Long COVID facts and findings: a large-scale online survey in 74,075 Chinese participants

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Summary

Background Research on long COVID in China is limited, particularly in terms of large-sample epidemiological data and the effects of recent SARS-CoV-2 sub-variants. China provides an ideal study environment owing to its large infection base, high vaccine coverage, and stringent pre-pandemic measures.

Methods This retrospective study used an online questionnaire to investigate SARS-CoV-2 infection status and long COVID symptoms among 74,075 Chinese residents over one year. The relationships between baseline characteristics, vaccination status, pathogenic infection, and long COVID were analyzed using multinomial logistic regression, and propensity matching.

Findings Analysis of 68,200 valid responses revealed that the most frequent long COVID symptoms include fatigue (30.53%), memory decline (27.93%), decreased exercise ability (18.29%), and brain fog (16.87%). These symptoms were less prevalent among those infected only once: fatigue (24.85%), memory decline (18.11%), and decreased exercise ability (12.52%), etc. Women were more likely to experience long COVID, with symptoms varying by age group, except for sleep disorders and muscle/joint pain, which were more common in older individuals. Northern China exhibits a higher prevalence of long COVID, potentially linked to temperature gradients. Risk factors included underlying diseases, alcohol consumption, smoking, and the severity of acute infection (OR > 1, FDR < 0.05). Reinfection was associated with milder symptoms but led to a higher incidence and severity of long COVID (OR > 1, FDR < 0.05). Vaccination, particularly multiple boosters, significantly reduced long-term symptoms by 30%–70% (OR < 1, FDR < 0.05). COVID-19 participants also self-reported more bacterial, influenza and mycoplasma infections, and 8%–10% of patients felt SARS-CoV-2-induced chronic diseases.

Interpretation This survey provides valuable insights into long COVID situation among Chinese residents, with 10%–30% (including repeated infection) reporting symptoms. Monitoring at-risk individuals based on identified risk factors is essential for public health efforts.

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Research in context

Evidence before this study

Over the past year, many Chinese residents have experienced SARS-CoV-2 infections, however, statistical data on long COVID remain limited. We searched PubMed database using the keywords "long COVID" and "China" to retrieve papers published on or after January 1, 2023. We found 235 records, of which 83 were reviews or systematic reviews. The remaining studies were roughly classified into two categories. The first category included studies addressing pathogenesis, abnormal molecular markers, or genetic factors of long COVID. The second category included studies exploring the association between long COVID symptoms and baseline characteristics, although the samples were mainly concentrated in Shanghai, Beijing, Guangzhou, and Hong Kong, limiting their representativeness of the entire country. Moreover, these studies often focused on specific symptoms such as gastrointestinal problems, sleep disorders, or menstruation abnormalities. Third, most samples in these studies were derived from infections caused by SARS-CoV-2 sub-variants circulating before 2022 (such as BA.1, BA.2, and even earlier sub-variants), which could not reflect the long COVID situation following the Chinese pandemic wave caused by sub-variants such as BA.4, BA.5, BF.7, and XBB. Fourth, many previous long COVID studies focused on discharged patients (including moderate and severe cases), whereas most people infected in the past year did not require hospitalization. In summary, epidemiological data on long COVID among a large number of Chinese residents is lacking. Further investigation is needed to clarify the baseline characteristics, immune backgrounds, and impact of reinfection on long COVID.

Added value of this study

The current prevalence of long COVID and its related factors in China are poorly understood. China's long-term, strict epidemic prevention strategies have reduced severe cases and deaths giving the population a relatively pure immune and infection background. The vast number of infections and broad vaccine coverage has also rendered Chinese data an excellent model for studying long COVID. In this study, we investigated the SARS-CoV-2 infection status of 74,075 Chinese residents over the past year, elucidating the epidemiological characteristics of long COVID, and identifying multiple related exposure factors. To the best of our knowledge, this is currently China's largest publicly available long COVID epidemic survey and has worldwide applications.

Implications of all the available evidence

This study demonstrates the prevalence of long COVID among 68,200 valid Chinese participants. Statistical results show that approximately 10%–30%, including those with repeated infections, experienced long COVID symptoms. The results underscore the need to prioritize long COVID diagnosis and treatment, particularly for affected population. Additionally, this study identified multiple risk factors for long COVID, including underlying diseases, smoking or alcohol consumption, severity of acute illness, recurrent infections, being females. Protective factors, such as COVID-19 vaccines, particularly booster doses, were also uncovered, providing valuable insights for identifying and monitoring long COVID-susceptible populations.

Introduction

SARS-CoV-2, the causative agent of COVID-19, has evolved into various sub-variants and serotypes.[1,2] The increasing prevalence of long COVID, also known as post COVID-19 condition or post-acute sequelae of SARS-CoV-2 infection, has become significant public health concern.[3,4] Long COVID is defined as the persistence or emergence of new symptoms three months after the initial infection with no other explanation,[3,4] affecting an estimated 140 million people worldwide.[5] It can impact multiple organ systems and lead to cognitive impairments and emotional disorders.[3,6] Typical symptoms include fatigue, post-exertional malaise, brain fog, dizziness, gastrointestinal symptoms, heart palpitations, decreased libido, impaired smell or taste, thirst, chronic cough, chest pain, hair loss, etc.[7] Any person infected with SARS-COV-2 may suffer from long COVID, and the prevalence rates vary widely, ranging from 10% to 60%.[3,8–12] COVID-19 vaccination has been shown to substantially reduce the risk of long COVID.[3,13–16]

The mechanisms behind long COVID are complex, involving sustained virus and residue existence, induction of latent virus activation, gut microbiota dysfunction, endothelial and coagulation dysfunction, autoantibody disorders, and hormonal imbalances.[3,17] There are currently no specific clinical indicators for diagnosing long COVID patients.[3,17] Self-reported symptoms or clinical follow-up designed around typical symptoms remain the main diagnostic method, with additional tests, such as blood examinations and imaging.[3,18]

Research on the long COVID in China is limited, focusing mainly on hospitalized patients, and earlier SARS-CoV-2 variants, or individual symptoms.[6,11,19,20] Under China's long-term dynamic zero-COVID-19

strategy, severe illness and death occurrences have decreased significantly.[21] Compared to other early open areas, Chinese residents have a relatively similar background regarding infection and immunity. However, the characteristics of long COVID in the general population remain unclear following the adjustment of the dynamic zero-COVID-19 strategy.

