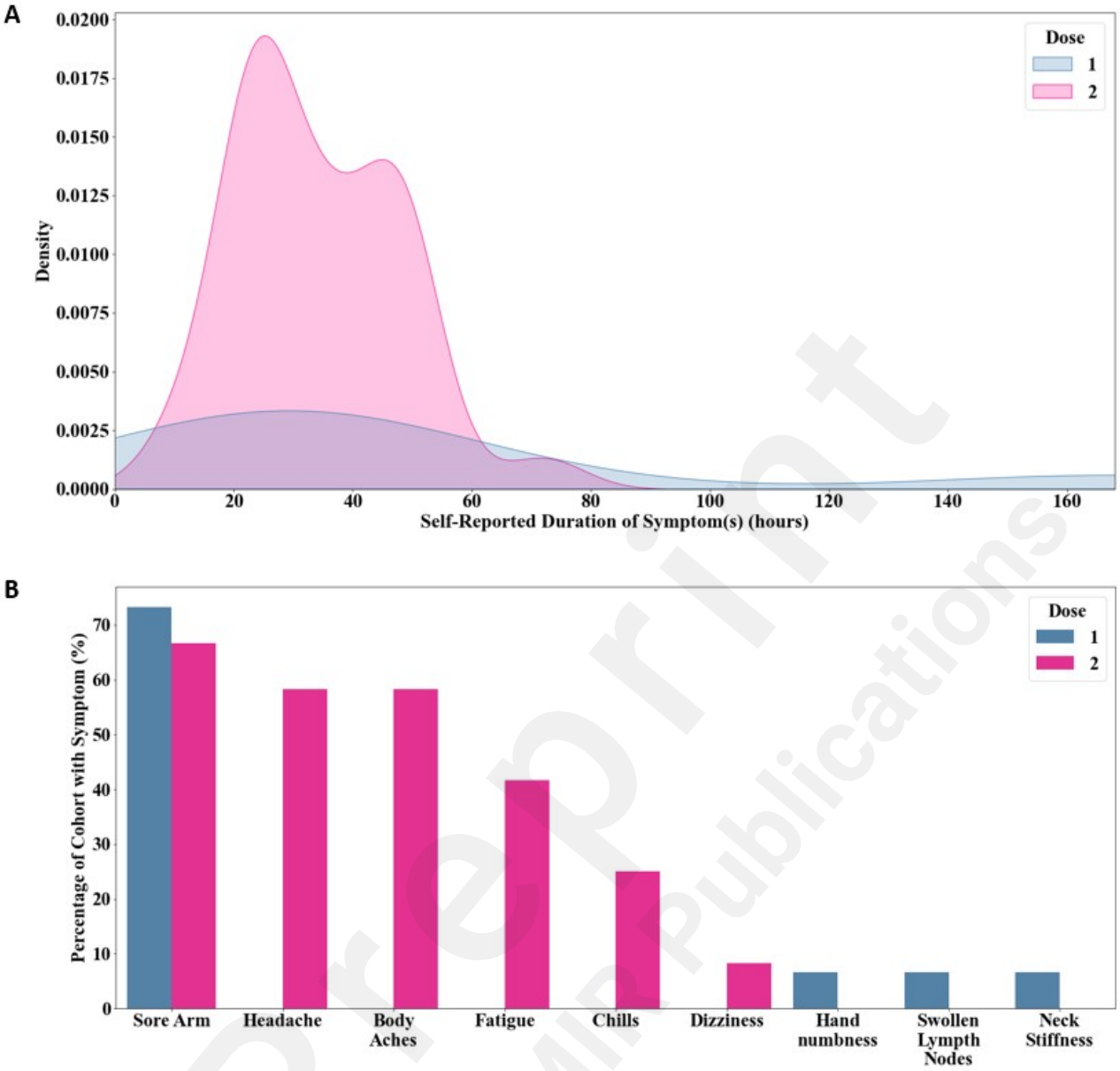

Figure 3. (A) Self-reported symptom duration following Dose 1 and Dose 2 of COVID-19 vaccine. (B) Type of symptoms experienced by participants, by vaccine dose.

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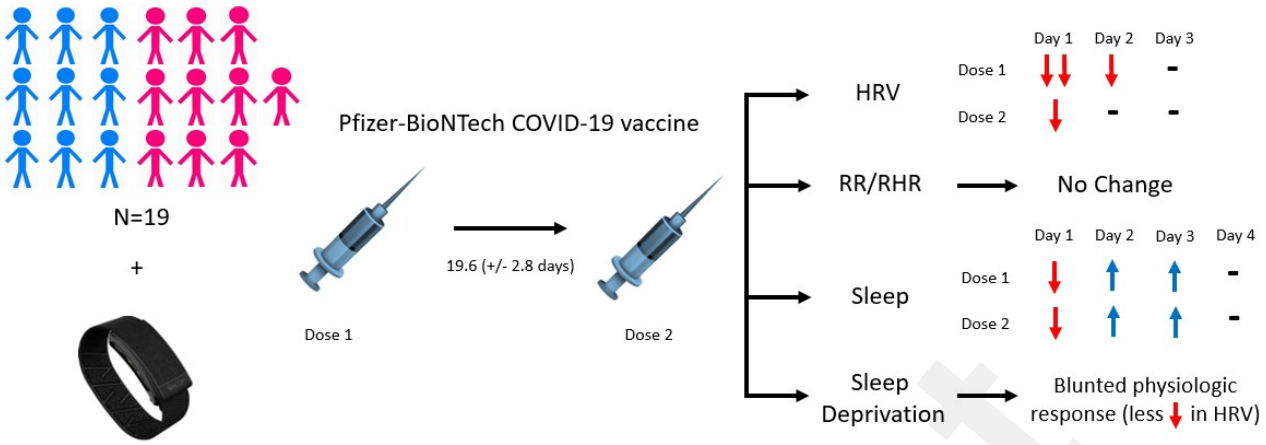


