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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

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Supplementary Materials for:

Safety of the fourth COVID-19 BNT162b2 mRNA (second booster) vaccine: prospective and retrospective cohort study

Matan Yechezkel, MSc[1], Merav Mofaz, MSc[1], Amichai Painsky PhD[1], Tal Patalon, MD[2], Sivan Gazit, MD[2], Erez Shmueli, PhD[1,3,+] , Dan Yamin, PhD[1,4,+,*]

[1]Department of Industrial Engineering, Tel Aviv University, Tel Aviv, Israel.

[2]Kahn Sagol Maccabi (KSM) Research & Innovation Center, Maccabi Healthcare Services, Tel Aviv, Israel.

[3]MIT Media Lab, Cambridge, MA, USA.

[4]Center for Combatting Pandemics, Tel Aviv University, Tel Aviv, Israel.

[+]Equal contribution

*Corresponding author. Email: dan.yamin@gmail.com

Keywords: COVID-19 vaccine, second COVID-19 booster vaccine, BNT162b2, adverse effects, wearable sensors

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Study Design

In this study we will analyze data that were already collected and will be collected as part of the PerMed study [1]. Participants in the PerMed study are recruited for a period of two years, during which they are equipped with a Garmin Vivosmart 4 smartwatches and are asked to wear them as much as they could. In addition, participants install two applications on their mobile phones: an application that passively collects data from the smartwatch and a dedicated mobile application which allows participants to fill a daily questionnaire and to report their vaccine date and specific hour. In this study, we will consider for each participant, the 7-days period prior to any vaccination dose as the baseline period.

Participants

The inclusion criteria for the PerMed study includes those aged > 18 years. Individuals who are not eligible to give and sign a consent form of their free are excluded. In this study, we will analyze the data of participants aged 18 years and above, who reported receiving at least one dose of the BNT162b2 mRNA COVID-19 vaccine after joining the PerMed study. To recruit participants and ensure they complete all the study's requirements, we will hire a professional survey company. Potential participants will be recruited through advertisements in social media, online banners, and word-of-mouth. The survey company is responsible for guaranteeing the participants meet the study's requirements, in particular, that the questionnaires are filled daily, ensuring the smartwatches are charged constantly and worn properly, and assisting participants resolve technical problems.

Study procedures

Before participation in the study, all participants will be advised orally and in writing about the nature of the experiments and give written, informed consent. At this time, participants will be asked to complete an enrollment questionnaire that includes demographic information and health status. In addition, participants will be asked to install two applications on their mobile phones: an application that passively collects data from the smartwatch and the PerMed application, which allows participants to fill in the daily questionnaires. Participants will be given instructions regarding the self-reported symptoms questionnaires and how to operate the smartwatch, which they will wear as much as they can.

Enrollment questionnaire

All participants will fill a one-time enrollment questionnaire that includes demographic questions and questions about the participant's health condition in general. Specifically, the questionnaire will include the following: age, gender, height, weight and underlying medical conditions (Listed in Table 1, main text). Other questions such as name, address, phone and email will be recorded and used by the survey company to contact the participants. The answers will be filled-in directly by the survey company to the study's secured dashboard.

Monitoring device

Participants will be equipped with Garmin Vivosmart 4 smart fitness trackers. Among other features, the smartwatch provides all-day heart rate and heart rate variability and during-night blood oxygen saturation level tracking capabilities [2].

The optical wrist heart rate (HR) monitor of the smartwatch is designed to continuously monitor a user's heart rate. The frequency at which heart rate is measured varies and may depend on the level of activity of the user: when the user starts an activity, the optical HR monitor's measurement frequency increases.

Since heart rate variability (HRV) is not easily accessible through Garmin's application programming interface (API), we use Garmin's stress level instead, which is calculated based on HRV. Specifically, the device uses heart rate data to determine the interval between each heartbeat. The variable length of time between each heartbeat is regulated by the body's autonomic nervous system. Less variability between beats correlates with higher stress levels, whereas an increase in variability indicates less stress [3]. A similar relationship between HRV and stress was also seen in [4,5].

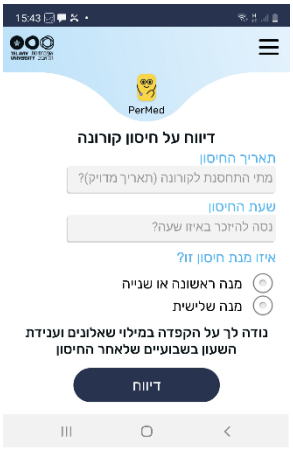
The Pulse Ox monitor of the smartwatch uses a combination of red and infrared lights with sensors on the back of the device to estimate the percentage of oxygenated blood (peripheral oxygen saturation, SpO2%). The Pulse Ox monitor is activated each day at a fixed time for a period of four hours (the default is 2AM-6AM).

Examining the data collected in our study, we identified an HR sample roughly every 15 seconds, an HRV sample every 180 seconds, and an SpO2 sample every 60 seconds.

While the Garmin smartwatch provides state-of-the-art wrist monitoring, it is not a medical-grade device, and some readings may be inaccurate under certain circumstances, depending on factors such as the fit of the device and the type and intensity of the activity undertaken by a participant [6–8].

Vaccination questionnaire

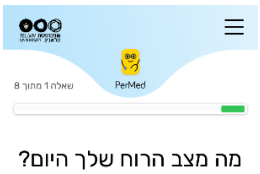
The vaccination questionnaire we will use includes the following question:



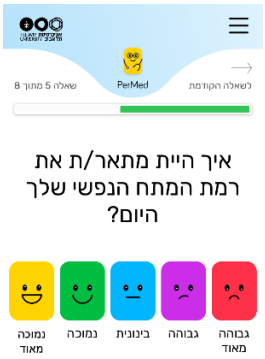
COVID-19 vaccination – date, time and dose number. [note, this is for validation as vaccination data are reported in the EMR]

Daily questionnaires

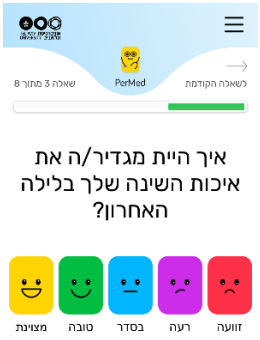
All participants will complete the daily self-reported questionnaire in a dedicated application (the PerMed mobile application). The daily questionnaire we will use includes the following questions:



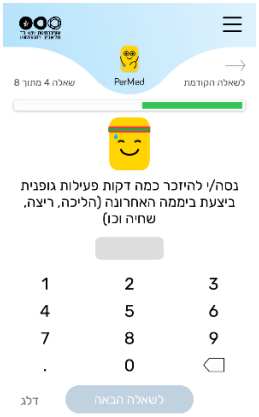
How is your mood today? • Awful (-2)• Bad (-1)• OK (0)• Good (1)• Excellent (2)



How would you describe the level of your stress during the last day?• Very Low (-2)• Low (-1)• Medium (0)• High (1)• Very high (2)



How would you define your last night sleep quality?• Awful (-2)• Bad (-1)• OK (0)• Good (1)• Excellent (2)



Try to remember how many minutes of sports activity you performed on the last day?

Have you experienced one or more of the following symptoms in the last 24 hours?• My general feeling is good, and I have no symptoms• Heat measured above 37·5• Cough• Sore throat• Runny nose• Headache• Shortness of breath• Muscle aches• Weakness / fatigue• Diarrhea• Nausea / vomiting• Chills• Confusion• Loss of sense of taste / smell• Another symptom.