This study, employing a large-scale online survey of 74,075 Chinese participants, aims to clarify the epidemiological characteristics of long COVID in China after adjusting dynamic zero-COVID-19 strategy, and reveals contributing factors, providing valuable insights for China and global research on the condition.

Methods

Participants and ethical declaration

This project was conducted in China from November 22, 2023, to January 24, 2024. The *Questionnaire on Long-Term Symptoms After SARS-CoV-2 Infection* was mainly distributed in the form of a referral system, with participants calling on others to join. Each individual could submit up to three questionnaires, including those completed on behalf of family members. Participation was voluntary, and all participants were informed of their rights and interests through an online consent process before completing the survey. A total of 74,075 questionnaires were collected. This study was approved by the Research Ethics Committee of the Institute of Microbiology, Chinese Academy of Sciences (No. APIMCAS2023006-1).

Questionnaire design and topic setting

The questionnaire (Supplementary Method 1) was designed and distributed via the Wenjuanxing platform (https://www.wjx.cn). Participants accessed the questionnaire by clicking on the provided link, where they could read and respond to the questions. The survey covered various topics, including region of residence, sex, age, COVID-19 vaccination status, underlying diseases, smoking and drinking habits, SARS-CoV-2 infection, COVID-19 diagnosis methods, other pathogen infections, COVID-19's impact on other diseases and long COVID symptoms, etc (Supplementary Method 1). For the long COVID questions, we adapted from the international version of the *Symptom Burden Questionnaire for Long COVID* (SBQ-LC).[22] Long COVID was defined as the persistence or onset of new symptoms three months after the initial SARS-CoV-2 infection, with these symptoms lasting for at least two months and no other identifiable cause. To streamline the assessment, the questionnaire was simplified to focus on 24 common long COVID symptoms using multiple-choice questions (Supplementary Method 1). For participants who experienced multiple infections, we asked them report details only for their first and most recent infections.

Questionnaire quality control

We eliminated invalid questionnaires through a systematic filtering process to improve reliability. Duplicate questionnaires were removed based on participant ID, IP addresses, sex, and age. Questionnaires were excluded if the completion time was less than 20 seconds or exceeded 12 hours. Questionnaires with inconsistent responses regarding vaccine dosages and combinations were removed (e.g., vaccine dosage: 3 doses but vaccine combination: 3 doses of inactivated vaccine + 1 dose of protein vaccine). Questionnaires with conflicting multiple-choice options for underlying diseases were removed (e.g., selecting both "no underlying disease" and "diabetes"). Inconsistent information regarding the timing of first and last infections also resulted in exclusion. Questionnaires were further eliminated if they contained contradictory multiple-choice selections regarding other pathogenic infections in confirmed COVID-19 patients and non-COVID-19 participants. Responses that reported unreasonable severity for the first or last infection symptoms were removed (e.g., selecting the same severity level for all symptoms). Questionnaires with unreasonably long COVID symptoms were removed (e.g., selecting all symptoms as obvious or severe). Questionnaires with IP addresses outside of China were excluded. Based on these stringent criteria, 5875 questionnaires were removed, leaving 68,200 (92.07%) high-quality responses for analysis.

Acute and long COVID symptom statistics

In this study, long COVID refers to the continuation or development of new symptoms 3 months after the initial SARS-CoV-2 infection, without any other explanation. The time since the first SARS-CoV-2 infection was used as reference point to calculate the approximate post-infection duration. Specifically, participants were asked to recall and chose how many months had passed since their first infection when filling out the questionnaire, with available options of < 1, 1, 3, 6, 9, or 12 months (Table S12). The prevalence of long COVID at 3, 6, 9, and 12 months after the first infection was then analyzed. To ensure the accuracy of symptom statistics, only participants who self-reported a confirmed SARS-CoV-2 infection, diagnosed through self-administered rapid antigen tests or nucleic acid detection rather than speculation, were included in the symptom statistics analysis. Moreover, each acute or long COVID symptom was self-reported with four severity level options: non-symptomatic (0 points), slightly symptomatic (1 point), obviously symptomatic (2 points) and severely symptomatic (3 points) (Supplementary Method 1).[15] However, the "slightly symptomatic" option was excluded from the final symptom statistic, as it is more prone to be influenced by psychological factors, recall bias, and post pandemic stress. Additionally, when comparing these results with those from our initial survey, conducted

during the acute infection phase, the reported frequency of acute symptoms, excluding the "slightly symptomatic", was similar between the two surveys. Therefore, to mitigate the potential overestimation of symptoms due to recall bias, we only included the self-reported "obvious" symptom and "severe" symptom for acute and long COVID symptom statistics. This approach significantly enhanced the accuracy of symptom prevalence data.