Figure 4. Graphical Abstract: 19 subjects, 53% female, who were vaccinated with two doses of the Pfizer-BioNtech COVID-19 vaccine (mean time between doses 19.6 days +/- 2.8 days), transmitted continuous physiologic data via the WHOOP device. Changes from baseline were observed in HRV, and were most pronounced on Day 1 and 2 for Dose 1 and Day 1 only for Dose 2. RR and RHR were unaffected following vaccination. Sleep duration initially decreased on Day 1 post vaccine Dose 1 and Dose 2, with a compensatory increase from Day 2-4, prior to return to baseline. Sleep deprivation was associated with a blunted HRV response and pre-medication was associated with less change in RR and increases in REM and deep sleep percentages.

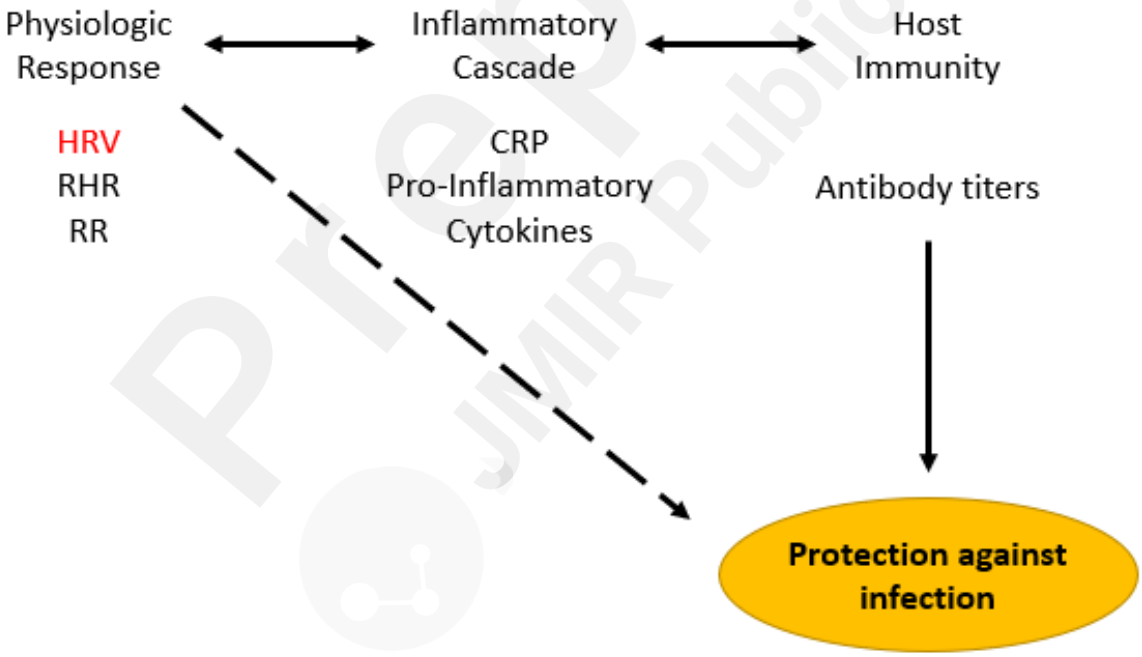
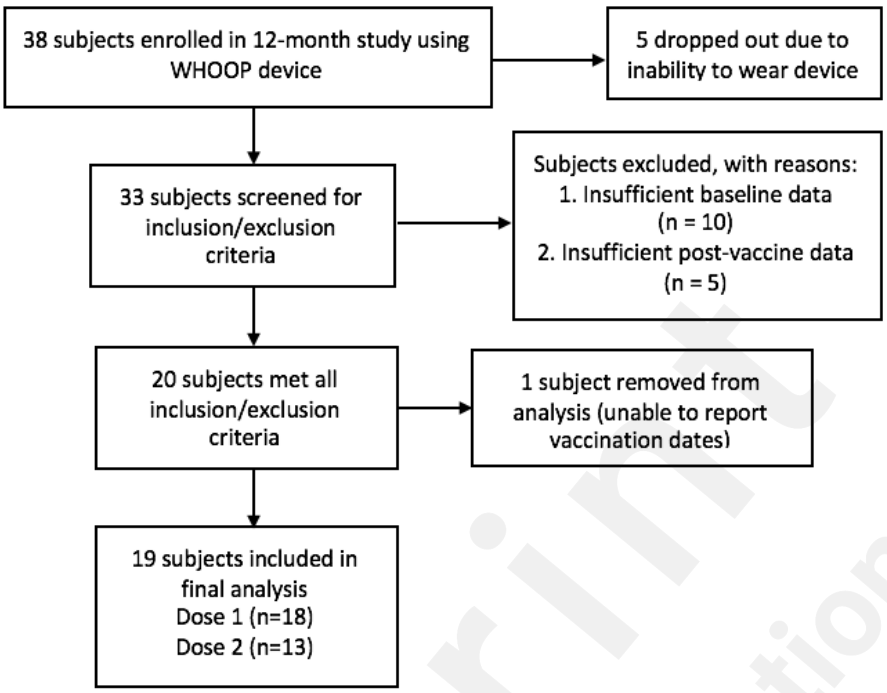


