# Long covid outcomes at one year after mild SARS-CoV-2 infection: nationwide cohort study

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## ABSTRACT

### OBJECTIVES

To determine the clinical sequelae of long covid for a year after infection in patients with mild disease and to evaluate its association with age, sex, SARS-CoV-2 variants, and vaccination status.

### DESIGN

Retrospective nationwide cohort study.

### SETTING

Electronic medical records from an Israeli nationwide healthcare organisation.

### POPULATION

1 913 234 Maccabi Healthcare Services members of all ages who did a polymerase chain reaction test for SARS-CoV-2 between 1 March 2020 and 1 October 2021.

### MAIN OUTCOME MEASURES

Risk of an evidence based list of 70 reported long covid outcomes in unvaccinated patients infected with SARS-CoV-2 matched to uninfected people, adjusted for age and sex and stratified by SARS-CoV-2 variants, and risk in patients with a breakthrough SARS-CoV-2 infection compared with unvaccinated infected controls. Risks were compared using hazard ratios and risk differences per 10 000 patients measured during the early (30-180 days) and late (180-360 days) time periods after infection.

### RESULTS

Covid-19 infection was significantly associated with increased risks in early and late periods for anosmia and dysgeusia (hazard ratio 4.59 (95% confidence interval 3.63 to 5.80), risk difference 19.6 (95% confidence interval 16.9 to 22.4) in early period; 2.96 (2.29 to 3.82), 11.0 (8.5 to 13.6) in late period), cognitive impairment (1.85 (1.58 to 2.17), 12.8, (9.6 to 16.1); 1.69 (1.45 to 1.96), 13.3 (9.4 to 17.3)), dyspnoea (1.79 (1.68 to 1.90), 85.7 (76.9 to 94.5); 1.30 (1.22 to 1.38), 35.4 (26.3 to 44.6)), weakness (1.78 (1.69 to 1.88), 108.5, 98.4 to 118.6; 1.30 (1.22 to 1.37), 50.2 (39.4 to 61.1)), and palpitations (1.49 (1.35 to 1.64), 22.1 (16.8 to 27.4); 1.16 (1.05 to 1.27), 8.3 (2.4 to 14.1)) and with significant but lower excess risk for streptococcal tonsillitis and dizziness. Hair loss, chest pain, cough, myalgia, and respiratory disorders were significantly increased only during the early phase. Male and female patients showed minor differences, and children had fewer outcomes than adults during the early phase of covid-19, which mostly resolved in the late period. Findings remained consistent across SARS-CoV-2 variants. Vaccinated patients with a breakthrough SARS-CoV-2 infection had a lower risk for dyspnoea and similar risk for other outcomes compared with unvaccinated infected patients.

### CONCLUSIONS

This nationwide study suggests that patients with mild covid-19 are at risk for a small number of health outcomes, most of which are resolved within a year from diagnosis.

## WHAT IS ALREADY KNOWN ON THIS TOPIC

More than 500 million people have been infected with SARS-CoV-2, with most of them experiencing mild disease

Long covid is defined as symptoms persisting or new symptoms appearing beyond four weeks from the primary diagnosis of covid-19

The clinical sequelae one year after mild covid-19 and their association with age, sex, SARS-CoV-2 variants, and vaccination status are still unclear

## WHAT THIS STUDY ADDS

Patients with mild covid-19 had an increased risk for a small number of health outcomes, most of which resolved within a year from diagnosis

Children had fewer outcomes, which mostly resolved in the late period, sex had a minor effect on risk of outcomes, and findings remained consistent across SARS-CoV-2 variants

A lower risk for dyspnoea and similar risk for other outcomes was observed in vaccinated patients with breakthrough covid-19 infection compared with unvaccinated patients

## Introduction

More than two years into the global pandemic, SARS-CoV-2 has caused more than 600 million confirmed cases of covid-19 worldwide, resulting in more than 6.5 million deaths as of November 2022.[1] Since the beginning of the pandemic, several variants of the virus have been identified, among which five were defined as variants of concern by the World Health Organization: alpha, beta, gamma, delta, and omicron.[2] These variants differ in transmissibility, disease course, and disease severity.[3] Furthermore, they may affect disease diagnostics, decrease susceptibility to treatments, reduce vaccine mediated protection from severe illness, and potentially affect the long term health outcomes after SARS-CoV-2 infection, also known as long covid outcomes.

The acute disease caused by SARS-COV-2 is diverse and can range from asymptomatic or mild respiratory disease to a multisystem life threatening syndrome.[4] Most cases resolve within two to four weeks of the initial symptoms' appearance; however, an increasing body of evidence shows long term sequelae, also referred to as long covid.[5-19] The clinical definition

of long covid is still evolving, but so far it has been defined as persistent symptoms or appearance of new symptoms beyond four weeks from the diagnosis of primary covid-19, which cannot be attributed to an alternative condition.[20 21] It may present with various multi-organ symptoms such as dyspnoea, fatigue, myalgia, cough, cognitive dysfunction, chest pain, and palpitations, which vary in prevalence and severity. The immunological mechanisms and pathophysiology of long covid are still being studied, but some risk factors have already been identified, including older age; pre-existing comorbidities such as obesity, cardiovascular disease, chronic lung disease, kidney disease, hypertension, and diabetes mellitus; initial disease severity; and female sex.[5-7 11 15 22-25] As of March 2022 an estimated 1.5 million people in the UK (2.4% of the population) completed a self-reported survey describing long covid symptoms persisting for more than four weeks after the initial infection, mainly fatigue, shortness of breath, loss of smell, loss of taste, and difficulty concentrating.[26]

Current efforts focus on assessing the prevalence of long covid and monitoring its clinical manifestations; however, these efforts are hampered by non-standardised study designs, differences in data quality, and the lack of appropriate comparative methods in most studies.[13] Most of the data to date came from population surveys without controls, and the observational studies of large datasets also lack comparison with an appropriate control group. To provide efficient continuous treatment and prevent adverse events related to potential long term effects and delayed symptoms of covid-19, determining the magnitude and severity of this phenomenon and distinguishing it from similar clinical manifestations that occur normally or following infections with other pathogens is essential.

Extreme global efforts to mitigate transmission of SARS-CoV-2 and prevent deterioration to severe illness were focused on developing a vaccine quickly. So, less than a year into the pandemic, the first mRNA based covid-19 vaccine was developed, followed by an international scale vaccination campaign.[27 28] International assessments of vaccine efficiency have shown that a two dose regimen of the BNT162b2 vaccine is highly effective across all age groups (≥16 years) in preventing symptomatic and asymptomatic SARS-CoV-2 infections and covid-19 related hospital admissions, severe disease, and death. Furthermore, administration of a third booster dose has also been shown to be effective in reducing covid-19 cases and severe illness.[29-33] Despite the cumulative evidence of the covid-19 vaccines' ability to reduce disease burden and severity, whether immunisation protects against the long term sequelae of breakthrough covid-19 infection is still unknown.[34-36]

The main objective of this study was to compare the long term incidence of a large set of health outcomes between uninfected people and patients with mild covid-19. Additionally, we studied the associations between mild covid-19 and long lasting health outcomes in different age and sex subgroups and after infection with different SARS-CoV-2 variants. Finally, we assessed the differences in long covid clinical sequelae between vaccinated and unvaccinated people who recovered from a mild disease.

## Methods

### Study settings

In this study, we analysed electronic health records from the comprehensive database of Maccabi Healthcare Services (MHS), the second largest health maintenance organisation in Israel. Israeli citizens are required to become members of one of the four health maintenance organisations in the country. MHS covers a quarter of the Israeli population, with a nationally representative sociodemographic distribution. The database contains medical data of a stable population of more than 2.5 million people collected since 1993 with an approximately 1% annual attrition rate. It includes longitudinal data for all covid-19 diagnoses, deterioration, recovery, and post-recovery follow-up in outpatient clinics. Detailed demographic information, diagnoses, chronic disease registries, administrative billing codes, medication dispensations, full laboratory data from a single central laboratory, and all other complementary services that are offered by the health fund were all included in the dataset. In addition, the Israeli Ministry of Health collects and shares covid-19 data with all the Israeli health funds, including the results of all SARS-CoV-2 polymerase chain reaction (PCR) testing, admissions to hospital with covid-19, and covid-19 immunisations dates. PCR tests were offered to all Israeli citizens free of charge with no need for referral throughout the entire study period. Consequently, 76% of MHS' members had at least one PCR test during the study period.

### Eligibility criteria (study population)

The study included all MHS members with a PCR test for SARS-CoV-2 (positive or negative) between 1 March 2020 and 1 October 2021, with at least one year's membership in the health organisation before the test. We excluded from the study all patients who were admitted to hospital with covid-19 during the 30 days after infection, aiming to investigate long covid in patients with mild disease. The criteria for hospital admission of patients with covid-19 in Israel were consistent throughout the study period, in accordance with guidelines set by the Ministry of Health.[37] To distinguish between new outcomes and existing ones, we further excluded patients who had the considered outcome before the PCR test (index date). However, the exclusion criteria were different for different outcome types: for outcomes reflecting a chronic state (for example, asthma, diabetes), we excluded patients with any occurrence of that outcome in the past; for outcomes reflecting a temporary state (for example, cough, weakness) we excluded patients with occurrence of that outcome in the previous year.