Multivariate analysis and propensity score matching

To identify long COVID-related factors, binary or multinomial multi-factor logistic regression was employed to adjust for confounding variables and to calculate the exposure factor contributions. Specifically, when analyzing the impact of a factor on outcome variables, other potential confounders such as age, gender, region, underlying disease, smoking, drinking, vaccine status, and the severity of acute phase were adjusted as much as possible. The severity of acute illness was categorized based on the medical treatment status of SARS-CoV-2 infected individuals, including four levels: "No hospital required", "Hospital required", "Hospitalization required for treatment", and "Emergency or ICU rescue". The "No hospital required" group was as a reference dummy variable control. Additionally, the 18–29 age group and the unvaccinated group served as control dummy variables in the multivariate analysis. The nnet R package (https://cran.r-project.org/web/packages/nnet/) was utilized for the multinomial logistic regression analysis. For baseline adjustment, propensity score matching was performed using the MatchIt R package (https://cran.r-project.org/web/packages/MatchIt/). Matching was based on factors such as age, gender, region, underlying disease, smoking, drinking, vaccine status to ensure balanced groups for comparison. A single-factor comparative analysis was then performed to compare the COVID-19 and non-COVID-19 responses. To maximize sample retention, a 3:1 matching ratio was employed, and the standard mean difference (SMD) was used to assess the effectiveness of propensity score matching between groups.

Statistical analysis

Data quality control and statistical analyses were performed using R software (Version 4.1.2). The decimal point retention principle was the R default Banker's rounding. Categorical data were described by frequency or percentage (%), and the significance of frequency differences between groups was calculated by using $\chi 2$ test. A p-value of ≤ 0.05 was considered statistically significant. For multivariate regression analysis, the FDR method was applied to adjust the p-values.

Role of the funding source

This study was supported by the China Postdoctoral Science Foundation (grant number: 2022M723344 and 2023M743729), Guangdong Basic and Applied Basic Research Foundation (grant number: 2023A1515110489), and the Bill & Melinda Gates Foundation (grant number: INV-027420). The funders did not participate in any aspect of the study, including conception and design, data collection, data analysis, interpretation, recruitment or writing of the manuscript. We declared that this study did not receive any compensation from pharmaceutical companies or other agencies. All authors confirm that they had full access to all the data in the study and had final responsibility to submit for publication.

Results

China maintain a considerable proportion of long COVID symptoms

In this survey, after excluding questionnaires with incomplete or inaccurate information, 68,200 responses were included in the analysis (Fig. 1a). Most participants were located in the eastern, northern, central, and southern region of China (Fig. 1b). 57.41% respondents were women, and 95.26% of all participants were aged between 18 and 60 years (Fig. 1c and d). Among the respondents, 4123 individuals were self-reported uninfected, while 57,024 reported having been infected with SARS-CoV-2 at least once (Table 1). Nearly all participants had received at least one dose of the SARS-CoV-2 vaccine, with the majority (67.99%) receiving three doses. Additionally, 75.58% had received their last vaccine dose more than 12 months prior (Fig. S1a–c and Table 1). Among the participants, 9.24% were smokers and 5.47% reported drinking alcohol (Fig. S1d–e and Table 1). The most common underlying conditions were chronic rhinitis (18.98%), chronic pharyngitis (14.61%), hypertension (6.76%), allergies (6.23%), and gastrointestinal diseases (5.9%) (Fig. S1f and Table 1). Regarding SARS-CoV-2 infection, more than half the participants (56.1%) reported being diagnosed positive once, 23% reported two positive diagnoses, and 3.9% reported being positive three times. Only 6.05% of the respondents indicated that they had never been infected with SARS-CoV-2 (Fig. S1g). The main diagnostic methods reported were rapid antigen and nucleic acid testing (Fig. S1h). Most participants (76.39%) reported their first infection occurring at least 12 months prior, providing a useful time span for studying long COVID (Fig. 1e). Additionally, 39.06%, 14.06%, and 16.81% of the re-infected participants reported that their last infection occurred more than 12, 9, and 6 months, respectively (Fig. S1i).

According to the four severity scale options of 24 long COVID symptoms (Supplementary Method 1), we calculated the prevalence of various long COVID symptoms at 3, 6, 9, and 12 months after the first SARS-CoV-2 diagnosis. As outlined in the methods section, we only included self-reported "obvious" and "severe" symptom options for statistical purposes, excluding "slight"