Figure 5. Hypothetical connection between physiologic response measured by wearables (HRV, RHR, RR), inflammatory response (serum CRP and pro-inflammatory cytokine levels) and host immunity dictated by antibody response to vaccination. Wearable monitoring of physiologic metrics could potentially be a simple and effective way to track efficacy of vaccine-mediated protection against infection (dashed arrow). HRV highlighted, as this parameter showed the greatest changes in the current study.

Supplementary Materials:



Supplementary Figure 1: Study Flow Chart. 38 subjects were initially enrolled in the study. 33 were screened for inclusion and exclusion criteria, yielding 19 subjects that were included for final analysis (18 subjects for Dose 1 and 13 subjects for Dose 2).

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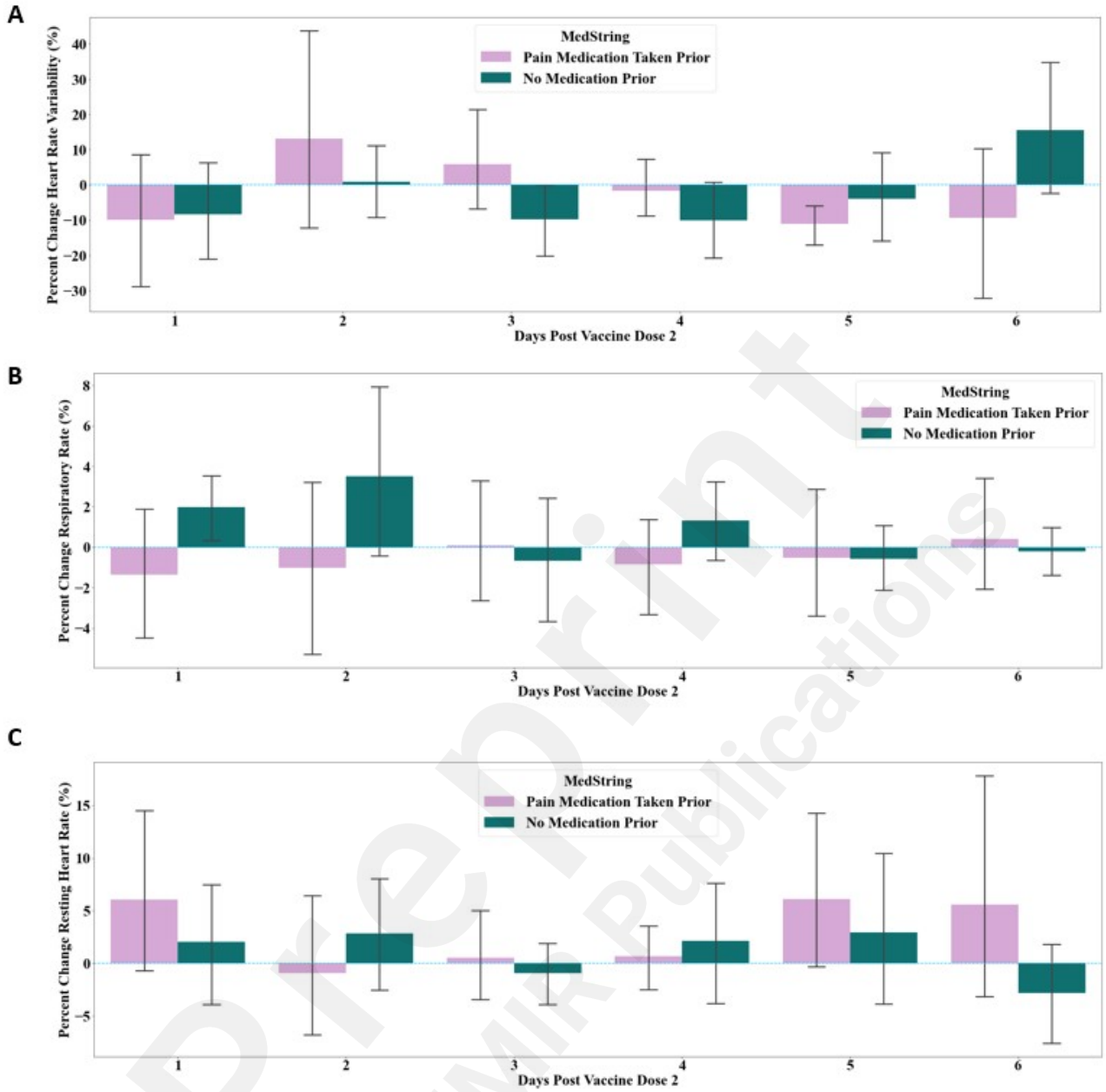