### Study design

In this retrospective cohort study, we evaluated health outcomes in unvaccinated people with SARS-CoV-2 infection compared with people without SARS-CoV-2 infection, controlling for age and sex and with stratification by SARS-CoV-2 variants, and in vaccinated versus unvaccinated people infected with SARS-CoV-2. We used symptoms and diagnoses recorded by physicians as ICD-10 (international classification of diseases, 10th revision) codes to obtain information on outcomes potentially related to long covid. These outcomes could be documented repeatedly by the physicians, allowing longitudinal capture of the patients' clinical status. We matched eligible patients with a first positive PCR test for SARS-CoV-2 in a one-to-one ratio to eligible patients with a negative PCR test and no previous positive PCR test. To overcome biases related to infection, we applied both matching and weighting methods. We applied exact matching for major confounders to ensure tight balance and inverse weighting via propensity scores for weaker confounders to retain sufficient sample size. We applied exact matching on age (year of birth), sex, month of test, and covid-19 immune status on the day of the PCR test (unvaccinated, partially vaccinated, second dose covid-19 vaccine, and covid-19 booster). We used only data available on or before the day of the PCR test when applying the coupling. If during the follow-up period an unexposed patient (PCR negative) was infected with SARS-CoV-2, we censored the follow-up of the entire matched pair. This patient then re-started follow-up as an exposed patient (PCR positive) and was matched to a new unexposed person.[38] We calculated the propensity scores via a logistic regression model for the probability of being SARS-CoV-2 positive, including the following pre-existing chronic conditions: cardiovascular disease, immune deficiency, pre-diabetes status, diabetes, hypertension, chronic kidney disease, cancer, obesity, and chronic obstructive pulmonary disease, as well as

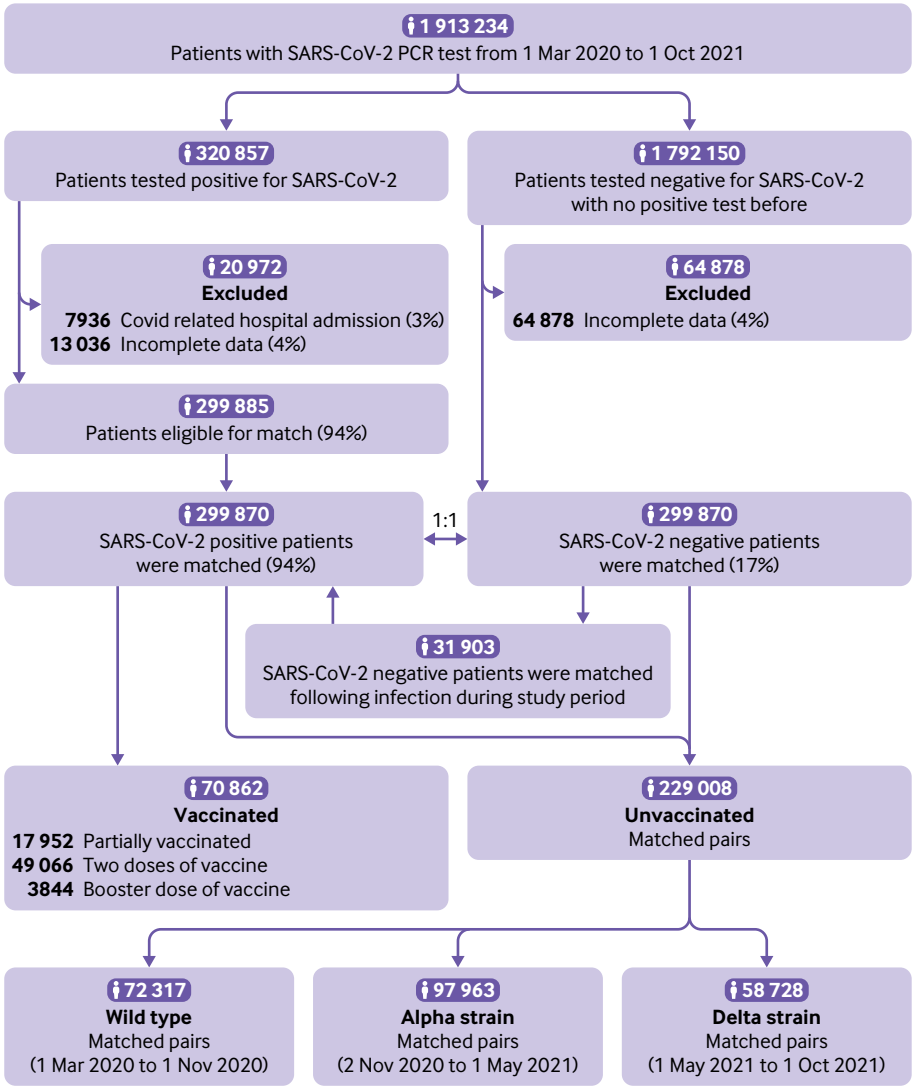


**Fig 1 | Study population and cohort selection. Schematic representation of cohort and sub-cohorts selection. People who were included in matched negative SARS-CoV-2 cohort and tested positive during study were added to positive cohort and re-matched. SARS-CoV-2 variants were determined according to variant dominance at time of polymerase chain reaction (PCR) testing**

alcohol intake, smoking status, sector (general secular Israeli population, Israeli-Arab, ultra-Orthodox Jewish), residential socioeconomic level (scale from 1 to 10 categorised into three groups: low 1-3, medium 4-6, high 7-10), and history of influenza vaccination in the previous three years. The residential sector and socioeconomic scores came from the Israel Central Bureau of Statistics and additional previously described data sources.[39 40] The follow-up of the matched pair was terminated at the earliest of the following conditions: end of the study period, death, leaving MHS, or a second infection of the exposed patient determined by a positive PCR test more than 90 days after the first infection date.

Firstly, to quantify the risk for long term health outcomes associated with mild SARS-CoV-2 infection in unvaccinated people, we analysed a sub-cohort of unvaccinated SARS-CoV-2 infected and non-infected pairs during wild-type virus and alpha variant periods and compared all reported covid-19 outcomes between pairs (we did not include the delta variant owing to insufficient follow-up). We categorised age into six age groups: three children's subgroups (0-4, 5-11, and 12-18 years) and three adults' subgroups (19-40, 41-60, and >60) (supplementary table S2a). The follow-up period was from the second to 12th month after the PCR test, to target outcomes related to covid-19 after the acute period (first month).

Secondly, to assess the risk for long term health outcomes in patients with mild covid-19 caused by different SARS-CoV-2 variants, we used the same sub-cohort of paired unvaccinated people and applied an additional match by age and sex between pairs infected with each variant. We then analysed covid outcomes by comparing wild-type SARS-CoV-2 with the alpha (B.1.1.7) variant and by comparing wild-type SARS-CoV-2 and the alpha variant with the delta (B.1.617.2) variant. We classified the infections into variants on the basis of the PCR test date and according to the dominant variant at that time. The dominant variant of each period was declared by the Israeli Ministry of Health (variant comprised ≥90% of cases at the peak period on the basis of genetic sequencing): wild type SARS-CoV-2 was dominant from 1 March 2020 to 1 November 2020, the alpha variant was dominant from 2 November 2020 to 1 May 2021, and the delta variant was dominant from 2 May 2021 to 1 October 2021 (fig 1; supplementary figure S1).[41-43]

Thirdly, to evaluate the association between the vaccination status of infected patients and long term health outcomes, we analysed a sub-cohort of vaccinated and unvaccinated SARS-CoV-2 infected patients (≥12 years old), during the alpha and delta variants periods, with a follow-up time of 30-90 days. Full 90 day follow-up was available for 99% of the patients in the cohort. We considered patients vaccinated if infection occurred later than 14 days after the second dose of vaccine, as previously described,[44] and in accordance with Centers for Disease Control and Prevention (CDC) guidelines. We applied similar matching and weighting methods to those used for comparing SARS-CoV-2 infected and non-infected pairs to compare vaccinated and unvaccinated pairs.

### Outcomes

We compared incidence rates of several outcomes that might be associated with covid-19 in the short and long term after infection: symptoms, new diagnoses of chronic diseases, new acute complications, and new infectious diseases. A complete list of the study outcomes is provided in supplementary table S1. The set of outcomes for this study came from several resources including the CDC reports,[21] WHO publications,[45] Israeli Ministry of Health publications, and additional scientific reports (all referenced in supplementary table S1). In addition, we held consultations with an infectious disease specialist and family physicians at MHS and with physicians from a dedicated recovery clinic established for the benefit of covid-19 patients with long term symptoms. To obtain information about the outcomes, we used diagnoses reported by physicians as ICD-10 codes in the patients' medical files. Records of diagnoses that were included in free text only and not documented as ICD-10 codes were not included in the study. Extremely rare outcomes (fewer than 10 events overall, in both groups) are presented only in supplementary tables S1, S2b, and S2c. We classified the outcomes into two groups: recurrent events and first time events. For recurrent events, we took all the instances in which the diagnosis was registered in the medical files to estimate the length of time the patient experienced the diagnosis. For first time events, we took the first date during the follow-up period.[46]

As SARS-CoV-2 is a respiratory virus, presenting significant lingering respiratory related symptoms, we also analysed more specifically reports of pulmonary health outcomes and assessed the severity and health related burden by extracting the relevant dispensed drugs for obstructive airway disease (Anatomical Therapeutic Chemical code R03).

### Statistical analysis

We calculated hazard ratios and 95% confidence intervals for the positive versus negative covid-19 groups in the periods of 30-90 days, 30-180 days, and 180-360 days from infection, using inverse propensity score weighting Cox regression. We applied a similar analysis for SARS-CoV-2 infected patients, with hazard ratios and 95% confidence intervals of vaccinated versus unvaccinated patients for each outcome, using inverse propensity score weighting to balance the groups. We assessed possible effect modifications through inclusion of interaction terms in the model reflecting hazard ratios that differed by age and sex. We applied false discovery rate correction within each study objective to control for multiple hypotheses within the objective. We presented false discovery rate adjusted P values as Q values and took 0.05 as the cut-off for significance.

To estimate the burden of covid-19 outcomes, we calculated risk differences by using time to event

Kaplan-Meier analysis with inverse propensity score weighting. We calculated the risk differences per 10 000 people for the periods of 30-180 days, 30-360 days, and 180-360 days, to differentiate between short and long term outcomes. We tested the heterogeneity of hazard ratios between variants and sexes via a z score calculated as the difference between the two logs hazard ratio divided by the standard error. We used Python version 3.1 with the stats model, causallib, and liflelies packages for analyses.