Data Storage

Data collected from the mobile phone application and from the smartwatches will be stored on a secure server within Tel Aviv University facilities. The server runs a CentOS operating system and is located in Software Engineering Building at Tel Aviv University. This server is protected behind the university's firewall and is not connected to external networks. In addition, a secure connection through an SSL protocol and a trusted certificate will be obtained for the transfer of information from the mobile phone application into the secured server.

Access will be restricted to investigators in the study. The information from the mobile application will be stored in a structured manner on the secured server without any explicitly identifying information (name, ID number, email). Each participant will be assigned a coded participant number that will be used to identify the subject in the database. The code with the identified information will be stored in an encrypted form on a separate secured server that only the research manager will have access to. Access to all servers is restricted with username and password.

All (non-digital) questionnaires and signed informed consent documents will be stored in a secured cabinet in Tel Aviv University, to which only the research manager and the principal investigators will have access. No data collected as part of the study will be added to individuals' medical charts.

Data processing

We will perform several preprocessing steps. Concerning the daily questionnaires, in cases where participants will fill in the daily questionnaire more than once on a given day, only the last entry for that day will be considered, as it is reasoned that the last one likely best represented the entire day. Self-reported symptoms that are entered as the free text will be manually categorized. With regard to the smartwatch physiological indicators, data will first be aggregated per hour (by taking the mean value). Then, to impute missing values, we will perform a linear interpolation. Finally, data will be smoothed by calculating the moving average value using a five-hour sliding window.

Data Analysis and inclusion criteria

The questionnaire data will be preprocessed by manually categorizing any self-reported symptom entered as free text. If participants filled out the questionnaire more than once in one day, the last entry from that day was used in the analysis as it is likely more representative of the past day. Smartwatch data will be preprocessed as follows. First, we will compute the mean value of each hour of data. We will then perform a linear interpolation to impute missing hourly means. Lastly, we will smooth the data by calculating the five-hour moving average.

For each participant and each of the two booster doses, we define the 7-day period prior to vaccination as the baseline period. For the analyses involving self-reported questionnaires, we will include participants who submitted at least one questionnaire during the baseline period and at least one questionnaire during the seven days post-vaccination. The two questionnaires are required to understand the appearance of new reactions following vaccination. For the analyses involving smartwatch indicators, we will include participants who had at least one overlapping period of data (i.e., same day of the week and same hour during the day) during their baseline and post vaccination periods. The overlapping periods are required for computing the change in indicator values between the baseline and post-vaccination periods.

To compare the changes in specific smartwatch indicators (heart rate, HRV-based stress, resting heart rate, and step counts) over the 0-42 days post vaccination, with those of the baseline period, we will perform the following steps. First, for each participant and each hour during the seven days post-vaccination, we will calculat the difference between that hour's indicator value and that of the corresponding hour in the baseline period (keeping the same day of the week and same hour during the day). Then, we will aggregate each hour's differences over all participants to calculate a mean difference and the associated 95% confidence interval, which is analogous to a one-sided t-test with a significance level of 0·05. To determine the statistical significance of daily differences between the baseline and post vaccination period, we will calculate the mean daily difference for each participant and then used a one-sample t-test for each day. To compare the first and second boosters, we calculate for each individual the difference between the daily changes in heart rate and heart rate variability-based stress, recorded after the second and the first booster

To understand the extent of new reactions, post vaccination, we will first note any pre-existing signs and symptoms reported in the last completed questionnaire during the baseline period. Next, we will calculate the percentage of participants who reported new (i.e., not pre-existing) systemic reactions in the 7-day period after vaccination from the following list: fatigue, headache, muscle pain, cold, fever, sore throat, cough, chills, vomiting or nausea, diarrhoea, dyspnoea, confusion, loss of taste and smell, Shortness of breath. Participants could also report any other symptoms using free text. For each reaction we use a binomial distribution to determine a 95% confidence interval.

Potential Risks & Risk management

No specific risks arising from the smartwatches are expected, as the device is already commercialized with no known adverse reactions. The main risk in this study is the leakage of private data which we intend to manage as we describe in the following section.

Privacy/Confidentiality

Results from this study will be handled at an aggregated level. Individual data records will remain confidential and will not be published or shared with any third party. Signed and dated informed consent forms, as well as data recording sheets (e.g., case report forms) will be stored in locked cabinets during the study and following its completion. A file containing the personal details of the participants will be coded to help preserve confidentiality and will be separated from all other data collected throughout the study. This file will be kept by the principal investigator. Data will be stored on computers in password-protected files.

The data obtained from the smartwatch used in this study will be linked to a coded participant number. The smartwatch does not include a GPS. The data collected by the PerMed application will arrive directly to PerMed back-end servers and will be stored securely.

Retrospective part

Description of the data

Data will be extracted from the Maccabi Healthcare Services (MHS) database. MHS is a nationwide health plan (payer-provider) representing a quarter of the population in Israel. The MHS database contains longitudinal data on a stable population of 2·2 million people since 1993 (with <1%/year moving out). Data are automatically collected and includes comprehensive laboratory data from a single central lab, full pharmacy prescription and purchase data, and extensive demographic data on each patient. MHS uses the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) coding systems as well as self-developed coding systems to provide more granular diagnostic information beyond the ICD codes. Medications are coded according to the Israeli coding system with translations to anatomical therapeutic chemical (ATC) classification system wherever available. Procedures are coded using Current Procedural Terminology (CPT) codes. We will access to the following data for each patient:

- Socio-demographics
    - Sex (binary)
    - Age (year of birth)
    - Socioeconomic status by address and according clinic when address is missing) (scale 1-20)
    - Supplementary insurance status (type of insurance structured 1-5)
    - Country of birth (coalesced into regions when necessary) and immigration date
    - Sector (clinic level data - Arab / Jewish/ ultra-orthodox Jewish)
    - Affiliation by district, sub-district (out of 2750 regions)
- Comorbidities
    - Charlson co-morbidity index (scale)
    - Chronic diseases (binary classifcation)
        - History of malignancies and active malignancy
        - Cardiovascular diseases (ischaemic heart disease, cerebrovascular disease/ all cardio sub registries).
        - Diabetes (taken from CRI registry)
        - Hypertension (taken from CRI registry)
        - Asthma
        - Chronic Lung Disease
        - Rheumatologic diseases
        - Chronic Kidney Disease
        - Immunocompromised Status
        - Chronic Liver Disease
        - Additional Chronic Diseases
- Acute and Chronic Medications (group of medications)
- Vaccination records
- Laboratory test results (binary classification for existence of infectious diseases)
- Prescription drugs ({ type, dosage number}
- Hospitalization history ({ admission data, primary service, duration})
- Outpatient history (admission data, primary service, ICD diagnosis code)
- BMI ({date ,value}}
- Smoking status {date, yes/no}

Data collection and storage

We will receive access to the data from the medical records of 250,000 random members of Maccabi and the 5,000 participants from the prospective cohort. MHS is a nationwide health plan (payer-provider) representing a quarter of the population in Israel. The MHS database contains longitudinal data on a stable population of 2·2 million people since 1993 (with <1%/year moving out). Data are automatically collected and includes comprehensive laboratory data from a single central lab, full pharmacy prescription and purchase data, and extensive demographic data on each patient. MHS uses the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) coding systems as well as self-developed coding systems to provide more granular diagnostic information beyond the

ICD codes. Medications are coded according to the Israeli coding system with translations to anatomical therapeutic chemical (ATC) classification system wherever available. Procedures are coded using Current Procedural Terminology (CPT) codes.