Supplementary Figure 2: Pre-Medication Subgroup Analysis. Percent change from baseline in (A) Heart Rate Variability, (B) Respiratory Rate, and (C) Resting Heart Rate, measured 6 days following COVID-19 Vaccine Dose 2 is reported for subjects who pre-medicated prior to vaccination (purple) and subjects who did not pre-medicate (green). Data is reported as mean +/- standard deviation.

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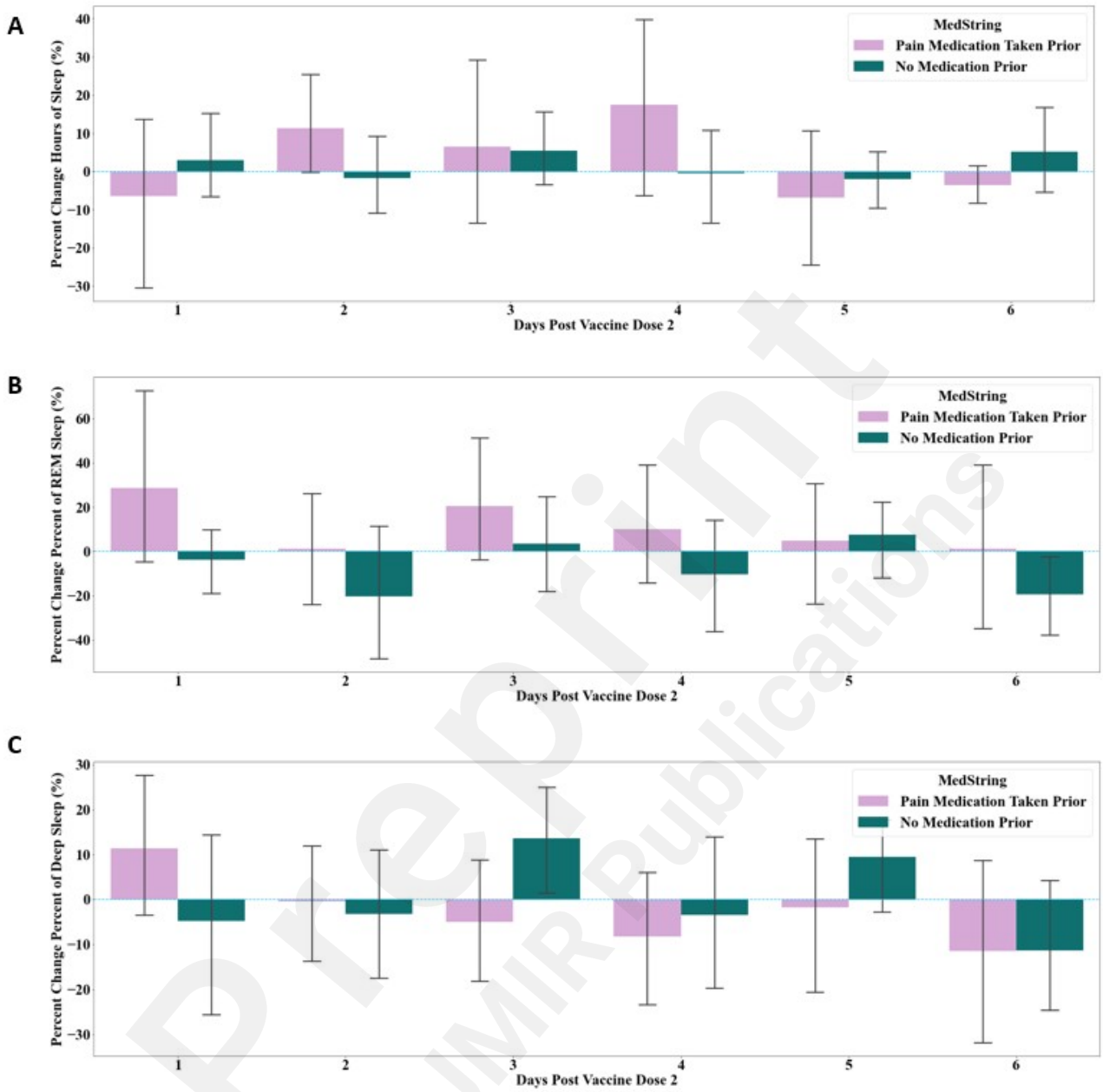

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Author contributions: AH and KD contributed equally to this work. AH, KD and BB designed the research study and refined the data collection plan; BB analyzed the data with input from AH and KD; AH, KD, and BB wrote the manuscript; AT, JM, SM, SB, JJ, and AT edited the manuscript.