### Patient and public involvement

Owing to the nature of this study and data privacy constraints, patients and members of the public were not involved in the design, analysis, and interpretation of the study. We aim to engage the public through wide dissemination of the findings in various health organisations and media outlets.

## Results

### Study population

The study cohort comprised 1 913 234 MHS members who did a SARS-CoV-2 PCR test between 1 March 2020 and 1 October 2021 (fig 1). Follow-up data for hospital admissions and health outcomes were available until 1 January 2022. We had 299 885 eligible members with complete data, who tested positive for SARS-CoV-2 and had not been admitted to hospital with covid-19 a month after their diagnosis. Of these, we matched 299 870 to people who tested negative and had similar age, sex, time of test, and vaccination status (see Methods section). The tested cohort had a median age of 25 years and 50.6% were female (table 1). The demographic proportion of the sectors and socioeconomic levels showed some variations between SARS-CoV-2 positive and negative people. The SARS-CoV-2 positive group had an increased

**Table 1 | Baseline characteristics of study cohort. Values are numbers (percentages) unless stated otherwise**

| Characteristics | SARS-CoV-2 positive (n=299 870) | SARS-CoV-2 negative (n=299 870) | Standardised mean difference | Standardised mean difference, weighted |
|---|---|---|---|---|
| Median (IQR) age, years | 25 (12-43) | 25 (12-43) | | |
| Age group, years: | | | 0.000 | 0.000 |
| 0-4 | 23 403 (7.8) | 23 403 (7.8) | | |
| 5-11 | 50 444 (16.8) | 50 444 (16.8) | | |
| 12-18 | 44 461 (14.8) | 44 461 (14.8) | | |
| 19-40 | 98 066 (32.7) | 98 066 (32.7) | | |
| 41-60 | 63 038 (21.0) | 63 038 (21.0) | | |
| >60 | 20 458 (6.8) | 20 458 (6.8) | | |
| Sex: | | | 0.000 | 0.000 |
| Female | 151 775 (50.6) | 151 775 (50.6) | | |
| Male | 148 095 (49.4) | 148 095 (49.4) | | |
| Vaccination status: | | | 0.000 | 0.000 |
| Unvaccinated | 229 008 (76.4) | 229 008 (76.4) | | |
| Partially vaccinated | 17 952 (6.0) | 17 952 (6.0) | | |
| Two vaccine doses | 49 066 (16.4) | 49 066 (16.4) | | |
| Booster dose | 3844 (1.3) | 3844 (1.3) | | |
| Dominant SARS-CoV-2 variant during testing: | | | 0.000 | 0.000 |
| Wild-type | 72 317 (24.1) | 72 317 (24.1) | | |
| Alpha | 114 395 (38.1) | 114 395 (38.1) | | |
| Delta | 113 158 (37.7) | 113 158 (37.7) | | |
| Cancer | 6953 (2.3) | 8990 (3.0) | 0.042 | 0.001 |
| Cognitive disease | 1762 (0.6) | 1528 (0.5) | 0.011 | 0.001 |
| Immune deficiency | 2842 (0.9) | 3204 (1.1) | 0.012 | 0.001 |
| Diabetes | 11 412 (3.8) | 9690 (3.2) | 0.031 | 0.001 |
| Pre-diabetes | 42 121 (14.0) | 40 500 (13.5) | 0.016 | 0.001 |
| Hypertension | 22 490 (7.5) | 19 516 (6.5) | 0.039 | 0.002 |
| Cardiovascular disease | 10 804 (3.6) | 11 960 (4.0) | 0.020 | 0.001 |
| Chronic kidney disease | 4756 (1.6) | 4829 (1.6) | 0.002 | 0.002 |
| Obesity | 63 418 (21.1) | 62 442 (20.8) | 0.008 | 0.000 |
| COPD | 1519 (0.5) | 1932 (0.6) | 0.018 | 0.001 |
| Alcohol | 1174 (0.4) | 1295 (0.4) | 0.006 | 0.001 |
| Smoking | 29 596 (9.9) | 37 626 (12.5) | 0.085 | 0.000 |
| History of flu vaccine in previous 3 years | 84 008 (28.0) | 101 732 (33.9) | 0.128 | 0.001 |
| Sector: | | | | |
| General Israeli | 213 125 (71.1) | 257 681 (85.9) | 0.371 | 0.002 |
| Jewish Orthodox | 66 233 (22.1) | 23 773 (7.9) | 0.413 | 0.003 |
| Israeli Arabs | 20 510 (6.8) | 18 298 (6.1) | 0.003 | 0.000 |
| Socioeconomic level: | | | | |
| Low | 95 594 (31.9) | 50 784 (16.9) | 0.355 | 0.003 |
| Medium | 104 105 (34.7) | 90 645 (30.2) | 0.096 | 0.001 |
| High | 100 171 (33.4) | 158 441 (52.8) | 0.400 | 0.001 |
| Median (IQR) follow up time, days | 304 (128-369) | 302 (131-371) | 0.012 | 0.012 |

COPD=chronic obstructive pulmonary disease; IQR=interquartile range.

| Reported health conditions | No of patients 30-180 days | No of events in SARS-CoV-2 positive/negative 30-180 days | No of patients 180-360 days | No of events in SARS-CoV-2 positive/negative 180-360 days |
|---|---|---|---|---|
| **Symptom** | | | | |
| Anosmia and dysgeusia | 162 387 | 344/90 | 150 177 | 208/83 |
| Respiratory disorders | 161 005 | 97/44 | 148 937 | 30/35 |
| Concentration and memory | 161 785 | 403/243 | 149 618 | 407/276 |
| Dyspnoea | 155 240 | 2853/1673 | 143 541 | 2035/1640 |
| Weakness | 150 829 | 3681/2023 | 139 581 | 2806/2107 |
| Hair loss | 159 395 | 1055/687 | 147 371 | 559/703 |
| Palpitations | 159 339 | 1015/734 | 147 340 | 833/773 |
| Chest pain | 151 539 | 2770/2125 | 140 058 | 2413/2479 |
| Muscle atrophy | 162 665 | 83/61 | 150 445 | 71/61 |
| Myalgia | 156 946 | 1287/1086 | 145 093 | 1200/1184 |
| Dizziness | 155 720 | 1389/1260 | 143 996 | 1515/1355 |
| Tremor | 162 240 | 154/143 | 150 044 | 150/164 |
| Tinnitus | 160 135 | 611/599 | 148 054 | 547/665 |
| Voice disorder | 161 119 | 412/347 | 149 016 | 443/395 |
| Arthralgia | 156 771 | 1139/1070 | 144 926 | 1217/1137 |
| Insomnia | 162 758 | 22/25 | 150 522 | 37/42 |
| Cough | 139 170 | 3851/3598 | 128 609 | 3774/3788 |
| Hyperhidrosis | 162 707 | 41/52 | 150 476 | 20/47 |
| Visual disturbances | 160 443 | 460/444 | 148 369 | 473/500 |
| Headache | 144 950 | 2847/2932 | 134 055 | 2905/3181 |
| Paraesthesia | 159 539 | 713/768 | 147 529 | 711/889 |
| Menstruation abnormalities | 123 816 | 385/392 | 114 014 | 347/389 |
| Abdominal pain | 135 627 | 4356/4671 | 125 372 | 4618/5104 |
| Bloody stool | 161 980 | 175/183 | 149 801 | 192/206 |
| Nausea or vomiting | 156 426 | 1236/1340 | 144 635 | 1371/1543 |
| Skin rash | 155 745 | 1162/1322 | 143 944 | 1089/1221 |
| Loss of appetite | 159 712 | 620/716 | 147 706 | 594/710 |
| Convulsions | 155 920 | 72/81 | 144 273 | 67/57 |
| Weight loss | 161 235 | 337/407 | 149 134 | 310/408 |
| Sore throat | 158 660 | 708/754 | 146 769 | 797/738 |
| Rhinorrhoea | 162 561 | 67/82 | 150 350 | 62/69 |
| Lymphadenopathy | 160 411 | 481/682 | 148 360 | 501/658 |
| Diarrhoea | 162 686 | 17/31 | 150 464 | 27/44 |

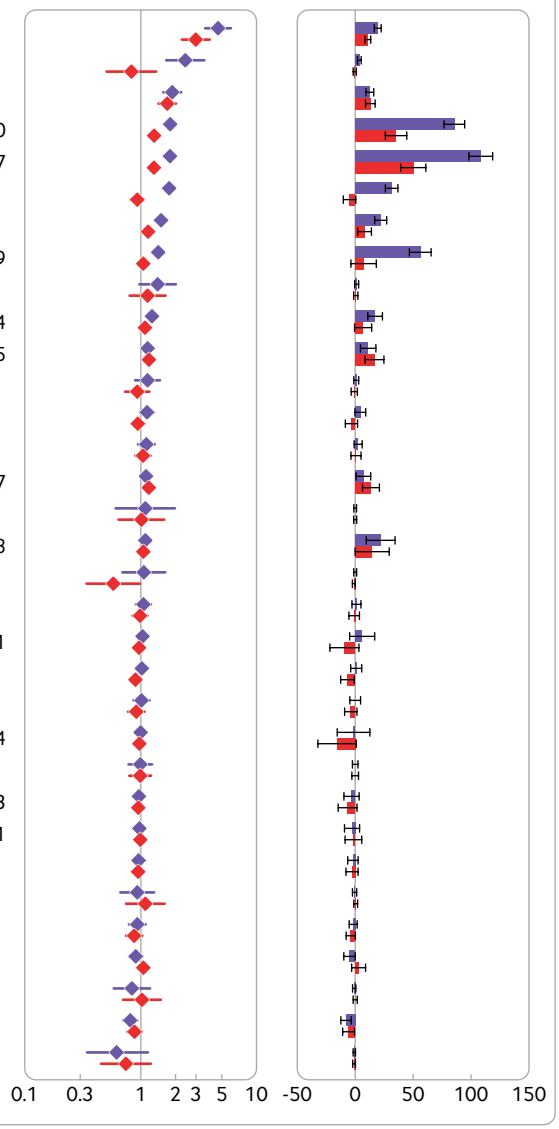


**Fig 2 | Risk for long term health outcomes after SARS-CoV-2 infection in patients with mild disease. Hazard ratios and risk differences per 10 000 patients of reported health outcomes (persistent symptoms) in unvaccinated SARS-CoV-2 infected patients with mild covid-19 during early and late periods**

representation of the Jewish Orthodox sector (22.1% *v* 7.9% in the SARS-CoV-2 negative group) and the low socioeconomic status level (31.9% *v* 16.9% in the SARS-CoV-2 negative group). Propensity score weighting eliminated these differences between the groups. The prevalence of comorbidities in SARS-CoV-2 positive and negative people was similar, and the propensity score weighting corrected the minimal differences observed between the groups.