As for the medical data, we will receive access to the EMR data after the following pseudonymisation procedures:

1. Healthcare identification number of the members will be coded.
2. Only year of birth is provided
3. Free text is removed. This means any text that was types/recorded/scanned manually by healthcare staff, and is not structured in the electronic system. This includes any documented conversations between healthcare staff and patient or summary of from meetings.
4. No audio, photos including scanned text, or video contents are provided.
5. The address of the members is not detailed, and only the statistical area is provided (Israel is stratified into 2733 statistical areas with around 2500-5000 individuals per region).

The data access of the retrospective part will be conducted at the MHS. The data are coded, viewed, stored and process only within the Maccabi research room. The researchers will connect to the research room via MD Clone platform, which is approved by the Ministry of Health. The user connects through a secure connection using Lightweight Directory Access Protocol and two factor authentication system.

Potential adverse events

We will examine 25 potential adverse events (Table S1) that were previously investigated in the context of COVID-19 vaccination [9].

Table S1. ICD-9 codes of the examined potential adverse events

Event	ICD-9 code
Acute Kidney Injury	ICD9 Code 584.[5-9]*
Anemia	ICD9 Code 28[0,1,3,4,5]*
Appendicitis	ICD9 Code 54[0-2]*
	ICD9 Code 47*
Arrhythmia	ICD9 Code 427*
	ICD9 Code 426*
Arthritis or Arthropathy	ICD9 Code 713*
	ICD9 Code 714.9*
	ICD9 Code 716.[4-9]*
	ICD9 Code 718.9
	ICD9 Code 719.[0,1,6,8,9]*
Bell's Palsy	ICD9 Code 351.0*
Cerebrovascular Accident	ICD9 Code 433
	ICD9 Code 433.[0,1,2,3,8,9]
	ICD9 Code 433.[0,1,2,3,8,9]1
	ICD9 Code 434*
	ICD9 Code 362.3[1-3]
	ICD9 Code 436*
Deep Vein Thrombosis	ICD9 Code 451
	ICD9 Code 451.[1-9]*
	ICD9 Code 453.[1,4]*

	ICD9 Code 453.8[0,2,3,4,5,6,7,8,9]
	ICD9 Code 671.[3,4]*
Herpes Simplex	ICD9 Code 054*
Herpes Zoster	ICD9 Code 053*
Intracranial hemorrhage	ICD9 Code 43[0,1,2]*
Lymphadenopathy	ICD9 Code 785.6*
	ICD9 Code 683*
	ICD9 Code 289.[2,3]*
Lymphopenia	ICD9 Code 288.5*
Myocardial Infarction	ICD9 Code 410*
Myocarditis	ICD9 Code 422*
	ICD9 Code 429.0*
	ICD9 Code 398.0*
	ICD9 Code 391.2*
Neutropenia	ICD9 Code 288.0
	ICD9 Code 288.0[0,3,4,9]
Other Thrombosis	ICD9 Code 444*
	ICD9 Code 557.[0,9]*
	ICD9 Code 557
	ICD9 Code 452*
	ICD9 Code 453
	ICD9 Code 453.[0,1,2,3,4,9]*
	ICD9 Code 453.[7,8]
	ICD9 Code 453.[7,8][2-9]
	ICD9 Code 437.6*
Paresthesia	ICD9 Code 782.0*
Pericarditis	ICD9 Code 420*
Pulmonary Embolus	ICD9 Code 415.1*
	ICD9 Code 673.[2,8]*
Seizures	ICD9 Code 345.[2,3]*
	ICD9 Code 780.3
	ICD9 Code 780.39
Syncope	ICD9 Code 780.2*
	ICD9 Code 992.1*
Thrombocytopenia	ICD9 Code 287.2*
	ICD9 Code 287.3
	ICD9 Code 287.3[0,1,3,9]
	ICD9 Code 287.5
Uveitis	ICD9 Code 360.12
	ICD9 Code 362.18
	ICD9 Code 363.0*
	ICD9 Code 363.2[0,1,2]

	ICD9 Code 363.1*
	ICD9 Code 364.[0,1,2,3]*
	ICD9 Code 053.22
	ICD9 Code 054.44
	ICD9 Code 091.5*
	ICD9 Code 098.41
	ICD9 Code 115.92
Vertigo	ICD9 Code 780.4*

* Any of the possible ICD-9 combination with a match

Appendix B – Data collection platform and data access

1.1 Architecture

The data collection platform contains several components that interact with each other (see Figure 2):

- **The PerMed application** – This application is installed on each participant's phone to collect sensors data and the self-reported daily questionnaires. It also handles the smartwatch pairing. The current version of the application supports both Android and iOS devices.
- **The smartwatch** - send the data to the Garmin Connect app on the smartphone, which then sends these data to Garmin's server.
- **The smartwatch application** – This application (currently Garmin) receives information from the smartwatch via Bluetooth and transmits it to the company's server. In addition, it provides a convenient interface for displaying the participant's smartwatch information.
- **The app server** – The webserver handles the database connectivity using REST API pages. It enables the server to authenticate users as they launch the application and write records to the database. A MySQL server stores the sensors' raw data and the answers to the daily questionnaires. At last, there is a batch processes running on the server that sends app notifications (daily reminder to fill the questionnaire).
- **The dashboard server** - hosts the dashboard pages, which assist in monitoring the quality of the information and controlling the experiment. The dashboard has access to participant information and signals indicating whether questionnaires were completed and the smart watch was worn without seeing its content directly. A batch process is responsible for aggregating raw data for dashboard statistics.
- **The smartwatch server** - A MySQL server stores the smartwatch data. A batch process is responsible for collecting the data from the Garmin server.

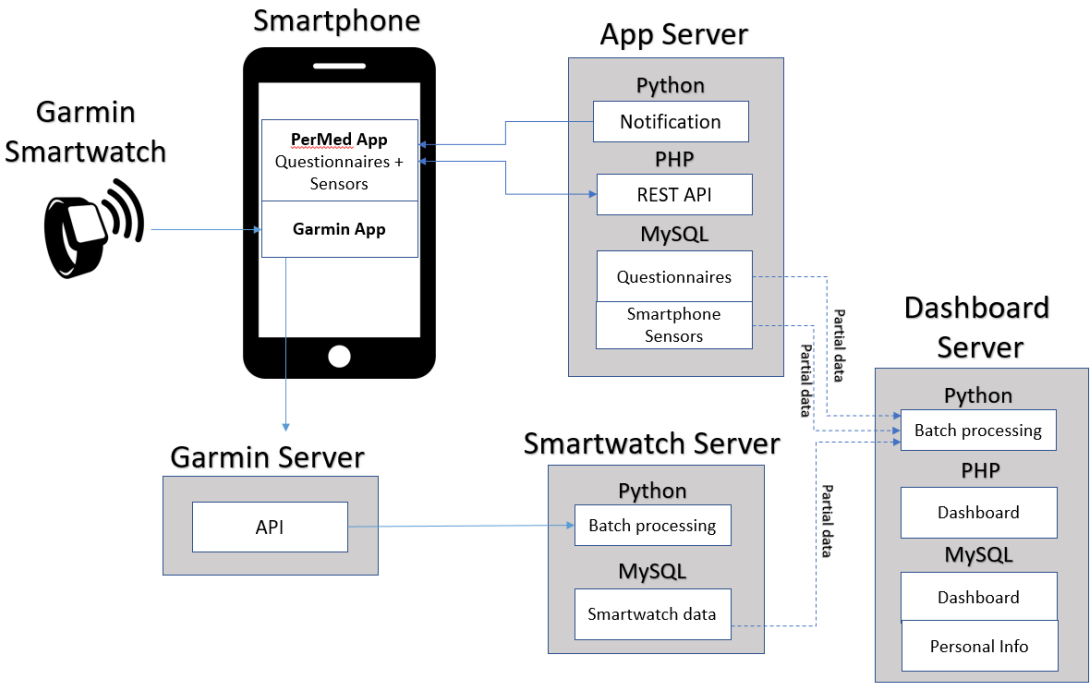


Figure S1. The high-level architecture of the PerMed's data collection platform.