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The study is registered on ClinicalTrials.Gov: NCT04304703 (https://www.clinicaltrials.gov/ct2/show/NCT04304703).

Conflicts of interest: None

Abbreviations:

COVID-19 - novel coronavirus SARS-CoV2
mRNA - messenger Ribonucleic Acid
RHR – resting heart rate
HRV – heart rate variability
RR – respiratory rate
CRP – C-reactive protein
REM – rapid eye movement
SWS – slow wave sleep
RMSSD – root mean square standard deviation
ms – milliseconds
bpm – beats per minute
rpm – respirations per minute

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Supplementary Files

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Figures

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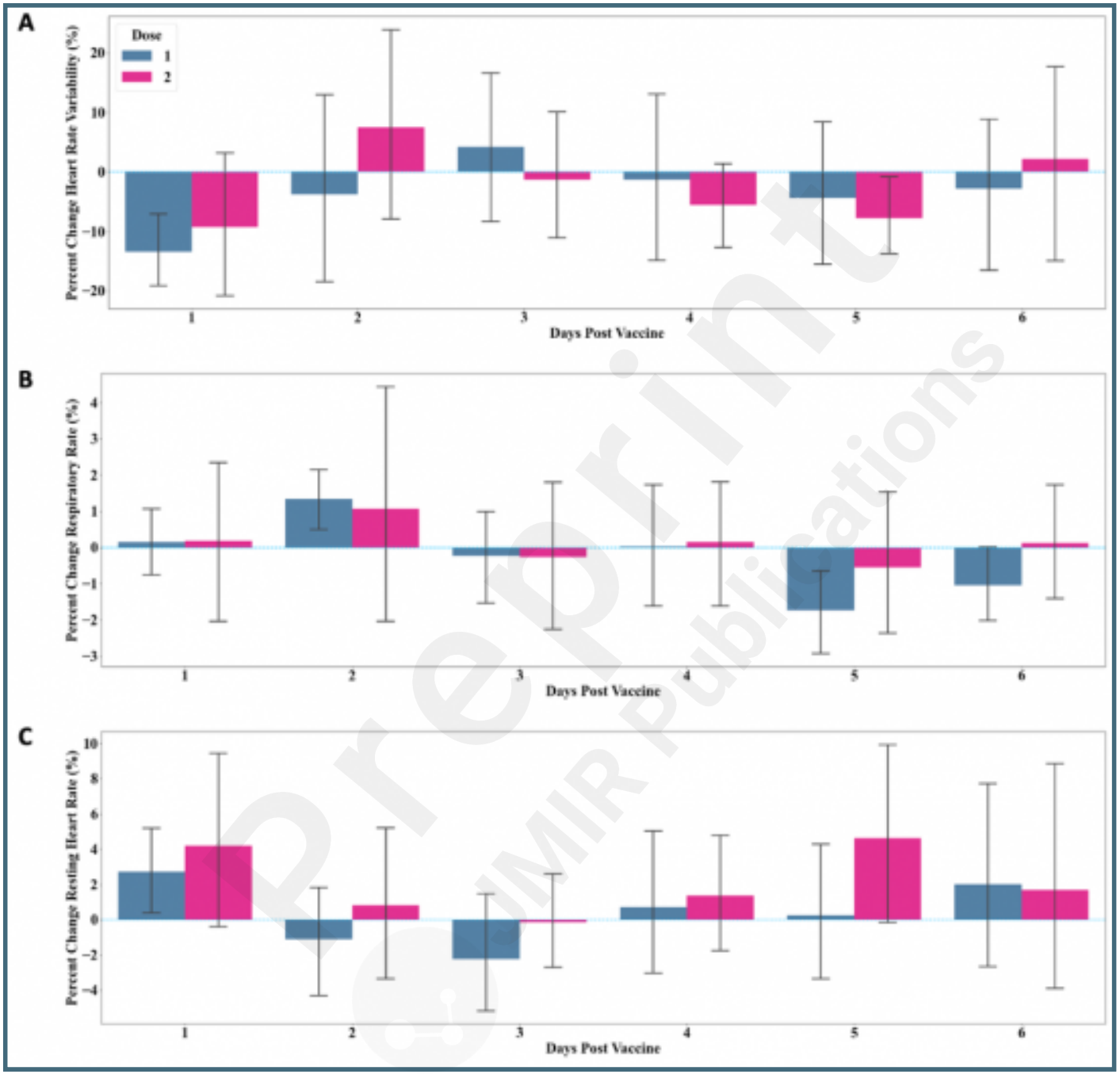
Percent change from baseline in (A) Heart Rate Variability, (B) Respiratory Rate, and (C) Resting Heart Rate, measured 6 days following COVID-19 Vaccine Dose 1 (blue) and 2 (magenta). Data is reported as mean +/- standard deviation.