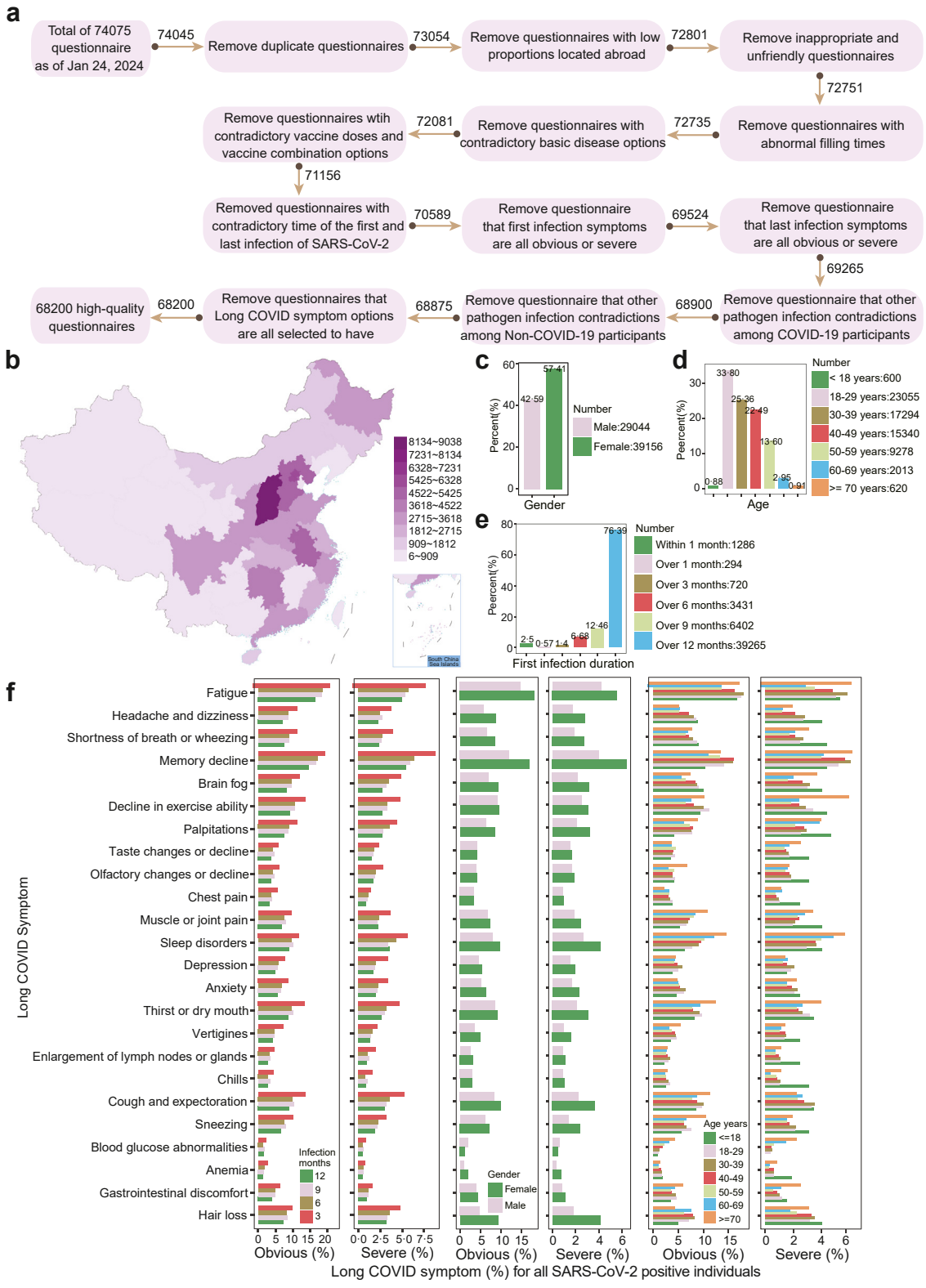


Fig. 1: Long COVID data statistics for the Chinese resident cohort. (a). The flowchart shows the quality control standards and process of the collected survey questionnaire. (b). The map of China displays the geographical distribution of the valid high quality samples collected. (c).

symptoms owing their susceptibility to bias and overestimation. The final statistical results of all COVID-19 participants revealed that the most common long-term COVID symptoms at 3, 6, 9, and 12 months were fatigue (30.53%, 24.18%, 23.54%, 21.46%), memory decline (27.93%, 23.37%, 22.57%, 20.05%), decreased exercise ability (18.29%, 13.88%, 13.75%, 11.89%), cough/expectoration (18.83%, 13.45%, 13.43%, 12.02%), thirst/dry mouth (18.06%, 12.83%, 13.17%, 11.28%, 9.44%), sleep disorders (17.41%, 13.94%, 13.51%, 12.45%) and brain fog (16.87%, 13.09%, 12.71%, 10.81%) (Fig. 1f and Table S1). However, among participants who reported only a single confirmed SARS-CoV-2 infection, the frequency of these long-term symptoms decreased, accompanied by the highest levels of fatigue (24.85%), memory decline (18.11%), decreased exercise ability (12.52%), with other symptoms reported by fewer than 10% of participants (Fig. S2a and Table S2). This suggests that the frequency of long COVID symptoms following a single infection aligns with previous reports, i.e. 10%–20%.[3,13] Conversely, the prevalence among all COVID-19 participants may represent the cumulative effects of repeated infection in the real world. In addition, some participants also reported long-term symptoms that require clinical diagnosis, such as blood glucose abnormalities, anemia, and enlarged lymph nodes or glands, etc (Fig. 1f). Moreover, as the recovery time post-infection increased, the proportion and severity of these symptoms gradually declined, with the most significant reduction occurring after three months (Fig. S2b).

Next, we stratified long COVID cases by gender, age and region. Most long COVID symptoms had appeared more frequently or severely in women, except for blood glucose abnormalities (Fig. 1f, Table S3), suggesting that women may be more susceptible to long COVID. The heterogeneity of long COVID was more pronounced across different age groups (Fig. 1f and Fig. S2a and Table S4). Symptoms such as fatigue, decreased exercise ability, muscle or joint pain, and sleep disorders were more prevalent in the 70 years old group, but the frequency varied unevenly across other age groups (Fig. 1f and Fig. S2a). Further multivariate analysis showed that after adjusting for confounding factors, compared with the 18–29 years old, multiple increased ages did not exhibit the hypothetical risk factors for long COVID, accompanied by multiple odds ratios (OR) less than 1 (Fig. S3). This may mean that increasing age in healthy individuals may not be a risk factor for long COVID, particularly when considering social and economic factors.

Since some provinces had fewer samples, we divide China's provinces into seven major regions for statistics. Interestingly, we found that in general, multiple long COVID symptoms were generally more prevalent in the northeast, northwest and northern China, while they were less common in central and eastern China (Fig. S2e and Table S5). Considering that the wave of infection among these participants was mainly concentrated in winter, and there are obvious temperature differences between winter and spring in northern and southern China, this result may indicate a regional temperature-related pattern in the distribution of long COVID symptoms.