1.2 The PerMed Dashboard

Participants will be recruited by a qualified external recruitment team headed by Tel Aviv University personal. The team receive limited information essential control the experiment. Thus, we developed a

dedicated dashboard for monitoring the quality of the information and control the experiment. This dashboard aims to identify data collection issues such as participants who did not fill the dailyquestionnaires or participants who did not charge the battery of their smartwatches. The dashboard alsohelps us identify problems that were not related to participants' cooperation, such as bugs in the mobileapp. This identification allow us to respond faster and provide timely solutions.

1.3 The Type of Data Collected and data access

Data collected by the platform arrive from four primary sources:

- **Enrolment questionnaire -** data were collected from a one-time enrollment questionnaire that includes basic personal characteristics such as socio-demographic information (e.g., age, gender,height, weight), general habits, health status, and a short Big Five personality questionnaire.
- **Daily questionnaire** – consists of questions on 1) wellbeing, 2) general health condition, 3) symptoms observed, 4) test results to diagnose infectious diseases, 4) vaccination or medicationconsumption (if relevant to the study question).
- **Smartphone sensor data** – consist of location, Wi-Fi, Bluetooth, screen, and activity.
- **Smartwatch data** - consist of heart rate data, accelerometer and gyroscope information and measures based on these data including active minutes, steps, distance, calories, and sleep level classification, including light, deep, REM, and awake periods.

The current research, aims to explore the safety of vaccination, is part of a larger study. Raw accelerometer data, mobile activity and GPS locations are generally considered sensitive information. In accordance with the data minimization principle, we did not extract these type of data for this vaccination safety research.

Appendix C – Prospective study participants' adherence

We employed a professional survey company to recruit participants and ensure they adhere to the study requirements. Participant recruitment was performed via advertisements on social media and word-of-mouth. Each participant signed an informed consent form after receiving a comprehensive explanation on the study. Then, participants completed a one-time enrollment questionnaire, were equipped with Garmin Vivosmart 4 smartwatches, and installed two applications on their mobile phones: (1) the PerMed application [1,10,11], which collects daily self-reported questionnaires, and (2) an application that passively records smartwatch data. Participants were asked to wear their smartwatches as much as possible. The survey company ensured that participants' questionnaires were filled at least twice a week, that their smartwatches were charged and properly worn, and that any technical problems with the mobile applications or smartwatch were resolved. Participants were monitored through the mobile application and smartwatches for a period of at least 49 days, starting seven days before vaccination. Participants also granted full access to their EMR data.

We implemented several preventive measures to minimize participant attrition and discomfort as a means to improve the quality, continuity and reliability of the collected data. First, each day, participants who did not fill their daily questionnaire by 7 pm received a reminder notification through the PerMed application. Second, we developed a dedicated dashboard that allowed the survey company to identify participants who repeatedly neglected to complete the daily questionnaire or did not wear their smartwatch for extended periods of time; these participants were contacted by the survey company (either by text message or phone call) and encouraged to better adhere to the study protocol. Third, to strengthen participants' engagement, a weekly personalized summary report was generated for each participant, which was available inside the PerMed application. Similarly, a monthly newsletter with recent findings from the study and useful tips regarding the smartwatch's capabilities was sent to the participants. At the end of the study, participants will receive all personal insights that were obtained and can keep the smartwatch as a gift.

Appendix D – Methods
Statistical analysis to examine potential changes in heart rate following vaccination

Rationale - The basic approach for the studied problem is to model the examined heart rate (HR) levels before the vaccination is applied and compare to their behavior afterward. Naturally, we expect time-dependent properties, such as autocorrelations and periodic trends. Thus, we examined the autocorrelation of the HR and partial autocorrelation on hourly bases 336 hours before vaccination (i.e., 14 days before vaccination until an hour before vaccination) (Figure S2A).