### Clinical sequelae of covid-19 in unvaccinated patients

We quantified the long term clinical sequelae associated with a mild SARS-CoV-2 infection in unvaccinated patients for 70 health conditions that were reported in the literature as being associated with covid-19 and grouped them under four categories: persistent symptoms, acute diagnoses, infectious diseases, and new diagnoses of chronic conditions (supplementary table S1). Uniquely in this study, we evaluated risk longitudinally using both hazard ratios and risk differences in a matched sub-cohort of SARS-CoV-2 positive and negative unvaccinated people supplementary (table S2a; fig 2; fig 3) during two time periods after a positive PCR test: the early phase (30-180 days; supplementary table S2b) and the late phase (180-360 days; supplementary table S2c).

| Reported health conditions | No of patients 30-180 days | No of events in SARS-CoV-2 positive/negative 30-180 days | No of patients 180-360 days | No of events in SARS-CoV-2 positive/negative 180-360 days |
|---|---|---|---|---|
| **Acute diagnosis** | | | | |
| Myocarditis | 162 841 | 11/5 | 150 600 | 12/10 |
| Diseases of pleura | 162 092 | 14/10 | 149 917 | 10/14 |
| Herpes simplex | 129 338 | 218/197 | 119 578 | 217/228 |
| Hyperreactive airway disease | 95 601 | 339/296 | 88 877 | 353/302 |
| Guillain-Barré syndrome | 162 853 | 11/11 | 150 609 | 7/3 |
| Hospital admission | 147 172 | 2451/2292 | 136 240 | 2410/2424 |
| Conjunctivitis | 148 671 | 2474/2366 | 137 431 | 2468/2462 |
| Venous thromboembolism | 161 976 | 211/201 | 149 803 | 198/182 |
| Appendicitis | 153 343 | 89/105 | 141 902 | 77/111 |
| Invasive pneumococcal | 156 136 | 50/49 | 144 428 | 63/57 |
| Respiratory failure | 162 660 | 9/12 | 150 445 | 8/10 |
| Ischaemic stroke and TIA | 159 687 | 43/73 | 147 678 | 54/53 |
| Cerebral haemorrhage | 162 070 | 12/19 | 149 905 | 10/15 |
| Encephalitis | 162 834 | 7/13 | 150 596 | 7/13 |
| **Infectious disease** | | | | |
| Streptococcal tonsillitis | 154 689 | 1489/1007 | 143 103 | 2087/1555 |
| Herpes zoster | 161 611 | 248/285 | 149 437 | 260/330 |
| **Chronic condition** | | | | |
| Pericarditis | 161 758 | 35/28 | 149 592 | 32/26 |
| Fatty liver | 148 501 | 382/324 | 137 156 | 358/337 |
| Hypertension | 138 312 | 253/207 | 127 606 | 237/203 |
| Diabetes mellitus | 152 515 | 183/140 | 140 991 | 209/163 |
| Cardiac arrhythmias | 154 039 | 165/152 | 142 459 | 113/137 |
| Diseases of nervous system | 138 284 | 329/326 | 127 577 | 337/306 |
| Pulmonary disease | 157 381 | 50/51 | 145 514 | 58/71 |
| Anxiety | 128 026 | 549/541 | 118 024 | 450/520 |
| Parkinsonism | 162 289 | 13/11 | 150 109 | 14/15 |
| Depression | 143 401 | 218/251 | 132 348 | 226/254 |
| Psychosis | 159 489 | 60/74 | 147 522 | 55/73 |
| Epilepsy | 158 564 | 48/61 | 146 672 | 47/38 |
| Ischaemic heart disease | 155 954 | 125/162 | 144 221 | 126/165 |
| Chronic kidney disease | 159 099 | 20/23 | 147 181 | 51/42 |
| Coeliac disease | 162 051 | 94/125 | 149 881 | 121/150 |
| Congestive heart failure | 161 295 | 39/61 | 149 241 | 32/40 |

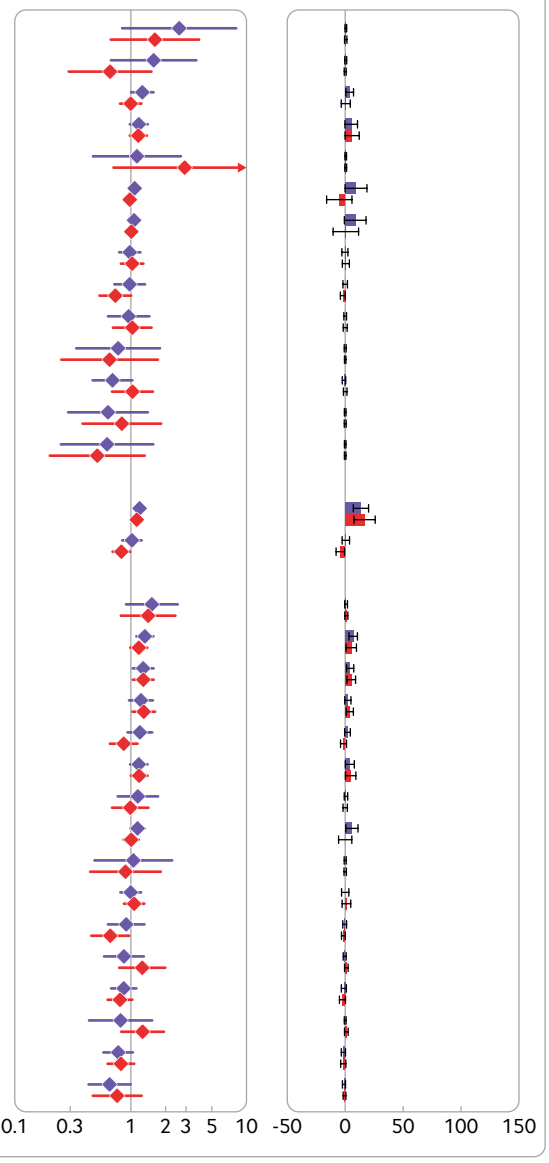


**Fig 3 | Risk for long term health outcomes after SARS-CoV-2 infection in patients with mild disease. Hazard ratios and risk differences per 10 000 patients of reported health outcomes (acute diagnoses, infectious diseases, chronic conditions) in unvaccinated SARS-CoV-2 infected patients with mild covid-19 during early and late periods. TIA=transient ischaemic attack**

The health outcomes that represent long covid showed a significant increase in both early and late phases. Anosmia and dysgeusia (early: hazard ratio 4.59 (95% confidence interval 3.63 to 5.8) and risk difference 19.6 (95% confidence interval 16.9 to22.4); late: 2.96 (2.29 to 3.82) and 11.0 (8.5 to 13.6), respectively), concentration and memory impairment (early: 1.85 (1.58 to 2.17) and 12.8 (9.6 to 16.1); late: 1.69 (1.45 to 1.96) and 13.3 (9.4 to 17.3)), dyspnoea (early: 1.79 (1.68 to 1.90) and 85.7 (76.9 to 94.5); late: 1.3 (1.22 to 1.38) and 35.4 (26.3 to 44.6)), weakness (early: 1.78 (1.69 to 1.88) and 108.5 (98.4 to 118.6), late: 1.30 (1.22 to 1.37) and 50.2 (39.4 to 61.1)), palpitations (early: 1.49 (1.35 to 1.64) and 22.1 (16.8 to 27.4); late: 1.16 (1.05 to 1.27) and 8.3 (2.4 to 14.1)), streptococcal tonsillitis (early: 1.18 (1.09 to 1.28) and 13.4 (6.8 to 19.9); late: 1.12 (1.05 to 1.20) and 16.6 (7.4 to 25.9)), and dizziness (early: 1.14 (1.06 to 1.23) and 11.4 (4.7 to 18.1); late: 1.17 (1.09 to 1.26) and 16.7 (8.6 to 24.8)) lingered a year after infection. To estimate the overall burden of these outcomes after SARS-CoV-2 infection, we assessed the risk difference for the complete year of follow-up after the acute disease phase (30-360 days; supplementary table S2d). The yearly burden measured was highest for weakness (risk difference 136.0, 121.8 to 150.1),