Severe illness in the acute phase and underlying diseases are risk factors for long COVID

By analyzing the recovery speed and medical status, we explored the impact of acute infection severity on long COVID using multivariable regression analysis. Results indicated that the longer the duration of acute infection, the higher the risk of developing long COVID (Fig. 2a and Fig. S4a). Compared with those whose symptoms improved significantly within 3 days, individuals who recovered within 3–7 days were at higher risk for long-term symptoms such as fatigue, headache and dizziness, memory decline, brain fog, taste changes, muscle or joint pain, thirst or dry mouth, and cough or expectoration (OR > 1, FDR < 0.05) (Fig. 2a and Fig. S4a and Table S6). The risk ratio increased exponentially with acute illness duration (OR > 2 or > 4, FDR < 0.05) (Fig. 2a and Fig. S4a and Table S6). Individuals who need to hospital had a significantly increased risk ratio (OR > 1, FDR < 0.05), and the risk ratio for those who required hospitalization and ICU treatment doubled (OR > 2, FDR < 0.05) (Fig. 2b and Fig. S4b and Table S7). Moreover, various underlying diseases were identified as risk factors for multiple long COVID symptoms, including chronic rhinitis, chronic pharyngitis, hypertension, allergy, gastrointestinal disease, gout and high uric acid, autoimmune diseases, osteoporosis, pulmonary diseases, diabetes, chronic liver or kidney disease, etc (Table S8). We also analyzed the association of smoking, drinking and long COVID as these behaviors are closely linked to underlying health conditions. Overall, smoking and drinking were risk factors for long COVID (OR > 1, FDR < 0.05), with smoking showing a stronger and more significant association with long COVID symptoms (Fig. S5a–d). These findings underscore the need for heightened attention to individuals with prolonged acute infection duration, severe illness,

The proportion of the different genders within the valid sample. (d). The proportion of different age groups in the valid sample. (e). The proportion of duration after first infection in the valid sample, defined as the time point after submitting the questionnaire minus the time point of first SARS-CoV-2 infection. (f). Statistics on the prevalence of long COVID symptoms in different durations after infection, age groups, and genders for all SARS-CoV-2 positive individuals.

Characteristic	Infected no./total (%)	Uninfected no./total (%)	Suspected no./total (%)	Unclear no./total (%)
Age range				
<18 years	444 (0.78%)	57 (1.38%)	62 (1.19%)	37 (1.99%)
18–29 years	18,522 (32.48%)	1578 (38.27%)	2230 (42.95%)	725 (38.96%)
30–39 years	15,212 (26.68%)	629 (15.26%)	998 (19.22%)	455 (24.45%)
40–49 years	13,258 (23.25%)	749 (18.17%)	999 (19.24%)	334 (17.95%)
50–59 years	7625 (13.37%)	781 (18.94%)	657 (12.65%)	215 (11.55%)
60–69 years	1552 (2.72%)	224 (5.43%)	171 (3.29%)	66 (3.55%)
≥70 years	411 (0.72%)	105 (2.55%)	75 (1.44%)	29 (1.56%)
Gender				
Male	23,549 (41.3%)	2278 (55.25%)	2314 (44.57%)	903 (48.52%)
Female	33,475 (58.7%)	1845 (44.75%)	2878 (55.43%)	958 (51.48%)
Area				
Central China region	7807 (13.69%)	537 (13.02%)	747 (14.39%)	218 (11.71%)
East China region	15,991 (28.04%)	996 (24.16%)	1124 (21.65%)	369 (19.83%)
North China region	18,238 (31.98%)	1422 (34.49%)	1852 (35.67%)	649 (34.87%)
Northeast China region	3736 (6.55%)	313 (7.59%)	450 (8.67%)	283 (15.21%)
Northwest China region	2837 (4.98%)	246 (5.97%)	286 (5.51%)	117 (6.29%)
South China region	4990 (8.75%)	389 (9.43%)	408 (7.86%)	131 (7.04%)
Southwest China region	3425 (6.01%)	220 (5.34%)	325 (6.26%)	94 (5.05%)
Smoking habits				
Never smoke	47,106 (82.61%)	2960 (71.79%)	4204 (80.97%)	1462 (78.56%)
Occasional smoking	5110 (8.96%)	425 (10.31%)	440 (8.47%)	193 (10.37%)
Frequent smoking	4808 (8.43%)	738 (17.9%)	548 (10.55%)	206 (11.07%)
Drinking habits				
Never drink	25,140 (44.09%)	1911 (46.35%)	2360 (45.45%)	988 (53.09%)
Occasional drinking	28,845 (50.58%)	1882 (45.65%)	2578 (49.65%)	764 (41.05%)
Frequent drinking	3039 (5.33%)	330 (8%)	254 (4.89%)	109 (5.86%)
COVID-19 vaccine				
Not vaccinated	1264 (2.22%)	133 (3.23%)	111 (2.14%)	26 (1.4%)
1 dose	735 (1.29%)	46 (1.12%)	72 (1.39%)	38 (2.04%)
2 doses	10,893 (19.1%)	767 (18.6%)	1071 (20.63%)	394 (21.17%)
3 doses	38,535 (67.58%)	2501 (60.66%)	3555 (68.47%)	1269 (68.19%)
4 doses	5162 (9.05%)	586 (14.21%)	361 (6.95%)	123 (6.61%)
5 doses	435 (0.76%)	90 (2.18%)	22 (0.42%)	11 (0.59%)
Basic medical situation				
Chronic rhinitis (No)	45,782 (80.29%)	3586 (86.98%)	4272 (82.28%)	1619 (87%)
Chronic rhinitis (Yes)	11,242 (19.71%)	537 (13.02%)	920 (17.72%)	242 (13%)
Chronic pharyngitis (No)	48,277 (84.66%)	3762 (91.24%)	4568 (87.98%)	1629 (87.53%)
Chronic pharyngitis (Yes)	8747 (15.34%)	361 (8.76%)	624 (12.02%)	232 (12.47%)
Asthma and chronic bronchitis (No)	55,163 (96.74%)	4033 (97.82%)	5045 (97.17%)	1806 (97.04%)
Asthma and chronic bronchitis (Yes)	1861 (3.26%)	90 (2.18%)	147 (2.83%)	55 (2.96%)
Pulmonary diseases (No)	56,240 (98.63%)	4084 (99.05%)	5118 (98.57%)	1832 (98.44%)
Pulmonary diseases (Yes)	784 (1.37%)	39 (0.95%)	74 (1.43%)	29 (1.56%)
Diabetes (No)	55,774 (97.81%)	3977 (96.46%)	5092 (98.07%)	1815 (97.53%)
Diabetes (Yes)	1250 (2.19%)	146 (3.54%)	100 (1.93%)	46 (2.47%)
Hypertension (No)	53,168 (93.24%)	3799 (92.14%)	4871 (93.82%)	1755 (94.3%)
Hypertension (Yes)	3856 (6.76%)	324 (7.86%)	321 (6.18%)	106 (5.7%)
Cardiovascular and cerebrovascular diseases (No)	56,461 (99.01%)	4064 (98.57%)	5135 (98.9%)	1840 (98.87%)
Cardiovascular and cerebrovascular diseases (Yes)	563 (0.99%)	59 (1.43%)	57 (1.1%)	21 (1.13%)
Gastrointestinal disease (No)	53,527 (93.87%)	3964 (96.14%)	4899 (94.36%)	1789 (96.13%)
Gastrointestinal disease (Yes)	3497 (6.13%)	159 (3.86%)	293 (5.64%)	72 (3.87%)
Chronic kidney disease (No)	56,836 (99.67%)	4106 (99.59%)	5173 (99.63%)	1854 (99.62%)
Chronic kidney disease (Yes)	188 (0.33%)	17 (0.41%)	19 (0.37%)	7 (0.38%)
Chronic liver disease (No)	56,624 (99.3%)	4099 (99.42%)	5153 (99.25%)	1848 (99.3%)