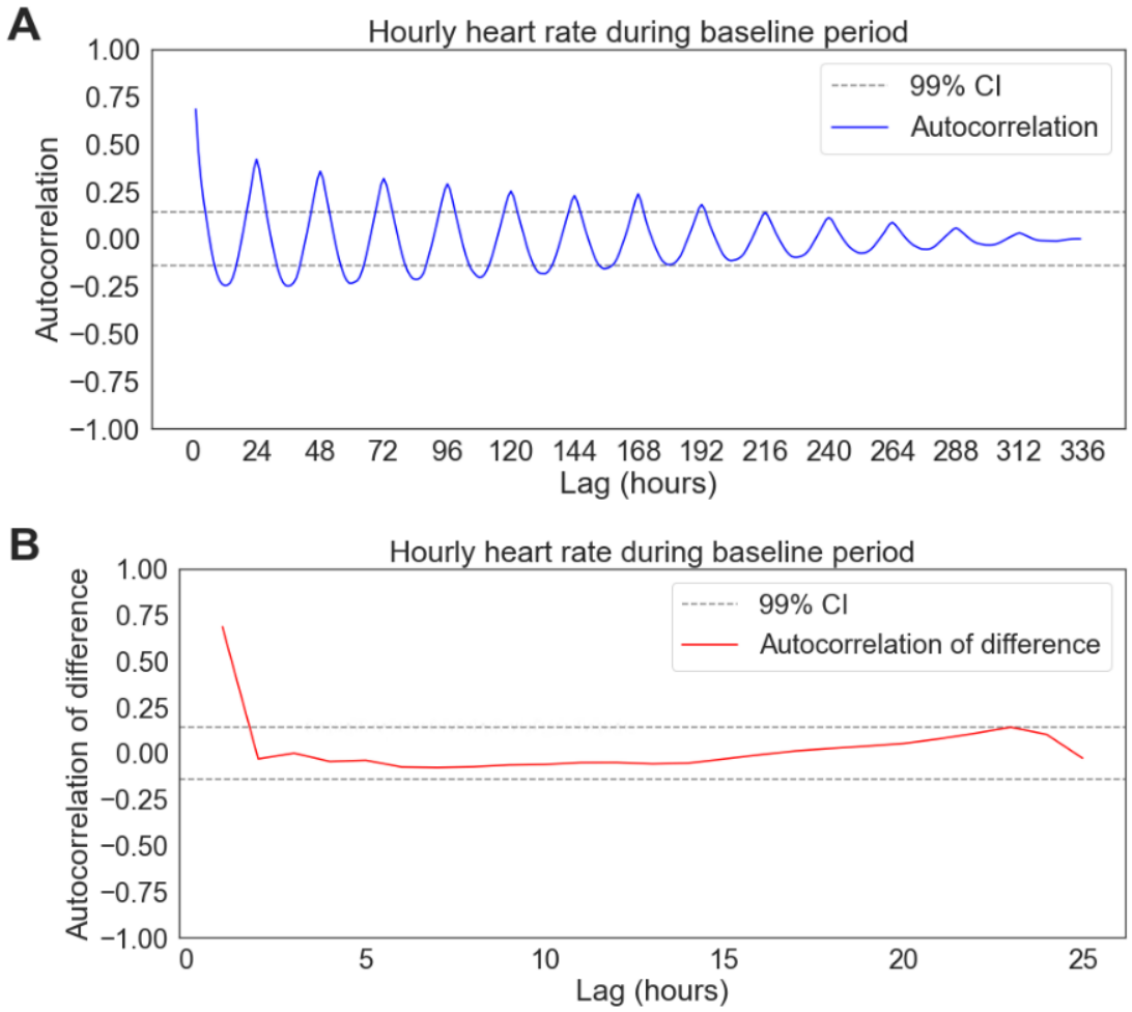


Figure S2. Average autocorrelation (A) and autocorrelation of the difference (B) between hourly average measurements of heart rate seven days before and after the third vaccination.

However, in this work, we study the effect of the vaccination and henceforth focus on the difference between the trends. Therefore, instead of modeling the symptoms' behavior, we model the differences in the symptoms' behavior over time. While there was also strong autocorrelation every 24 hours, the autocorrelation of the differences between

each hour and the same hour a week before revealed that this effect was primarily due to the lower order autocorrelations (Figure S2B). Moreover, in line with the reports in clinical trials, our test hypotheses are defined in days, which is likely to reduce autocorrelation concerns further.

More formally, let $X_1, \ldots, X_{14}$ be the examined HR over a 14-day time period before the vaccination is applied. Let X_{15} be the measured HR on the day of the vaccination, and $X_{16}, \ldots, X_{20}$ be the measurements over the five days that follow. Denote $Y_i = X_{i+7} - X_i$. That is, Y_i is the difference in the measured HR over a time period of an entire week. Specifically, $Y_1, \ldots, Y_7$ correspond to the time before the vaccination is applied, while $Y_9, \ldots, Y_{15}$ correspond to the days after. We argue that $Y_{12}, \ldots, Y_{15}$ follow the same statistical properties as $Y_1, \ldots, Y_7$ while Y_9, Y_{10}, Y_{11} do not. In words, after a three-day transition phase (corresponding to Y_9, Y_{10}, Y_{11}), the measured HR returns to its null behavior. Notice we denote $Y_1, \ldots, Y_7$ as the null, as it characterizes the differences in the measured HR before the vaccination is applied.

Our first task is to model the null distribution. In our experiment we have a total of 699 subjects which corresponds to 606 (Here we have more samples as we explore horizon of 14 days, and thus more participants follow the inclusion criteria) samples of the vector $Y_1, \ldots, Y_{20}$. Notice that the day of the week (denoted as d) in which the vaccination was applied differs between subjects. Therefore, we rearrange the vector $Y_1, \ldots, Y_7$ so that the days in the week are aligned. Specifically, we define Z_i as the difference in the measured symptom in the day of the week. We first show that $Z_1, \ldots, Z_7$ are follow the same mean and variance and are very weakly correlated.

We begin our analysis by testing the equivalence of means over $Z_1, \ldots, Z_7$. For this purpose, we apply the Kruskal-Wallis test. This test is a non-parametric alternative to the standard one way ANOVA, which does not assume the data follow a specified distribution [12]. However, as opposed to the standard ANOVA, the Kruskal-Wallis tests the equivalence of medians and not the means. Therefore, we test the null hypothesis that $Z_1, \ldots, Z_7$ follow the same median and obtain a p-value of 0.96 (which means we cannot reject the null). Next, we test the equivalence of variances. Here, we turn to Brown-Forsythe test which examines the homogeneity of variances. We obtain a p-value of 0.21 which again does not reject the null. As we estimate the variances, we notice they are all approximately $S^2 = 30$. Finally, we test the first order autocorrelation. That is, we compute the autocorrelation of each studied individual and average the results among the entire group. We obtain an average of $\hat{\rho} = -0.07$ which is orders of magnitude smaller than S^2. Unfortunately, we cannot accept the hypothesis that $\rho = 0$, mostly due to the limited data that we possess.

Altogether, we conclude there is no significant effect to the day of the week d, and we may define a single null variable Z, which corresponds to the difference in the measured HR over a week's period of time. To visualize this, we refer to Figure S3. Here, we observe the measured HR behavior $Z_1, \dots, Z_7$ in an hourly resolution.

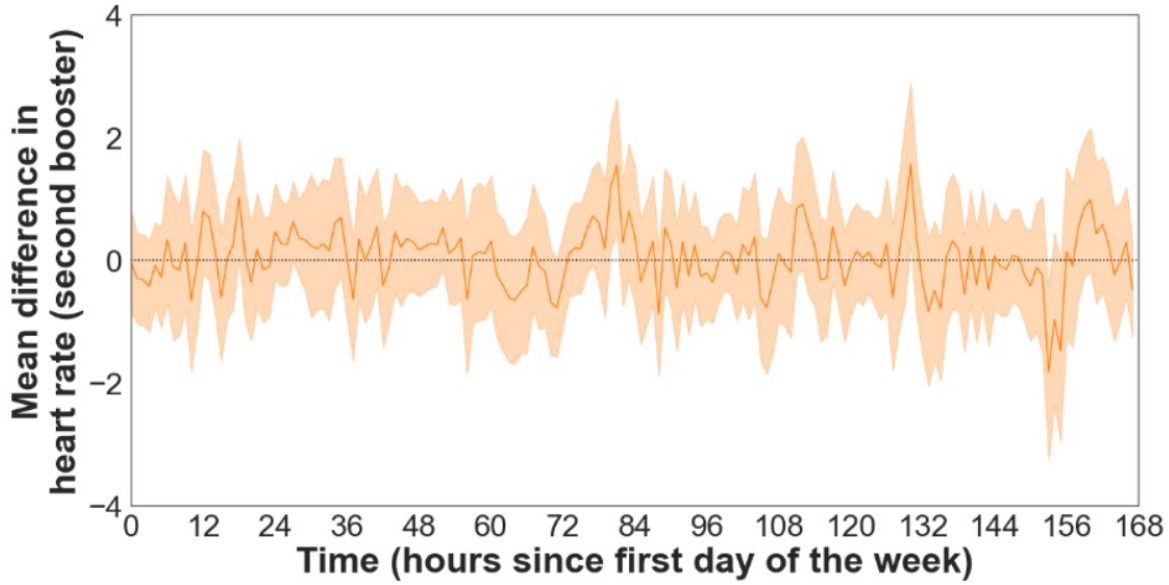


Figure S3. measured HR behavior $Z_1, \dots, Z_7$ in an hourly resolution. 0 represents the first hour of Z_1. 95% confidence intervals are presented as shaded regions.