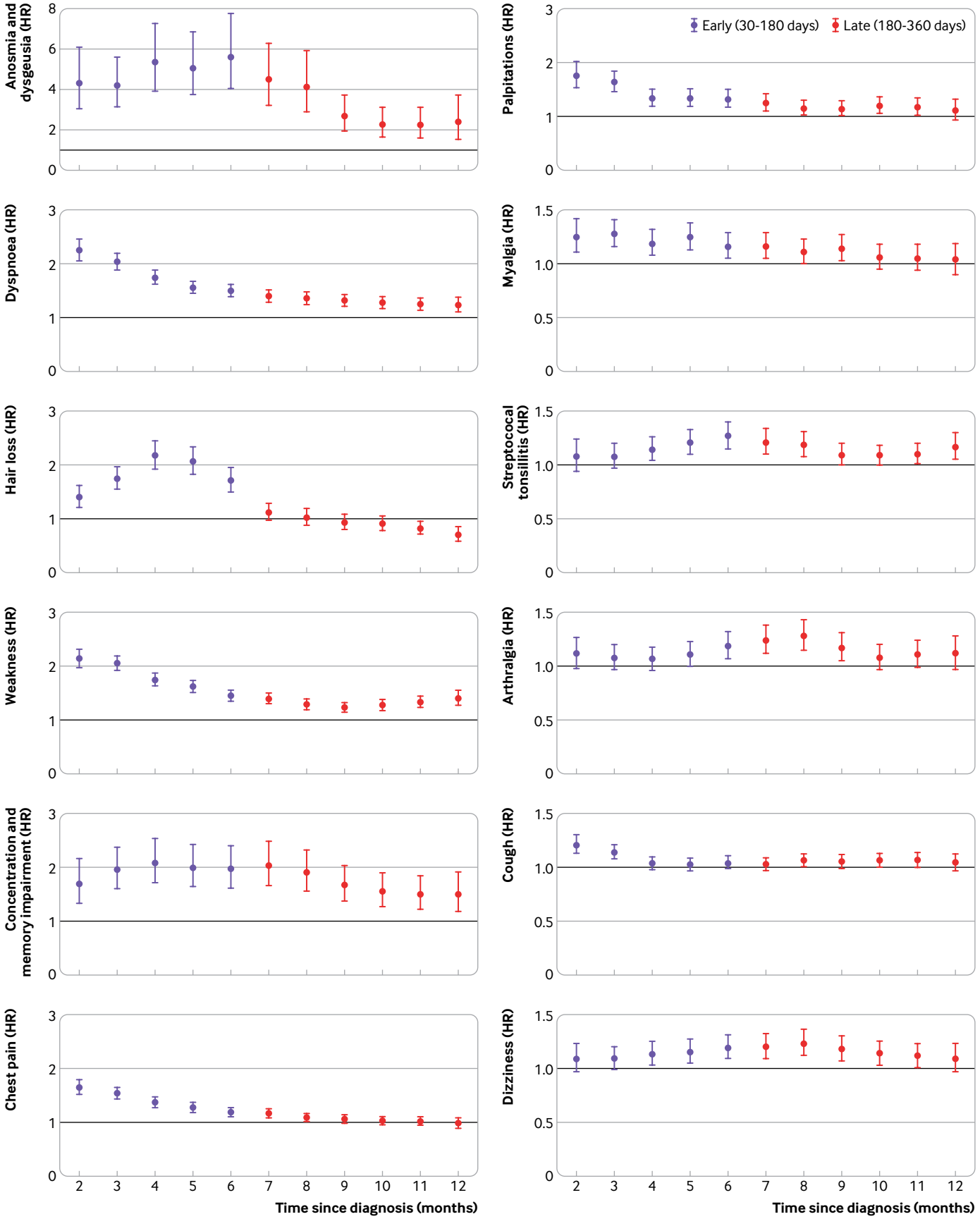


Fig 4 | Monthly risk of significant reported outcomes in unvaccinated infected patients. Hazard ratios (with 95% confidence intervals) for reported health outcomes that were significantly different for unvaccinated people infected with SARS-CoV-2 compared with matched uninfected people. Monthly risk of reported outcomes was evaluated longitudinally during early and late periods

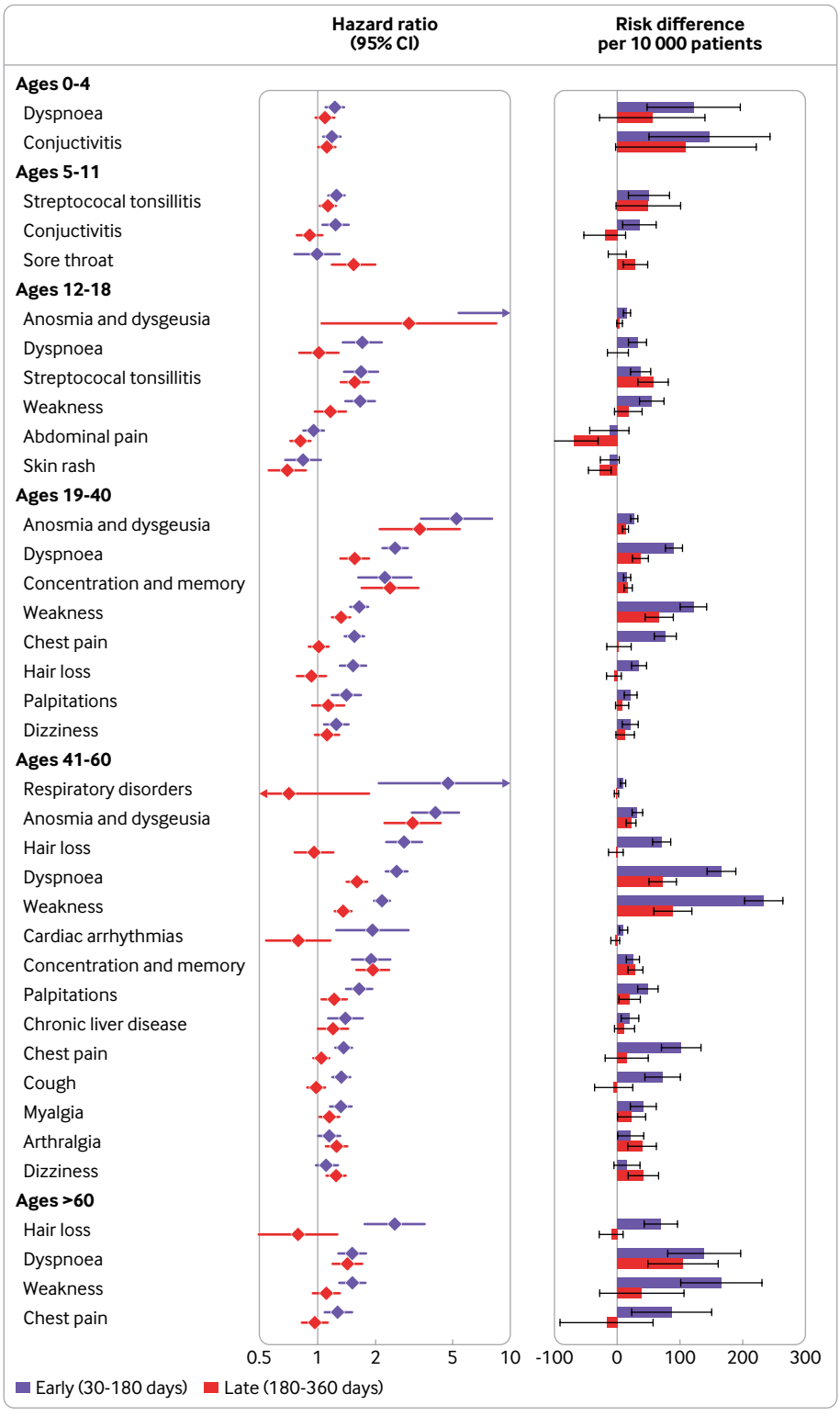


**Fig 5 | Risk of significant reported outcomes in different age subgroups. Hazard ratios and risk differences (with 95% confidence intervals) for all reported health conditions (supplementary tables S4a-l) were evaluated during early and late (orange) periods**

dyspnoea (107.4, 95.4 to 119.4), and streptococcal tonsillitis (31.8, 20.7 to 42.8).

Some health outcomes were significantly increased only during the early phase. These were respiratory disorders (conditions grouped under the ICD-10 code J98) (hazard ratio 2.4, 1.67 to 3.44; risk difference 3.7, 2.3 to 5.3), hair loss (1.75, 1.59 to 1.93; 31.6, 26.2 to 36.9), chest pain (1.41, 1.33 to 1.49; 56.3, 47.0 to 65.7), myalgia (1.24, 1.15 to 1.35; 17.5, 11.2 to 23.8), and cough (1.09, 1.04 to 1.14; 22.2, 9.7 to 34.6). We