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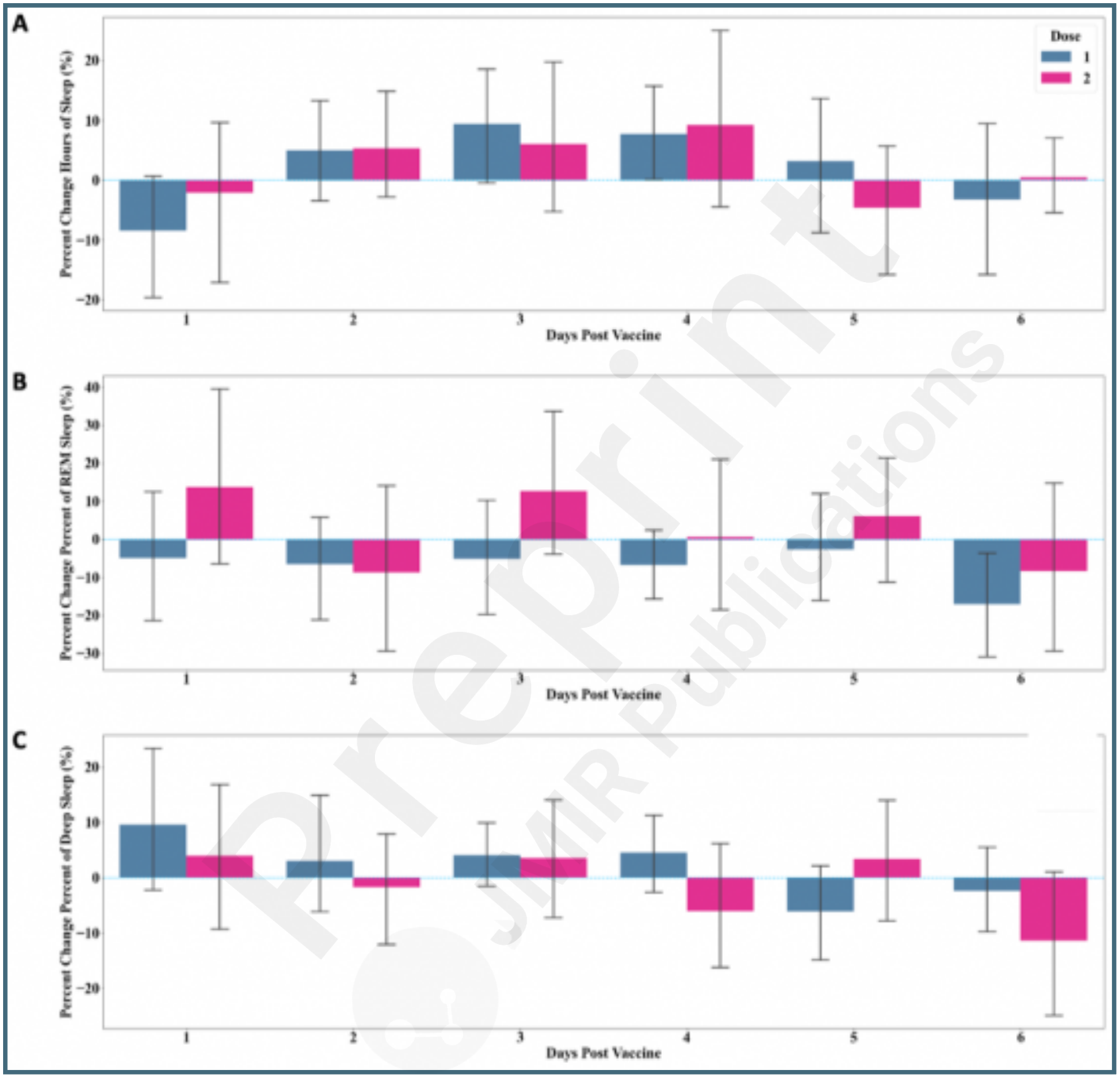