Once we establish that, we may discard the effect of d and proceed to argue that $Y_{12}, \dots, Y_{15}$ follow the same behavior as Z. For this purpose, we show that $Y_{12}, \dots, Y_{15}$ follow the same first order statistics as Z and Y_9, Y_{10}, Y_{11} follow different first statistics than the null. We apply the same tests described above and obtain a p-values of 0.62. Once again, we cannot reject the null. Finally, we examine Z, Y_9, Y_{10}, Y_{11}. Here, we obtain p-values <0.0001 for Kruskal-Wallis. This means we may reject the null hypothesis and conclude that these days do not follow the same distribution, as desired. Notice that all of our tests are valid for a significance level of 0.05, even after a Bonferroni correction for multiple comparisons is applied.

It is important to emphasize that despite a natural partitioning of the patients into different groups (for example, age, gender etc.), we did not observe a significant difference in the analysis. The reason for this phenomenon is the differences in measure approach (the variable Y_i), which excludes bias effects. Therefore, we treat all of our examinees as a single study.

Appendix E- Additional Results

Self-reported reaction to the second booster dose

The majority of participant did not report any new systematic reaction during the 7-day period post-vaccination. The most frequent reported reactions were fatigue, headache, muscle pain, cold, and a sore throat. These reactions faded in nearly all participants within three days (Figure S4).

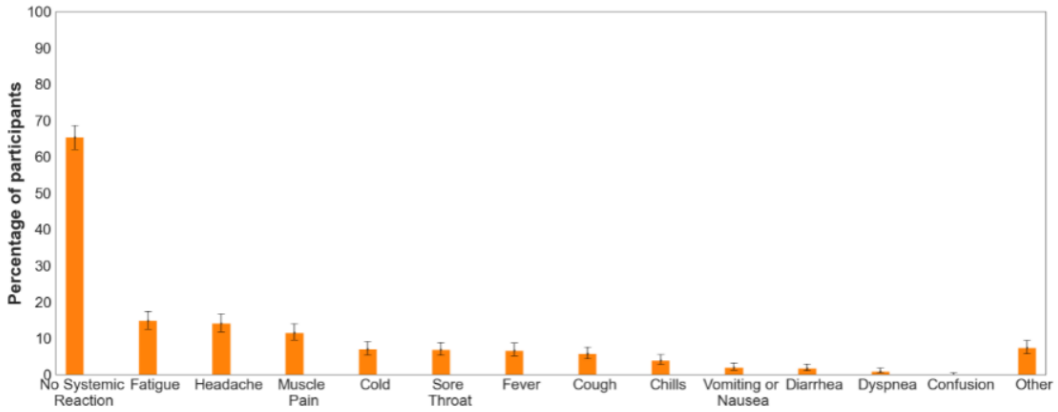


Figure S4. Self-reported reaction to the second booster dose. The bars represent the percentage of participants who reported a given reaction. Error bars represent 95% confidence intervals (n=648).

Difference in additional measures recorded by the smartwatch

We computed the differences in Resting Heart Rate (RHR) and steps recorded by the smartwatch during the seven days before and after vaccination. We also computed the differences in reported stress levels and sports duration as reported by participants via the PerMed application (Figure S5). We found a substantial rise in the RHR during the third day after vaccination compared to the seven days prior. We also found a substantial rise followed by a decline in the measurement of the step. No differences were observed between reported stress or duration levels after vaccination compared to the seven days prior.

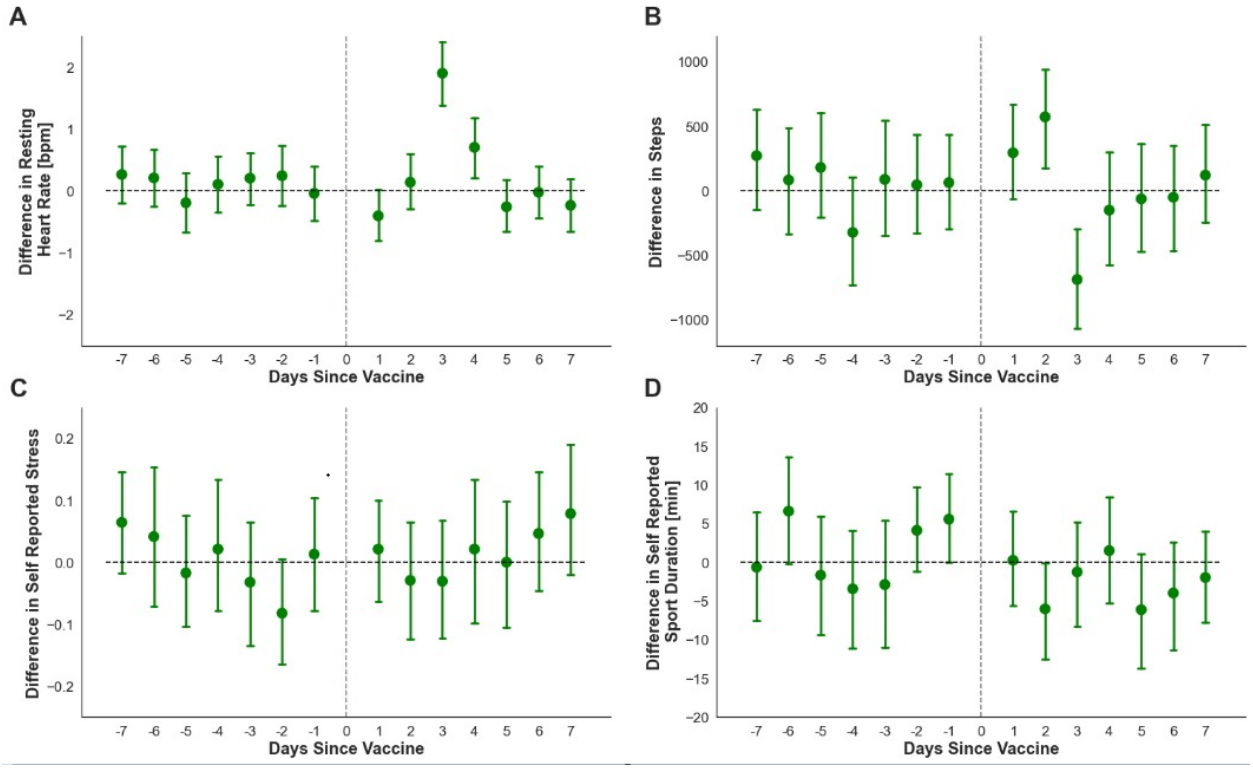


Figure S5. Difference in (A) daily resting heart rate (B) daily step counts (C), self-reported stress, (D) self reported sport duration. Difference was conducted by computing the mean values at time t to the ones observed seven days prior for each individual. The stress level was reported on a 1–5 Likert scale.

Since the daily data of Garmin have no specific related hour, the calendric date was used. Namely, 'zero' represents the difference in the indicator value between the date of vaccination and the value of the same day in the previous week.

However, to calculate the time differences in the well-being related indicators, we used the hour the participant reported on that value. Therefore in this case, 0 days post vaccination are counted as the time interval of 0 to 24 hours post vaccination.

Error bars indicate 95% CIs. Horizontal dashed lines indicate no change compared with the week before. Vertical dashed lines indicate the date of vaccination in panels (**A**) and (**B**) and the 24 hours post vaccination in panels (**C**) and (**D**).