(Table 1 continues on next page)

Characteristic	Infected no./total (%)	Uninfected no./total (%)	Suspected no./total (%)	Unclear no./total (%)
(Continued from previous page)				
Chronic liver disease (Yes)	400 (0.7%)	24 (0.58%)	39 (0.75%)	13 (0.7%)
Gout and high uric acid (No)	55,639 (97.57%)	4017 (97.43%)	5082 (97.88%)	1832 (98.44%)
Gout and high uric acid (Yes)	1385 (2.43%)	106 (2.57%)	110 (2.12%)	29 (1.56%)
Benign tumor (No)	56,619 (99.29%)	4103 (99.51%)	5155 (99.29%)	1852 (99.52%)
Benign tumor (Yes)	405 (0.71%)	20 (0.49%)	37 (0.71%)	9 (0.48%)
Malignant tumors (No)	56,633 (99.31%)	4100 (99.44%)	5160 (99.38%)	1849 (99.36%)
Malignant tumors (Yes)	391 (0.69%)	23 (0.56%)	32 (0.62%)	12 (0.64%)
Autoimmune diseases (No)	56,582 (99.22%)	4102 (99.49%)	5155 (99.29%)	1847 (99.25%)
Autoimmune diseases (Yes)	442 (0.78%)	21 (0.51%)	37 (0.71%)	14 (0.75%)
Allergy (No)	53,306 (93.48%)	3946 (95.71%)	4919 (94.74%)	1780 (95.65%)
Allergy (Yes)	3718 (6.52%)	177 (4.29%)	273 (5.26%)	81 (4.35%)
Osteoporosis (No)	56,137 (98.44%)	4055 (98.35%)	5103 (98.29%)	1818 (97.69%)
Osteoporosis (Yes)	887 (1.56%)	68 (1.65%)	89 (1.71%)	43 (2.31%)

Table 1: **Demographic characteristics by infection status of the questionnaire participants.**

and multiple underlying diseases, as they may be at greater risk for long COVID.

COVID-19 vaccines are generally protective against long COVID

Prior to the widespread SARS-CoV-2 infection in China, most people had already received a COVID-19 vaccine. Based on the vaccine history of the participants, we analyzed the association between vaccination and long COVID, and found a positive protective effect (Table S9). First, vaccination significantly reduced the risk of various long COVID symptoms across different severity levels (OR < 1 FDR < 0.05), with a particularly strong protective effect on severe long COVID symptoms containing more significant items and generally smaller OR values (OR < 1 FDR < 0.05) (Fig. 3 and Fig. S6 and Table S9). Second, receiving booster shots further enhanced the protective effects, reducing the prevalence of various long COVID symptoms (OR < 1 FDR < 0.05) (Fig. 3 and Fig. S6 and Table S9). Third, the protective effect of only receiving one or two COVID-19 vaccine doses on long COVID was limited, possibly owing to weakened protection over time (Fig. 3 and Fig. S6 and Table S9). Specifically, two doses of the adenovirus vector vaccines, three inactivated + 1 adenovirus vector vaccines, three inactivated + 1 protein subunit vaccines, three protein subunit vaccines, three inactivated vaccines, and three inactivated vaccines significantly reduced the risk of symptom such as fatigue, memory decline, brain fog, decline in exercise ability, palpitations, muscle or joint pain, sleep disorders, depression, anxiety, thirst or dry mouth, gastrointestinal discomfort, blood glucose abnormalities, and hair loss (OR < 1, FDR < 0.05). Although two doses of vaccine and a single dose were associated with increased gastrointestinal discomfort (OR = 1.43, FDR = 0.0704) and headache and dizziness (OR = 1.44, FDR = 0.085); the risks of lymphoid and glandular enlargement (OR = 1.6, FDR = 0.0669) and muscle or joint pain symptoms (OR = 1.41, FDR = 0.0594) were specifically linked to two doses of the adenovirus vector vaccine and three doses of the protein subunit vaccines, respectively. However, these vaccines' protective effects outweighed their risks that are not significant enough (Fig. 3). These findings emphasize the crucial role of COVID-19 vaccination in mitigating a wide range of long COVID symptoms, particularly highlighting the importance of receiving booster shots.