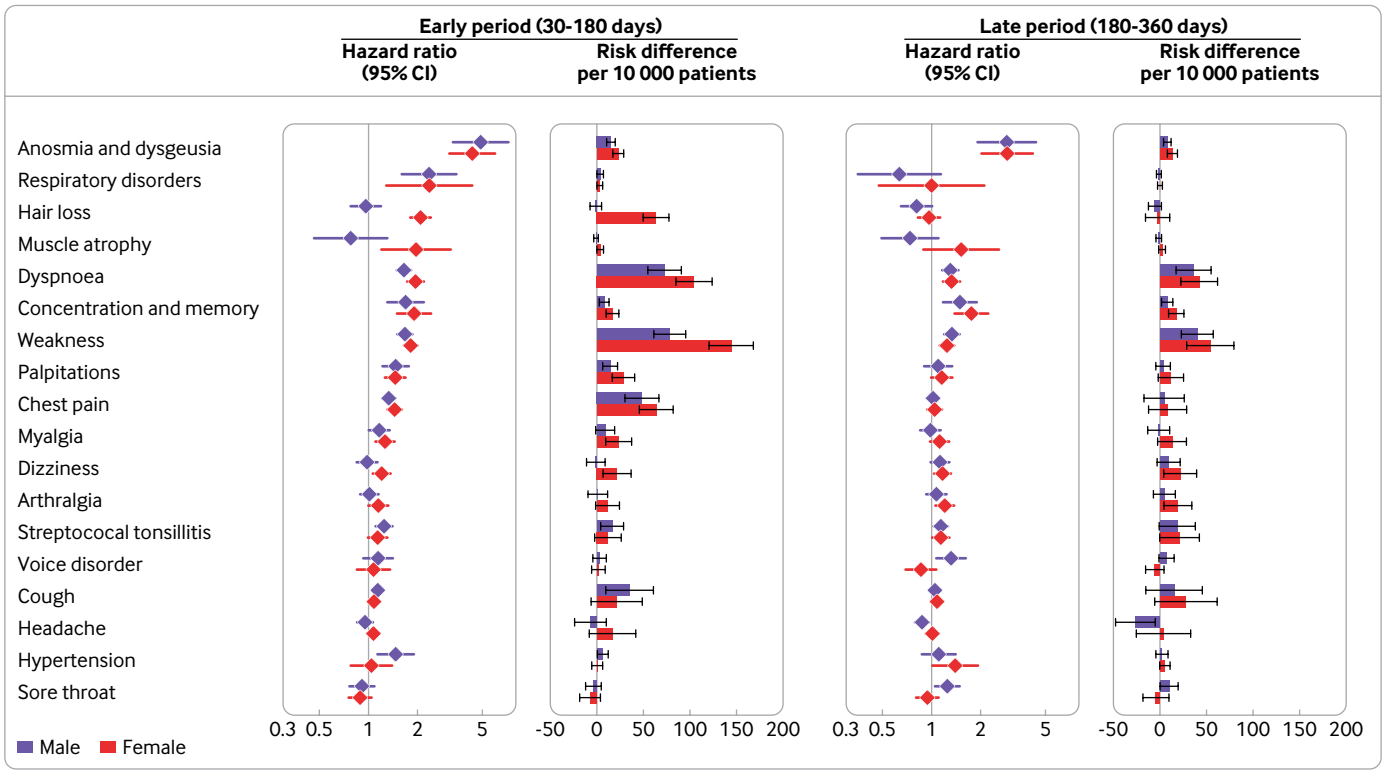


**Fig 6 | Risk of significant reported outcomes in male and female patients. Hazard ratios and risk differences (with 95% confidence intervals) for all reported health conditions (supplementary tables 5b and5c) were evaluated during early and late periods**

also observed a significant increase in the hazard ratio for fatty liver (1.31, 1.13 to 1.52) during the early time period. To establish whether the increased risk for this diagnosis was biased due to a higher testing rate, we did additional analysis and showed that people who tested positive for SARS-CoV-2 had more liver enzyme tests than did those who tested negative, leading to increased detection of this asymptomatic diagnosis (supplementary figure S2). We observed a similar increase for glucose and haemoglobin, supporting the hypothesis that people with covid-19 were tested more often. Normalising by the testing rate yielded a non-significant difference between the two groups.

The hazard ratio for arthralgia was significantly increased during the late period. However, the relative difference was similar during the two time periods (early: hazard ratio 1.11 (1.02 to 1.20) and risk difference 7.3 (1.3 to 13.4); late: 1.17 (1.08 to 1.27) and 13.8 (6.6 to 21.1) respectively).

We observed a significantly lower risk for lymphadenopathy in people with covid-19 in the early phase (hazard ratio 0.81, 0.72 to 0.91). To determine whether this was a reported outcome associated with the SARS-CoV-2 infection and not a side effect caused by covid-19 vaccination during follow-up, we did additional analysis. We measured higher vaccination rates among SARS-CoV-2 negative people (29%; 62 558/214 046) compared with those testing positive (15%; 31 063/214 046), who were less likely to get vaccinated after recovery. Verification was performed for lymphadenopathy, censoring each exposed-unexposed pair once a vaccination event occurred. The resulting hazard ratio (0.98, 0.84 to 1.14) was not significantly different between SARS-CoV-2 positive and negative people.

As SARS-CoV-2 is a respiratory virus, presenting significant lingering respiratory related symptoms, we analysed more specifically reports of pulmonary health outcomes and assessed the severity and health related burden by analysing prescriptions for the relevant drugs. Our analysis indicated that people who tested positive for SARS-CoV-2 had an increased risk for both pulmonary disease treated with prescription drugs (risk difference 25.7, 18.1 to 33.3) and pulmonary disease not treated with prescription drugs (92.6, 81.3 to 103.9). Nevertheless, the percentage of drug prescriptions among patients diagnosed as having pulmonary disease was similar between SARS-CoV-2 positive and negative patients (23.8% (1157/4860) *v* 24.3% (828/3408)), indicating that the severity of pulmonary conditions after SARS-CoV-2 infection was similar to pulmonary conditions in people without SARS-CoV-2 infection (see supplementary table S3).

To better understand the timeline of the health outcomes that changed significantly after SARS-CoV-2 infection, we analysed the reports monthly (fig 4; supplementary table S2e). The outcomes had different monthly hazard ratios during the first year after a diagnosis of covid-19. Hazard ratios for dyspnoea, palpitations, weakness, cough, and chest pain peaked close to infection and declined from the second month

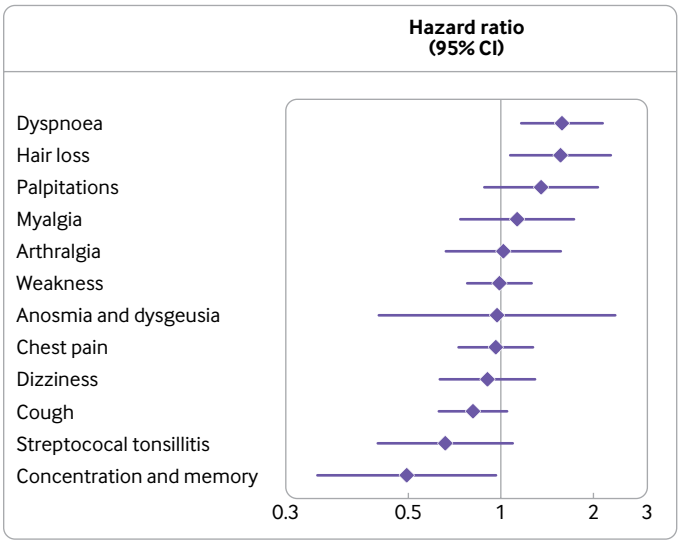


**Fig 7 | Hazard ratios (with 95% confidence intervals) for long covid health outcomes 30-90 days after infection for unvaccinated versus vaccinated patients. Health outcomes that were significantly related to SARS-CoV-2 infection were assessed in vaccinated and unvaccinated patients (supplementary tables 8a-b)**

onward. Whereas the hazard ratios for dyspnoea and weakness in infected patients remained higher throughout the late phase (dyspnoea: hazard ratio 2.26 (2.06 to 2.47) at the second month to 1.23 (1.10 to 1.38) at the 12th month; weakness: 2.14 (1.97 to 2.31) to 1.40 (1.27 to 1.55)), those for palpitations and chest pain returned to baseline within eight months of diagnosis of covid-19 and that for cough by the fourth month. Anosmia and dysgeusia was the most distinctive outcome among infected patients, peaking six months after diagnosis (hazard ratio 5.58, 4.02 to 7.76) and then slowly declining, remaining significantly higher than in uninfected people even a year after infection (2.37 (1.52 to 3.70) at the 12th month). Similarly, concentration and memory impairment had significant hazard ratios throughout the year after diagnosis, peaking at four months (2.08, 1.71 to 2.53) and slowly declining. Hair loss had distinct outcome reporting kinetics, elevating slowly, peaking at four months post-infection (hazard ratio 2.17, 1.92 to 2.44), and then declining to reach baseline seven months post-infection. The hazard ratio for streptococcal tonsillitis was elevated in SARS-CoV-2 positive patients from four to eight months after diagnosis, peaking at six months (hazard ratio 1.27, 1.15 to 1.40).

### Long covid clinical sequelae in different age and sex subgroups

As age was an important indicator for disease severity, we compared health outcomes by age subgroups for a year after infection to establish whether age modified the association between mild covid-19 and long term outcomes. Patients of all age groups who tested positive for SARS-CoV-2 had multiple health outcomes with significantly increased hazard ratios (supplementary tables S4a-l; fig 5).

The 41-60 years subgroup had the highest number of long covid health outcomes that were significantly elevated in both time periods during the year after infection (supplementary tables S4e and S4k): anosmia and dysgeusia (early: hazard ratio 4.05 (3.11 to 5.28) and risk difference 32.2 (23.9 to 40.5); late: 3.1 (2.26 to 4.25) and 22.5 (14.6 to 30.4), respectively), dyspnoea (early: 2.57 (2.30 to 2.87) and 166.5 (143.9 to 189.1); late: 1.59 (1.42 to 1.78) and 72.8 (51.3 to 94.3)), weakness (early: 2.15 (1.98 to 2.34) and 233.7 (203.4 to 264.1); late: 1.35 (1.24 to 1.47) and 88.8 (58.3 to 119.3)), concentration and memory impairment (early: 1.9 (1.54 to 2.33) and 25.2 (14.9 to 35.5); late: 1.93 (1.61 to 2.3) and 29.2 (17.7 to 40.7)), and palpitations (early: 1.64 (1.43 to 1.89) and 49.1 (33.0 to 65.2); late: 1.22 (1.06 to 1.4) and 20.0 (3.1 to 37.0)). Although not significantly increased in the early phase, dizziness and arthralgia showed significantly higher risk during the late phase (dizziness: hazard ratio 1.25 (1.13 to 1.38) and risk difference 42.0 (18.0 to 66.1); arthralgia: 1.26 (1.13 to 1.4) and 39.6 (16.9 to 62.3), respectively).