Potential adverse events following the first booster dose compared to its baseline

We compared the frequency of potential adverse events 25 days pre- (baseline) and post-vaccination in a pairwise fashion. We observed only one positive significant risk difference in lymphadenopathy (risk difference: 8·982; 95% CI, 1·684 to 16·279) after the first booster uptake, among individuals who received also the second booster (Table S2). Furthermore, there were one event of myocarditis post-vaccination (risk difference: 0·561; 95% CI, 0·000 to 1·684). We also found no significant risk difference for pericarditis (risk difference, -0·561; 95% CI, -2·807 to 1·684).

Table S2. Adverse events associated with SARA-CoV-2 first booster dose (among individuals who also received the second booster, n=17,814).

Event	Number of individuals with event before the first booster**	Number of individuals with event after the first booster**	Risk difference first booster (95% CI) * *No. of events/10,000 persons*
Acute Kidney Injury	13	5	-4·491 (-9·543 to 0·0)
Anemia	259	191	-38·172 (-61·188 to -14·595)
Appendicitis	8	6	-1·123 (-5·052 to 2·807)
Arrhythmia	196	144	-29·191 (-49·399 to -8·982)
Arthritis or Arthropathy	40	32	-4·491 (-14·034 to 5·052)
Bell's Palsy	7	5	-1·123 (-5·052 to 2·807)
Cerebrovascular Accident	119	80	-21·893 (-37·611 to -6·736)
Deep Vein Thrombosis	1	2	0·561 (-1·123 to 2·807)
Herpes Simplex	17	11	-3·368 (-8·982 to 2·245)
Herpes Zoster	31	24	-3·929 (-12·35 to 3·929)
Intracranial hemorrhage	8	2	-3·368 (-6·736 to 0·0)
Lymphadenopathy	14	30	8·982 (1·684 to 16·279)
Lymphopenia	0	0	-
Myocardial Infarction	21	15	-3·368 (-10·104 to 3·368)
Myocarditis	0	1	0·561 (0·0 to 1·684)
Neutropenia	14	8	-3·368 (-8·42 to 1·684)
Other Thrombosis	3	1	-1·123 (-3·368 to 1·123)
Paresthesia	69	51	-10·104 (-22·454 to 1·684)
Pericarditis	3	2	-0·561 (-2·807 to 1·684)
Pulmonary Embolus	11	4	-3·929 (-8·42 to 0·0)
Seizures	2	2	0·0 (-2·245 to 2·245)
Syncope	39	35	-2·245 (-11·788 to 7·298)
Thrombocytopenia	14	9	-2·807 (-7·859 to 2·245)
Uveitis	1	3	1·123 (-1·123 to 3·368)
Vertigo	171	133	-21·332 (-40·418 to -2·245)

* The risk difference and confidence interval were estimated with the use of percentile bootstrap method with 10,000 repetitions.
** 42-day period consider before/after the booster dose.

Myocarditis and Pericarditis following the Primary series and first booster

We extended the analysis to examine whether these events are also associated with the primary series (i.e., first and second doses) in participants eligible to receive the second dose in Israel. This population includes individuals older than 60 years of age or individuals over 18 with certain comorbidities that have already received their first booster. Table S3 specifies basic characteristics (age group, sex, comorbidities, and vaccine dose) for each of the members that were diagnosed with myocarditis or pericarditis within 42 days after receiving the primary series or the first booster .Altogether, seven were diagnosed with myocarditis, and 19 were diagnosed with pericarditis out of 44,003 individuals and 132,009 vaccine episodes in total.

Table S3. Myocarditis and Pericarditis following the Primary series and first booster (among individuals eligible for the second booster**,** n= 44,003)

Age group	Sex	Comorbidities	Diagnosis	Vaccine dose	Number of individuals with event
60+y	Female	Yes	Myocarditis	Primary series	2
60+y	Female	Yes	Myocarditis	First booster	1
<60y	Male	Yes	Myocarditis	First booster	1
<60y	Male	Yes	Myocarditis	Primary series	3
60+y	Female	Yes	Pericarditis	First booster	2
60+y	Male	No	Pericarditis	Primary series	1
60+y	Male	Yes	Pericarditis	First booster	2
60+y	Male	Yes	Pericarditis	Primary series	6
<60y	Female	Yes	Pericarditis	First booster	1
<60y	Female	Yes	Pericarditis	Primary series	3
<60y	Male	Yes	Pericarditis	First booster	2
<60y	Male	Yes	Pericarditis	Primary series	2

An alternative matching-process analysis

We conducted an alternative analysis in which persons vaccinated with the second booster were matched in a 1:1 ratio to persons vaccinated with the first booster only.

We matched vaccine recipients and controls on variables associated with the probability of both vaccination and infection or severity of COVID -19: age (based on four age groups: 0-59y, 60-69y, 70-79y, and ≥80y), sex, the total number of coexisting conditions from a list identified by the Centers for Disease Control and Prevention (CDC) as risk factors for severe COVID-19 as of December 20, 2020. These matching variables are consistent with a large-scale retrospective study aimed at determining the safety of the primary (i.e., first and second doses) BNT162b2 mRNA Covid-19 Vaccine course [9]. Because our study aims to evaluate the safety of the second booster rather than the safety of COVID-19 vaccines in general, the controls were extracted from the pool of the individuals who already received the first booster (i.e., one cannot receive the second booster without receiving the first) rather than unvaccinated individuals. We note that when the second booster was offered, ~96.5% of the population >60 (i.e., those eligible for the second booster) received at least one vaccine dose. The health behavior and health consumption of those who remain unvaccinated at that time (3.5%) are inherently different from the rest of the population and, thus, cannot be used as controls. Likewise, because individuals were eligible to receive the second booster at least three months (84 days) after COVID-19 infection, controls also had to meet this criterion.

Each day from December 30, 2021, to July 22, 2022, all newly vaccinated persons were matched in a 1:1 ratio to controls. For each person, follow-up lasted for 42 days. It ended at the earliest of the following events: vaccination with the second booster of the matched control (for vaccinated persons), a week before positive-PCR diagnosis with COVID-19, death, or the end of the 42 days. Newly vaccinated persons with the second dose were eligible for inclusion in the study, even if they had previously been selected as a control. For each adverse event, matched pairs with a previous diagnosis of the event (i.e., 42 days before follow-up) were excluded. These assumptions are in line with a previous large-scale study [9].

Altogether, we could match 14,181 pairs in total. Figure S6 describes the study population diagram for the matching process. Table S4 summarizes the results obtained.