SARS-CoV-2 reinfection reduces acute symptoms but increases the risk of long COVID

The impact of SARS-CoV-2 reinfection on acute and long COVID symptoms requires further clarification. Our analysis revealed that the severity score and frequency of acute symptoms in COVID-19 patients with reinfection were generally lower than those experienced during the first infection, such as fever: (43.17% & 28.43% vs 34.6% & 14.35%); fatigue: (42.73% & 28.24% vs 37.03 & 15.12%); headache and dizziness: (35.01% & 22.32% vs 29.12% & 12.16%); Chill and shivering: (25.56% & 14.73% vs 18.13 & 7.76%) (Fig. 4a and Fig. S7). The duration of the illness also significantly shortened during reinfection. The percentage of significant improvement within three days increased from 20.5% during the first infection to 31.27% during the last infection. Conversely, the proportion of improvement within 8–14 days decreased from 18.95% to 12.02%, and the percentage requiring more than 2 weeks for improvement dropped from 6.27% to 3.75% (Fig. 4b and c). Medical treatment demand during reinfection also decreased significantly, with the proportion of patients requiring hospital decreasing from first (15.14%) to last (13.87%) infection. Hospitalization rates dropped from 1.38% to 0.88%, and ICU

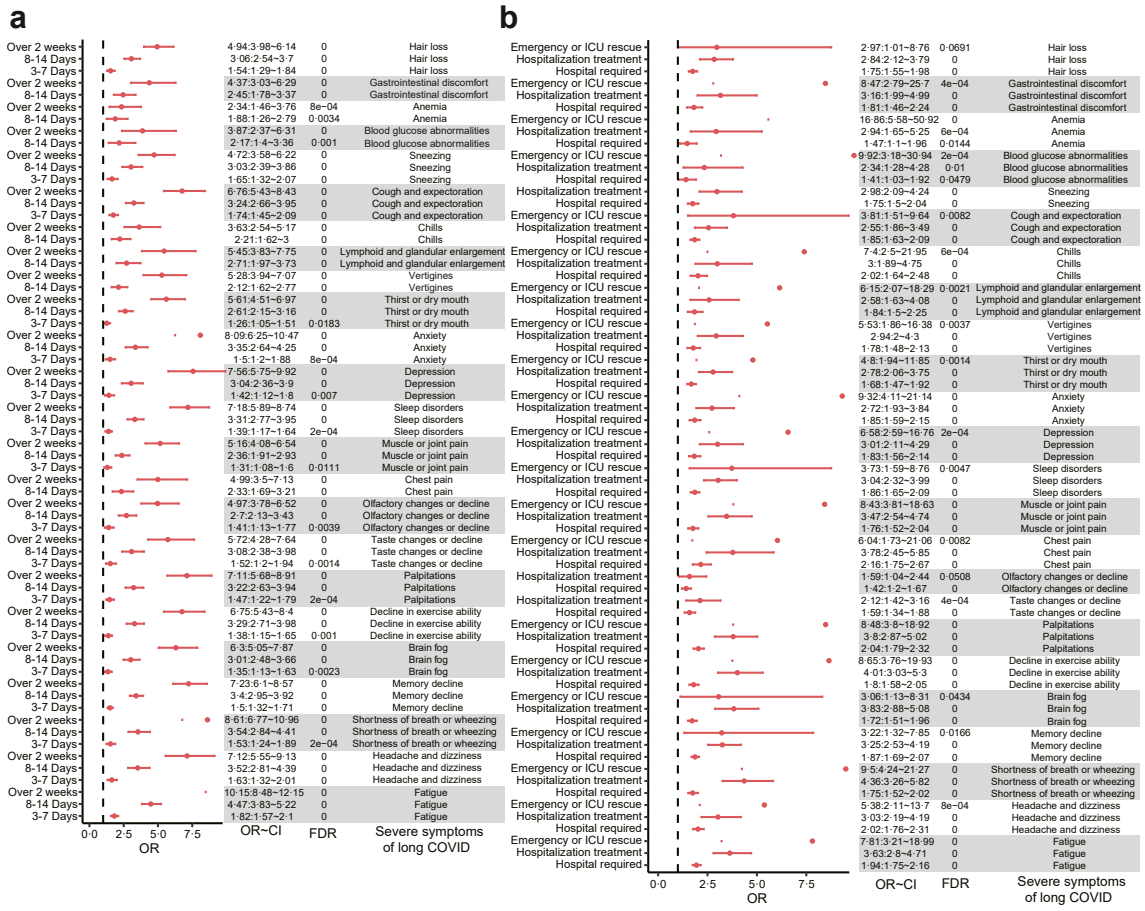


Fig. 2: The association between the acute phase of SARS-CoV-2 and severe long COVID symptoms. (a). The effect of the acute duration of SARS-CoV-2 on severe long COVID. The duration of SARS-CoV-2 infection is defined as the time within which the patient's symptoms significantly improved. Using a significant improvement within 3 days as the control, the effect of different disease duration to severe long COVID was calculated by adjusting for other confounding factors through multivariate logistic regression. (b). The effect of the severity of the SARS-CoV-2 acute phase disease to severe long COVID. Disease severity is indirectly reflected by the patient's medical treatment situation. Using no required hospital as a control, the contribution of different medical treatment levels to severe long COVID was calculated by adjusting for other confounding factors (age, gender, region, underlying disease, smoking, drinking, number of infections and vaccine status) through multivariate logistic regression. OR > 1 represents the risk factor, and OR < 1 represents the protective factor. The absolute value of OR represents the degree of effect of the exposure factor, which can be interpreted as a multiple of increasing or decreasing a certain long-term symptom. The p-value was adjusted using the FDR method.

admissions decreased from 0.11% to 0.07% (Fig. 4d and e). These data indicate that the acute symptoms and disease severity during SARS-CoV-2 reinfection are milder than those of the first infection. However, participants who experienced multiple infections were more likely to experience various long COVID symptoms with increased severity (Fig. 4f and Table S10). Moreover, the multivariate regression analysis indicated that having two infections posed a significant risk for many long COVID symptoms, and the risk ratio increased exponentially when the number of infections exceeds two (OR > 2, FDR < 0.05) (Fig. S8 and Table S10). These findings suggest that minimizing reinfection remains an important preventive measure to reduce the cumulative effects of long COVID.