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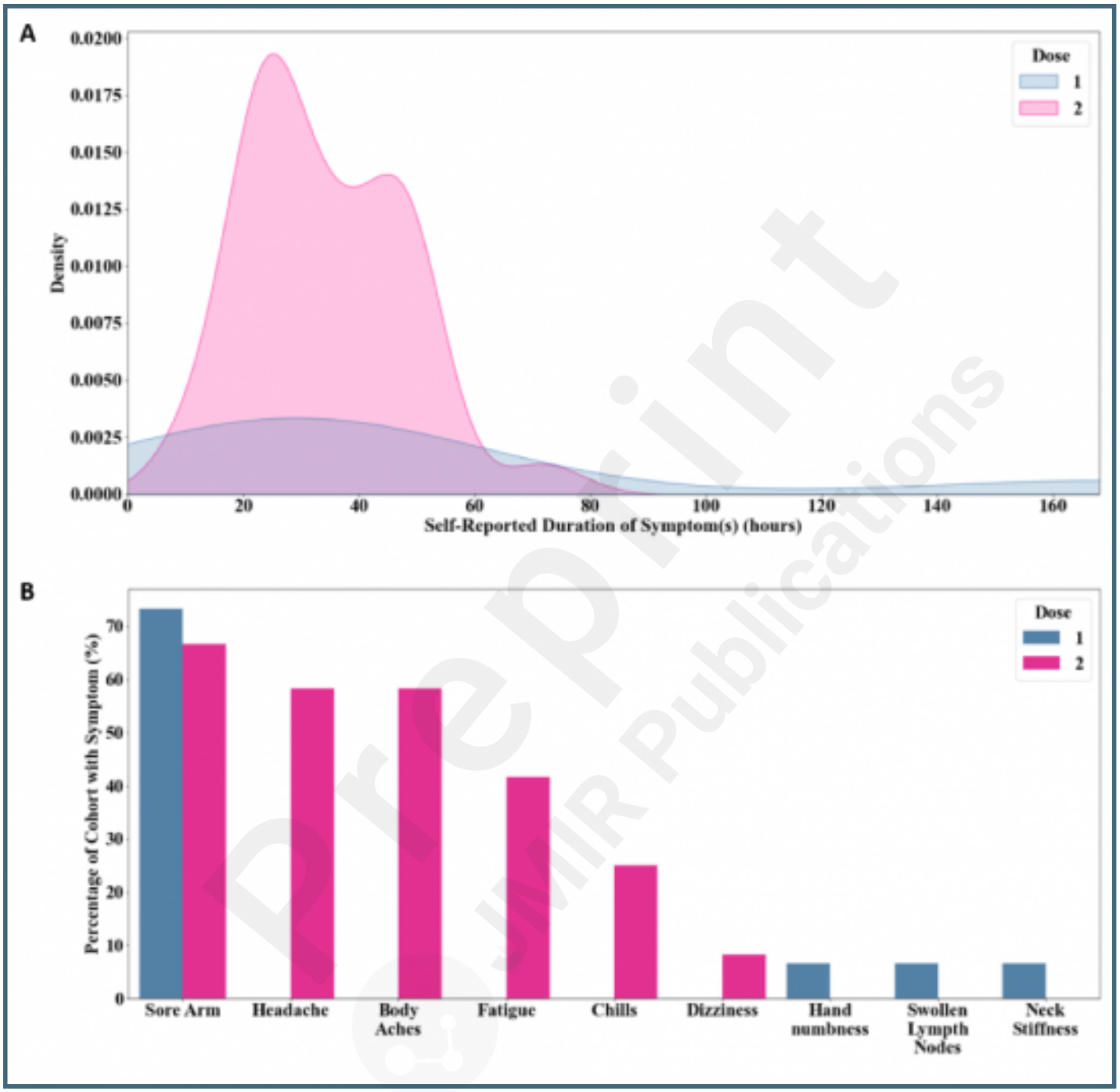
(A) Self-reported symptom duration following Dose 1 and Dose 2 of COVID-19 vaccine. (B) Type of symptoms experienced by participants, by vaccine dose.



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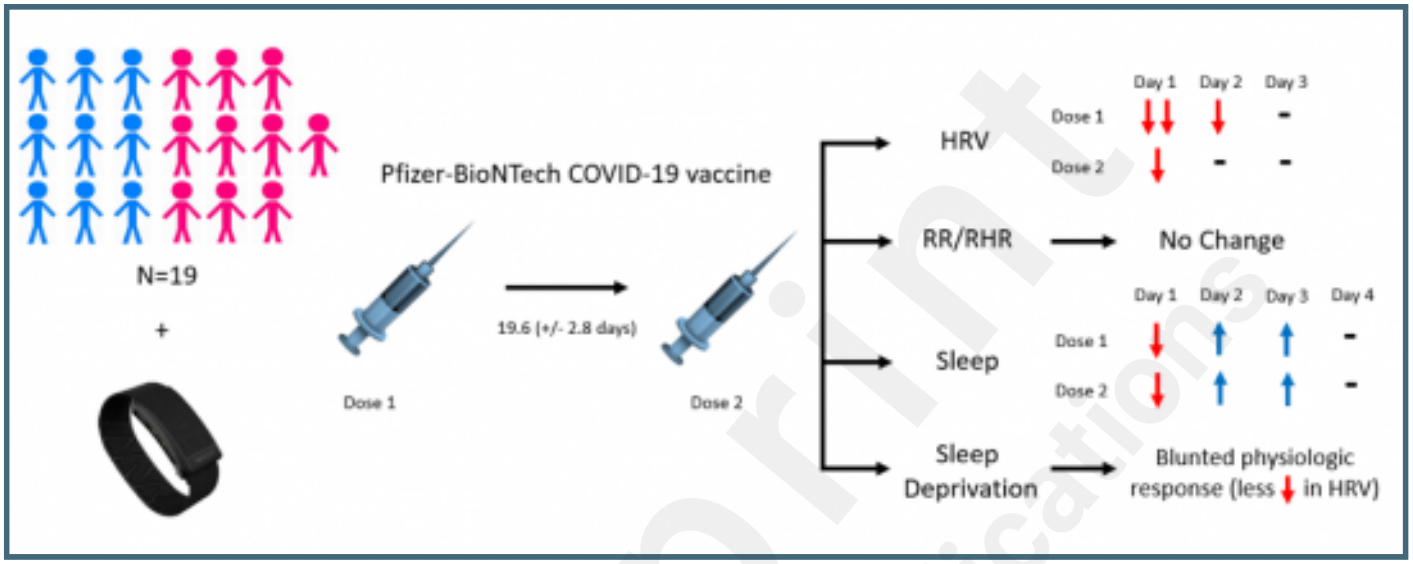