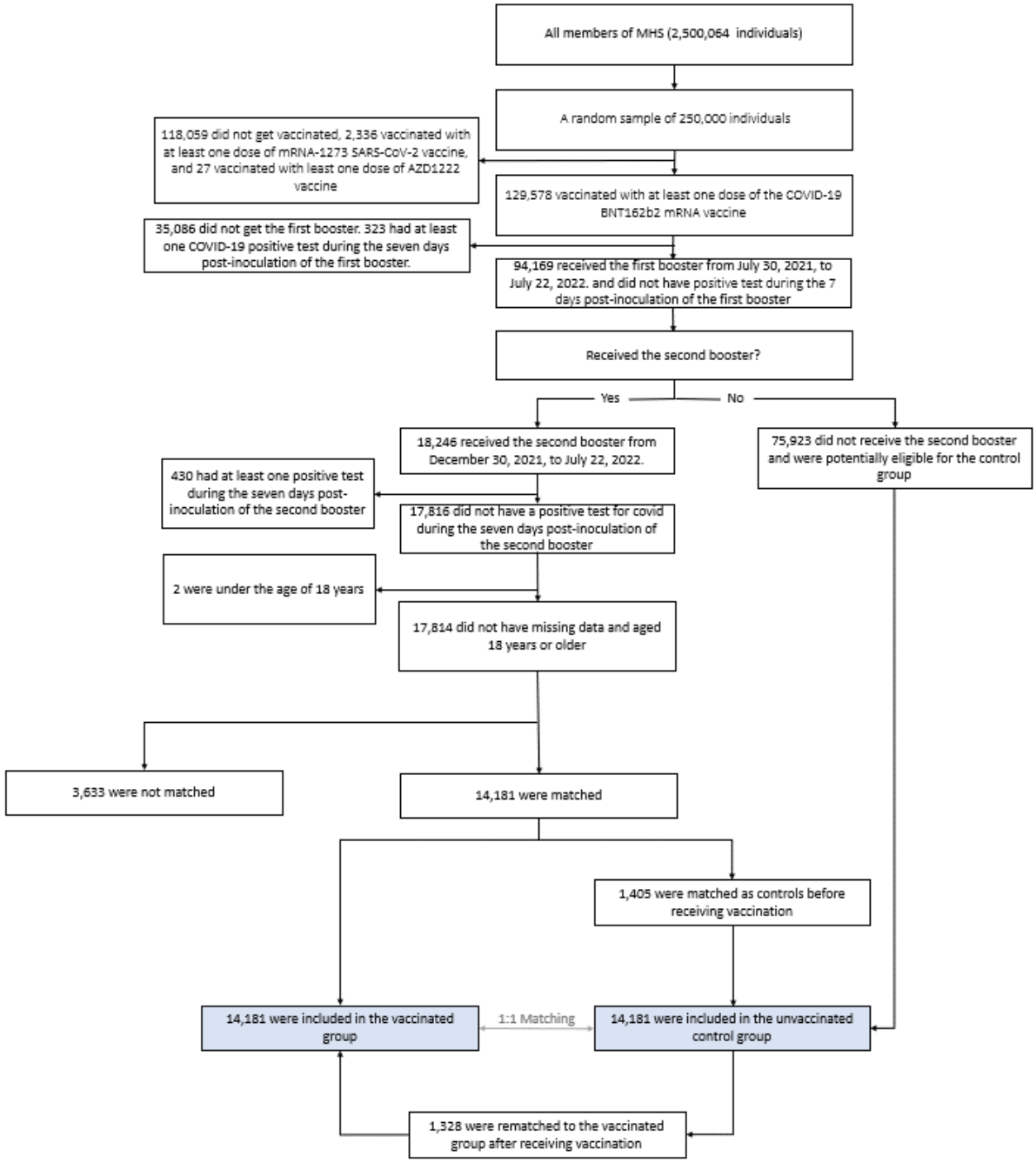


Figure S6. Study population diagram. Retrospective cohort matching process

Table S4. Adverse events associated with SARS-CoV-2 second booster – case-control analysis (n=14,181).

Event	Adverse-Events Cohort in Each Group	Vaccinated Group	Control Group	Risk Difference (95% CI) *No. of events/10,000 persons*
Acute Kidney Injury	14,166	5	10	-3·53 (-9·177 to 1·412)
Anemia	13,764	134	128	4·359 (-18·163 to 27·608)
Appendicitis	14,174	3	3	0·0 (-3·528 to 3·528)
Arrhythmia	13,836	112	113	-0·723 (-22·405 to 20·237)
Arthritis or Arthropathy	14,123	16	24	-5·665 (-14·869 to 2·832)
Bell's Palsy	14,168	5	3	1·412 (-2·117 to 5·647)
Cerebrovascular Accident	13,990	64	84	-14·296 (-31·451 to 2·859)
Deep Vein Thrombosis	14,176	3	5	-1·411 (-5·643 to 2·116)
Herpes Simplex	14,156	13	7	4·238 (-2·119 to 10·596)
Herpes Zoster	14,134	23	22	0·708 (-8·49 to 9·905)
Intracranial hemorrhage	14,167	8	2	4·235 (0·0 to 9·176)
Lymphadenopathy	14,147	17	15	1·414 (-6·362 to 9·189)
Lymphopenia	14,181	0	0	-
Myocardial Infarction	14,141	9	22	-9·193 (-16·972 to -1·414)
Myocarditis	14,179	0	1	-0·705 (-2·116 to 0·0)
Neutropenia	14,158	8	7	0·706 (-4·944 to 6·357)
Other Thrombosis	14,173	4	4	0·0 (-3·528 to 4·233)
Paresthesia	14,061	48	44	2·845 (-10·668 to 16·357)
Pericarditis	14,179	0	4	-2·821 (-5·642 to -0·705)
Pulmonary Embolus	14,165	6	2	2·824 (-0·706 to 7·06)
Seizures	14,167	4	3	0·706 (-2·823 to 4·235)
Syncope	14,091	30	28	1·419 (-9·226 to 12·064)
Thrombocytopenia	14,161	6	7	-0·706 (-5·649 to 4·237)
Uveitis	14,172	3	2	0·706 (-2·117 to 3·528)
Vertigo	13,917	117	119	-1·437 (-23·712 to 19·401)

* The risk difference and confidence interval were estimated with the use of the percentile bootstrap method with 10,000 repetitions.

Examining the relation between the severity of reported reactions between first and second boosters

To examine the relation between the severity of reported reactions to the second booster vs. the first booster, controlling for other explanatory variables (age, and interval between boosters), we fitted an ordinal logistic regression. We first categorized reactions into three levels "No Reaction", a "Mild Reaction", or a "Moderate-to-Severe Reaction" based on the same criteria used in a recent study [13], which is based on CDC and the Pfizer clinical trial [14,15] categorizations. Specifically, we categorized symptoms as follows:

- No reactions: no new reactions following vaccination
- Mild symptoms: abdominal pain, back or neck pain, feeling cold, feeling hot (and did not measure body temperature or body temperature reported <38·9ºC), muscle pain, weakness, headache, dizziness, vomiting, sore throat, diarrhea, cough, leg pain, ear pain, loss of taste and smell, swelling of the lymph nodes, fast heartbeat, and hypertension.
- Severe symptoms: chest pain, dyspnea (shortness of breath), fever above 38·9ºC, confusion, and chills.

Participants were either classified as having "No Reaction", a "Mild Reaction", or a "Severe Reaction", based on their most severe symptom reported in the seven days after each vaccination. Thus, if a participant reported one severe symptom for one day and mild symptoms for all three days after vaccination, the participant was classified as having a severe reaction. Participants could be categorized into different severity groups after each booster dose.

Our ordinal logistics regression model revealed a significant association between the severity of reported reactions to the second booster and the explanatory variables: age, the time interval between boosters, and the severity of reported reactions to the first booster (Table S5).

Table S5. Ordinal logistics regression model results for the severity of self-reported reactions

Coefficient	Value (95% CI)	P-value
# of Days between boosters	-0·009 (-0·016 to -0·002)	0·011
Age	-0·046 (-0·065 to -0·027)	<0·001
Severity of reported reactions to the first booster	1·177 (0·840 to 1·515)	<0·001
Intercept: No reaction/Mild	-1·707 (-3·562 to 0·148)	0·071
Intercept: Mild /Moderate to Severe	0·827 (0·633 to 1·022)	<0·001

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