The younger adults subgroup of 19-40 years (supplementary tables S4d and S4j) showed significantly increased risk in both phases during the first year after mild covid-19 for anosmia and dysgeusia (early: hazard ratio 5.23 (3.48 to 7.87) and 26.9 (21.3 to 32.6); late: 3.38 (2.13 to 5.37) and 13.2 (8.5 to 17.9), respectively), dyspnoea (early: 2.51 (2.19 to 2.89) and 90.7 (77.7 to 103.7); late: 1.55 (1.33 to 1.81) and 37.1 (24.7 to 49.5)), concentration and memory impairment (early: 2.23 (1.65 to 3.01) and 15.7 (10.0 to 21.5); late: 2.36 (1.71 to 3.27) and 17.4 (11.0 to 23.8)), and weakness (early: 1.65 (1.51 to 1.8) and 121.7 (100.8 to 142.5); late: 1.32 (1.2 to 1.46) and 67.3 (45.1 to 89.5)).

In the older age group >60 years (supplementary tables S4f and S4l), we observed increased risk during the early phase for hair loss (hazard ratio 2.51, 1.78 to 3.53; risk difference 69.6, 43.1 to 96.1), weakness (1.50, 1.30 to 1.73; 166.2, 101.0 to 231.3), dyspnoea (1.51, 1.30 to 1.75; 138.9, 81.0 to 196.9), and chest pain (1.26, 1.08 to 1.47; 87.1, 23.7 to 150.6). Only dyspnoea remained significantly increased throughout the late phase (hazard ratio 1.42, 1.20 to 1.67; risk difference 105.3, 49.6 to 160.9).

In the 12-18 years subgroup (supplementary tables S4c and S4i), streptococcal tonsillitis remained significantly high during early and late phases (early: hazard ratio 1.68 (1.40 to 2.02) and risk difference 37.4 (21.5 to 53.3); late: 1.55 (1.33 to 1.81) and 57.3 (33.2 to 81.4) respectively) whereas anosmia and dysgeusia (hazard ratio 23.50, 5.48 to 100.86; risk difference 15.6, 10.1 to 21.0), dyspnoea (1.70, 1.36 to 2.12; 32.4, 17.9 to 46.8), and weakness (1.66, 1.41 to 1.96; 55.2, 35.7 to 74.7) were significantly high during the early phase only.

In the 5-11 years subgroup (supplementary tables S4b and S4h), streptococcal tonsillitis was significantly higher during early and late phases (early: 1.25 (1.15 to 1.36) and risk difference 50.7 (17.9 to 83.5); late: 1.12

(1.05 to 1.21) and 50.0 (−1.5 to 101.5), respectively), whereas risk of conjunctivitis was significantly higher in the early phase (hazard ratio 1.24, 1.07 to 1.43; risk difference 35.7, 9.1 to 62.3) and sore throat during the late phase (1.54, 1.20 to 1.97; 29.7, 10.5 to 48.9).

In the youngest 0-4 years age group (supplementary tables S4a and S4g), we observed elevated risk for conjunctivitis (hazard ratio 1.18, 1.08 to 1.29; risk difference 147.3, 51.3 to 243.3) and dyspnoea (1.22, 1.11 to 1.35; 121.9, 47.8 to 196.0) only during the early phase.

Overall, dyspnoea was the most abundant outcome, appearing in five of the six age groups but remaining persistent throughout the first year after infection in the 19-40, 41-60, and >60 years age groups. Weakness appeared in four of the six age groups and remained persistent in the late phase only in the 19-40 and 41-60 age groups. We measured age related heterogeneity in the association with infection by interaction terms (supplementary tables S4m-n) and found it to be significant for dyspnoea (Q<0.001) and hair loss (Q=0.003) and marginally significant for weakness (Q=0.1).

We further explored whether long covid clinical sequelae differed between unvaccinated male and female patients with a positive SARS-CoV-2 PCR test (fig 6; supplementary tables S5a-c). For most health outcomes measured, male and female patients presented comparable hazard ratios, with one exception: in the early period, women showed significantly higher risk for hair loss (hazard ratio 2.09 (1.86 to 2.35) in women and 0.97 (0.80 to 1.17) in men). Interestingly, whereas hazard ratios for weakness and dyspnoea during the early period were comparable between male and female patients (Q values of 0.65 and 0.22, respectively), the risk difference for female patients was higher, indicating that they reported these symptoms more often than male patients did after infection (supplementary tables S5d-e). Effect modification by sex was significant only for hair loss, in the early period (Q for interaction <0.001).

### Comparison of long term health outcomes between SARS-CoV-2 variants

During the study period, three SARS-CoV-2 variants were prevalent in Israel: wild-type SARS-CoV-2 (March to November 2020), alpha variant (January to April 2021), and delta variant (July to October 2021). We sought to assess the long covid health outcomes in SARS-CoV-2 positive patients infected by the different variants (supplementary figure S1).

We compared the long covid outcomes that were significantly different in the entire unvaccinated cohort between matched sub-cohorts infected by the wild-type virus and the alpha variant (supplementary figure S3; supplementary tables S6a-c). We calculated the hazard ratios separately for each variant, measuring the lingering outcomes in the early and late periods after infection. Overall, the clinical manifestation of long covid was similar between patients infected by the wild-type and alpha variants, overlapping in both time periods. We compared the calculated risk of the long term outcomes in both variants and found no statistically significant difference between the wild-type virus and the alpha variant. Hazard ratios for anosmia and dysgeusia, concentration and memory impairment, dyspnoea, and weakness remained persistently higher through the year after infection for both wild-type and alpha strains.

Next, we evaluated whether the long covid clinical sequelae of the delta variant differed from those of the wild-type strain and alpha variant by analysing persistent symptoms 30-90 days after infection (supplementary figure S4; supplementary tables S7a-b). Considering our previous observation that infections with wild-type and alpha variants showed similar long covid clinical sequelae, we combined them for this specific analysis and compared them with the risk of outcomes after infection with the delta variant. We observed no significant difference in the hazard ratios for the measured outcomes between the wild-type/alpha and the delta variants.

### Association between SARS-CoV-2 vaccination and long covid health outcomes among patients with mild disease

During the study period, a SARS-CoV-2 vaccine was developed, which resulted in a nationwide vaccination campaign in Israel. The goal of this analysis was to assess whether the post-covid clinical sequelae differed between patients who were not vaccinated and those infected after vaccination. This analysis included 14 090 people older than 12 years with a median age of 35 years (supplementary table S8a). We compared vaccinated patients with breakthrough infection (defined as a positive PCR test ≥14 days after the second vaccine dose) with unvaccinated patients who tested positive for SARS-COV-2 (fig 7; supplementary table S8b). Our analysis showed that vaccinated people who became infected and had mild disease were at a significantly lower risk of prolonged dyspnoea than their unvaccinated controls (hazard ratio 1.58, 1.18 to 2.12). The risk for all the other long term health outcomes was comparable between the groups (supplementary table S8b). Additional analysis excluded patients who were vaccinated more than three months before testing positive for SARS-CoV-2 to disregard the vaccine's waning immunity. Results showed a similar risk for the outcomes between the two vaccine populations regardless of the time of vaccination (supplementary tables S9a-b).

## Discussion

This study examined the long term clinical outcomes of SARS-CoV-2 infection in people with mild disease, evaluating electronic health records data from the second largest health fund is Israel. We analysed retrospective data starting in March 2020, identifying people with a positive PCR test and no record of covid-19 related hospital admission in the following month. The quantitative approach we used to decipher the real world long covid manifestation included

following the sequelae of SARS-CoV-2 positive patients for a year after infection, dividing it into early and the late periods, and assessing the health outcomes reported in the electronic health record during these periods. Our analysis showed an increased risk for several health outcomes after mild covid-19 that was more prominent during the first six months after infection and decreased thereafter. Data showed that the risk varied between different age groups and slightly differed between male and female patients and with vaccination status. These findings could provide a clearer picture to clinicians and patients as to the long term presence and presentation of covid-19, reducing uncertainty and improving care.

### Comparison with other studies

As the pandemic advanced, it became clear that most infected people would have mild disease; however, reports describing long term symptoms after the acute phase raised major concerns. Reports of post-covid symptoms, new diagnoses of chronic illnesses, and early complications have been documented, reviewed, and mostly followed for up to seven months after infection.[8 9 14 47-49] Our analysis showed that of all the previously described symptoms and health outcomes, the risk of 13 outcomes was significantly higher in patients testing positive for SARS-CoV-2 compared with negative controls. Following these outcomes in the late period, up to a year post-infection, we showed that the risk for many of them decreased and was comparable to that in people who were not infected. Anosmia and dysgeusia, concentration and memory impairment, dyspnoea, weakness, streptococcal tonsillitis, and dizziness were still reported more frequently in infected patients a year after infection, indicating long lasting symptoms. Previous studies in patients with mild disease have been small in magnitude and followed patients for periods shorter than one year; however, even on a small scale, the presence of anosmia and dysgeusia, concentration and memory impairment, dyspnoea, and weakness has been repeatedly evident.[8 9 47] Reports claimed that efficient covid-19 containment strategies significantly reduced the prevalence of respiratory tract infections and transmission of other pathogens,[50 51] but we measured increased risk for streptococcal tonsillitis up to a year after SARS-CoV-2 infection. This may indicate an increased sensitivity for this bacterial infection after covid-19. In children, SARS-CoV-2 infection was also associated with a higher incidence of conjunctivitis. This may not necessarily be a direct link, but may rather mediated by reduced immunity leading to increased susceptibility to other viruses such as adenovirus, which, in turn, trigger conjunctivitis. Further investigation is needed to determine whether these increased risks are limited to streptococcal tonsillitis and conjunctivitis or reflect immunological health outcomes inherent to covid-19 in general. We note that reduced social distancing among infected patients may confound the associations between SARS-CoV-2 infection and later incidence of infectious diseases such as conjunctivitis and streptococcal infection.