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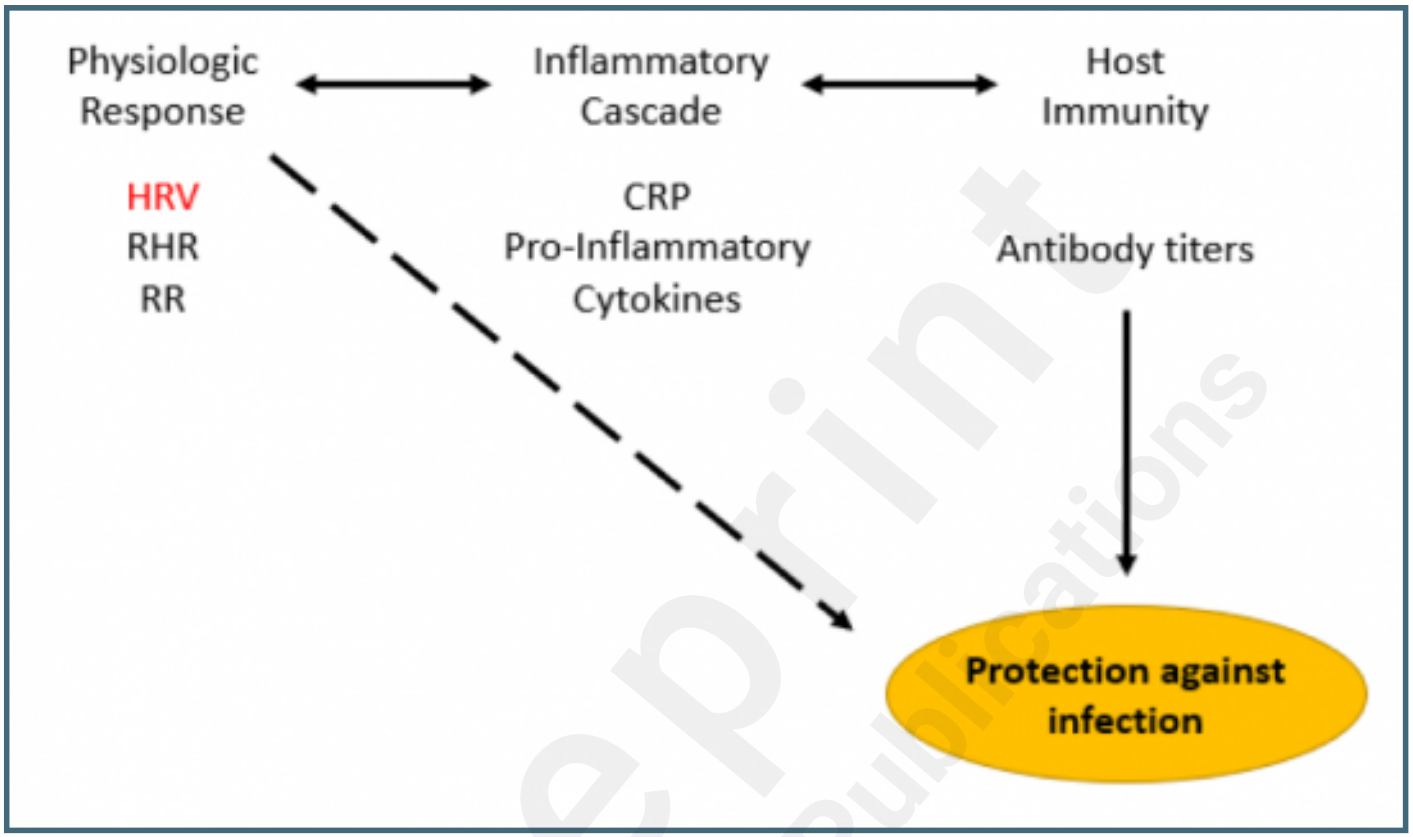
Hypothetical connection between physiologic response measured by wearables (HRV, RHR, RR), inflammatory response (serum CRP and pro-inflammatory cytokine levels) and host immunity dictated by antibody response to vaccination. Wearable monitoring of physiologic metrics could potentially be a simple and effective way to track efficacy of vaccine-mediated protection against infection (dashed arrow). HRV highlighted, as this parameter showed the greatest changes in the current study.



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Multimedia Appendixes

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Study Flow Chart. 38 subjects were initially enrolled in the study. 33 were screened for inclusion and exclusion criteria, yielding 19 subjects that were included for final analysis (18 subjects for Dose 1 and 13 subjects for Dose 2).
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Pre-Medication Subgroup Analysis. Percent change from baseline in (A) Heart Rate Variability, (B) Respiratory Rate, and (C) Resting Heart Rate, measured 6 days following COVID-19 Vaccine Dose 2 is reported for subjects who pre-medicated prior to vaccination (purple) and subjects who did not pre-medicate (green). Data is reported as mean +/- standard deviation.
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