### Findings in context

Our analysis assessed a very large variety of symptoms reported during the long covid period and demanded careful considerations to prevent biases and possible artefacts in the analysis. One important observation we made was that patients with covid-19 had more blood tests because of their illness, and this could lead to a false significant association in conditions such as fatty liver, which is highly prevalent yet asymptomatic and usually discovered by liver enzyme abnormalities in blood tests.[52 53] A second potential bias we observed was in the reports of lymphadenopathy, which was reported to be a side effect of the BNT162b2 mRNA covid-19 vaccine.[27] We measured a lower vaccination rate in the SARS-CoV-2 positive patients (15%; 31 063/214 046) than in the negative controls (29%; 62 558/214 046) after testing. Therefore, the lower risk for lymphadenopathy measured for SARS-CoV-2 positive patients may be a consequence of less lymphadenopathy in this population caused by the lower vaccination rate.

Overall, our observations show mostly mild long term morbidity that is associated with SARS-CoV-2 infection. The organs most affected by covid-19 are the lungs, presenting respiratory illness of different severity levels, widely described in patients admitted to hospital and also evident in patients with mild disease.[7 9 54] As the disease transfects the lungs, it creates clinical manifestations that include viral pneumonia, dyspnoea, and chest discomfort. Dyspnoea emerged as the most frequently reported respiratory symptom in patients with mild covid-19, lasting a year from diagnosis and resulting in increased numbers of prescriptions for related drugs. Nevertheless, the risk of receiving a prescription for a pulmonary diagnosis was independent of SARS-CoV-2 infection, indicating that the pulmonary outcomes following mild covid-19 are not severe and do not need increased drug treatment.

As disease severity, hospital admission, and death are dependent on age,[55] we assessed the different long covid health outcomes in age subgroups in the mild disease setting. The highest number of health outcomes shown to be persistent six months after covid were reported in the 41-60 years subgroup, with patients in the other age subgroups having fewer health outcomes reported. The risk for five outcomes in the 41-60 years subgroup remained significantly higher throughout the year after infection, but only dyspnoea remained significantly higher in the late period in the oldest subpopulation of >60 years. This might suggest that covid-19 would not be considered mild in older people if several symptoms persisted, resulting in patients being admitted to hospital and excluded from this study. Children had an increased risk of a small number of outcomes during the early phase, which then returned to baseline in the late phase.

The pattern that emerged during the pandemic has been of spikes of covid-19 cases followed by

decline, referred to as covid waves. As SARS-CoV-2 spread around the globe, it mutated and different viral variants were identified and became dominant in each covid wave. Reports have shown that variants presented variable transmission patterns, virulence, severity of disease symptoms, and compromised vaccine protection.[56-59] In this study, we analysed the heterogeneity between the dominating SARS-CoV-2 variants and long term health outcomes after mild infection. Comparison of the wild-type strain and the alpha variant up to a year after infection showed no significant differences in health outcomes, and variants showed similarity in both early and late time periods. Similarly, we observed no significant differences in health outcomes when comparing wild-type/alpha and delta strains for three months after infection. These results suggest that the wild-type, alpha, and delta variants resulted in similar long term covid-19 sequelae, and additional assessment of long term outcomes of the delta and the omicron variants may clarify whether long covid sequelae vary by different SARS-CoV-2 variants. The comparison of variants in this study was focused on relative terms. Although the association between infection and outcomes was similar across variants in terms of relative risk, the absolute risk difference depends on baseline risk and may thus differ between variants.

As the pandemic evolved, vaccines were developed and global vaccination campaigns showed that they could protect people from serious illness and prevent death. In Israel, the BNT162b2 SARS-CoV-2 mRNA vaccine was evaluated in a nationwide vaccination campaign and effectively reduced symptomatic covid-19, hospital admissions, severe disease, and death.[30 31] Recent studies have also shown that vaccination results in reduction in the risk of the post-acute sequelae of covid-19.[16 44 60] In this study, we assessed the association between vaccination status and long term health outcomes in patients with breakthrough infections and mild disease course. Our study did not measure protection from acquisition of infection or from severe illness, hospital admission, and death, so it does not contradict any of these proven benefits. Our findings suggest that mild covid-19 in vaccinated people was significantly associated with reduced risk for dyspnoea compared with unvaccinated patients up to three months after infection. This is in accordance with reports showing that vaccination before SARS-CoV-2 breakthrough infection partially reduced the risk of post-acute sequalae.[44]

### Strengths and limitations of study

This study had several strengths. We used longitudinal medical reporting on a national scale, based on electronic health records from a public health fund that includes representation of the heterogeneous Israeli population with its demographic and socioeconomic subpopulations, minimising selection bias. This diversity allows the findings to be generalisable to similar western populations worldwide. The longitudinal and detailed electronic health records allowed us to differentiate between health outcomes and new diagnoses that appeared after a covid-19 infection and exclude those that were previously documented in the patients' medical history. Furthermore, as all data on drug prescriptions, hospital admissions, PCR tests, and vaccinations were available to us, we were confident as to the validity and date of the covid-19 diagnosis, and we could exclude patients admitted to hospital with a more serious illness; the high testing frequency in Israel enabled us to build a reliable uninfected control group with those people who tested only negative. Our study included a large number of young infected patients with mild disease, including 118 308 infected under the age of 18; the overall median age was 25 years. This allowed for larger statistical power for these age groups, which comprise most patients with mild disease and yet were less represented in previous publications.[9] We specifically used electronic health records and not questionnaires, establishing clinically significant long term sequelae reported by medical professionals after interview and clinical evaluation of patients. Our matching methods with controls with a negative PCR test result allowed us to neutralise confounders (age, sex, date of infection, and vaccination status) while verifying contact with healthcare services regarding covid-19 and other conditions. The large dataset allowed us to do a detailed longitudinal analysis including more than 70 symptoms, acute diagnoses, infectious diseases, and chronic conditions that were followed for a year after verified SARS-CoV-2 infection, representing one of the longest follow-up studies in patients with mild covid-19 to date.

The study also had several limitations. We measured outcomes that were reported in structured medical coding in the electronic health record and had no access to diagnoses and outcomes reported in free text format, so these data might not completely reflect diagnoses and outcomes reported. Although we cannot rule out diagnostic errors of conditions with similar health outcomes, we believe that they are equally likely in both groups—that is, misclassification of outcomes is non-differential. Owing to the use of secondary data, the incidence of minor diagnoses may be underestimated. However, major symptoms likely need medical advice or treatment and are less likely to remain unreported and unrecorded. In addition, detection bias is likely to be non-differential between patients infected and not infected with SARS-COV-2. Patient reported outcomes such as weakness, cognitive impairment, anosmia, and dysgeusia are less objective than clinical diagnoses by physicians and might not be uniform and accurate. We cannot rule out potential behavioural and environmental differences between infected and uninfected people, which might cause overestimation of the incidence among the infected population. Namely, some health seeking bias may exist, in which patients with covid-19 may be more active in maintaining their health, including more frequent healthcare service use, resulting in higher reporting and increased screening for potential

covid-19 related outcomes in these patients. Infected patients may be more socially active or less cautious after their infection and thus potentially exposed to a higher risk of other infectious disease (such as group A *Streptococcus* and conjunctivitis). Infected patients are exempt from isolation after their infection, making them potentially more vulnerable to further infectious diseases than uninfected people. Nevertheless, this bias should decrease with time and affect the long term analysis less. We also cannot exclude additional confounders that affect long term outcomes of SARS-CoV-2 infection that were unavailable to us in this study. Furthermore, some of these outcomes (such as paediatric multisystem inflammatory syndrome) were reported at low frequency and therefore might need larger populations. Another weakness could be under-reporting of symptoms in the later periods, when patients had reported the outcomes close to diagnosis of covid-19 and did not continue reporting them as time from diagnosis advanced. This study also might be biased towards including vaccinated patients with symptomatic covid-19 in the analysis, as vaccinated patients were not obliged to get tested and those with no symptoms might have not been tested. In addition, the study was restricted to people who had PCR tests. However, the wide accessibility of PCR tests offered to all Israeli citizens free of charge without a need for referral minimises the concern about non-generalisability. Lastly, the follow-up period for the delta variant was limited to 90 days and needs longer evaluation.

## Conclusions

This study examined the associations of mild covid-19 following SARS-CoV-2 infection and long term health outcomes. Although the long covid phenomenon has been feared and discussed since the beginning of the pandemic, we observed that most health outcomes arising after a mild disease course remained for several months and returned to normal within the first year. This nationwide dataset of patients with mild covid-19 suggests that mild disease does not lead to serious or chronic long term morbidity in the vast majority of patients and adds a small continuous burden on healthcare providers. Importantly, the risk for lingering dyspnoea was reduced in vaccinated patients with breakthrough infection compared with unvaccinated people, while risks of all other outcomes were comparable.

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**Contributors:** MBB and SG contributed equally to this work. All authors contributed to study conception and design. TS did a comprehensive literature review. BM, TS, YY, NK, PA, and MBB defined the analysis plan. BM collected and analysed the data. BM, TS, YY, NK, PA, AEZ, SSBD, UL, MBB, and SG contributed to data interpretation. BM, TS, NFM, and MBB wrote the first draft of the manuscript. All authors contributed important intellectual insights to the critical revision of the manuscript and approved its final version. BM is the guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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**Competing interests:** All authors have completed the ICMJE uniform disclosure form at https://www.icmje.org/disclosure-of-interest/ and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

**Ethical approval:** The study was carried out in accordance with relevant guidelines and regulations. The protocol was approved by Maccabi Healthcare Services' institutional review board (MH6-0006-21) and received informed consent exemption. Data used were de-identified, presenting minimal risk to the rights and welfare of the subjects. All team members had GCP training and a completion certificate in effect.

**Data sharing:** Data supporting the findings of this study came from Maccabi Healthcare Services. Restrictions apply to the availability of these data, and they are therefore not publicly available. Owing to restrictions, these data can be accessed only by request to the authors and/or Maccabi Healthcare Services.

The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

**Dissemination to participants and related patient and public communities:** The results of this study will be disseminated to the public in a press release and on social media channels of the affiliated institutions.

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**Web appendix:** Supplementary materials