COVID-19 patients exhibit higher rates of other pathogenic infections

Previous studies have indicated that the acute or late COVID-19 patients may be susceptible to more pathogens, and this was partially attributed to immune debt.[23,24] Here, we showed that the COVID-19 group had a significantly higher rates of bacterial infections (4.34% vs 1.48%), influenza virus infections (10.88% vs 5.41%), and mycoplasma infections (3.57% vs 0.78%) (Fig. 5a and b). The non-COVID-19 respondents reported fewer

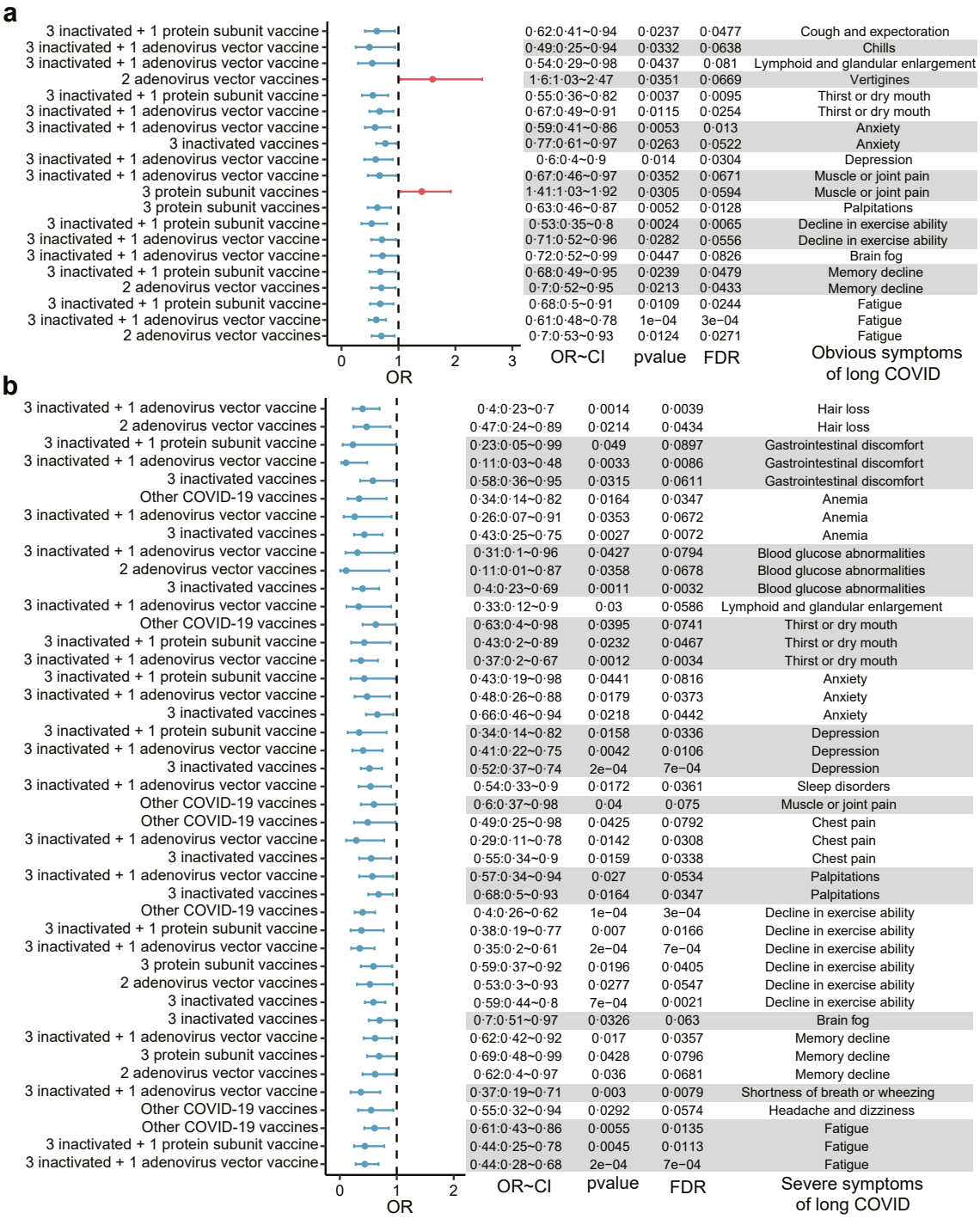


Fig. 3: Impact of different vaccine status to long COVID symptoms. (a–b). The effect of different vaccine status to obvious and severe long COVID, respectively. Using participants who had not received the COVID-19 vaccine as controls, the effect of different vaccine status to long COVID was calculated by adjusting for other confounding factors (age, gender, region, underlying disease, smoking, drinking, number of infections) through multivariate logistic regression. OR > 1 represents the risk factor, and OR < 1 represents the protective factor. The absolute value of OR represents the degree of effect of the exposure factor, which can be interpreted as a multiple of increasing or decreasing a certain long-term symptom. p-values were adjusted using the FDR method.

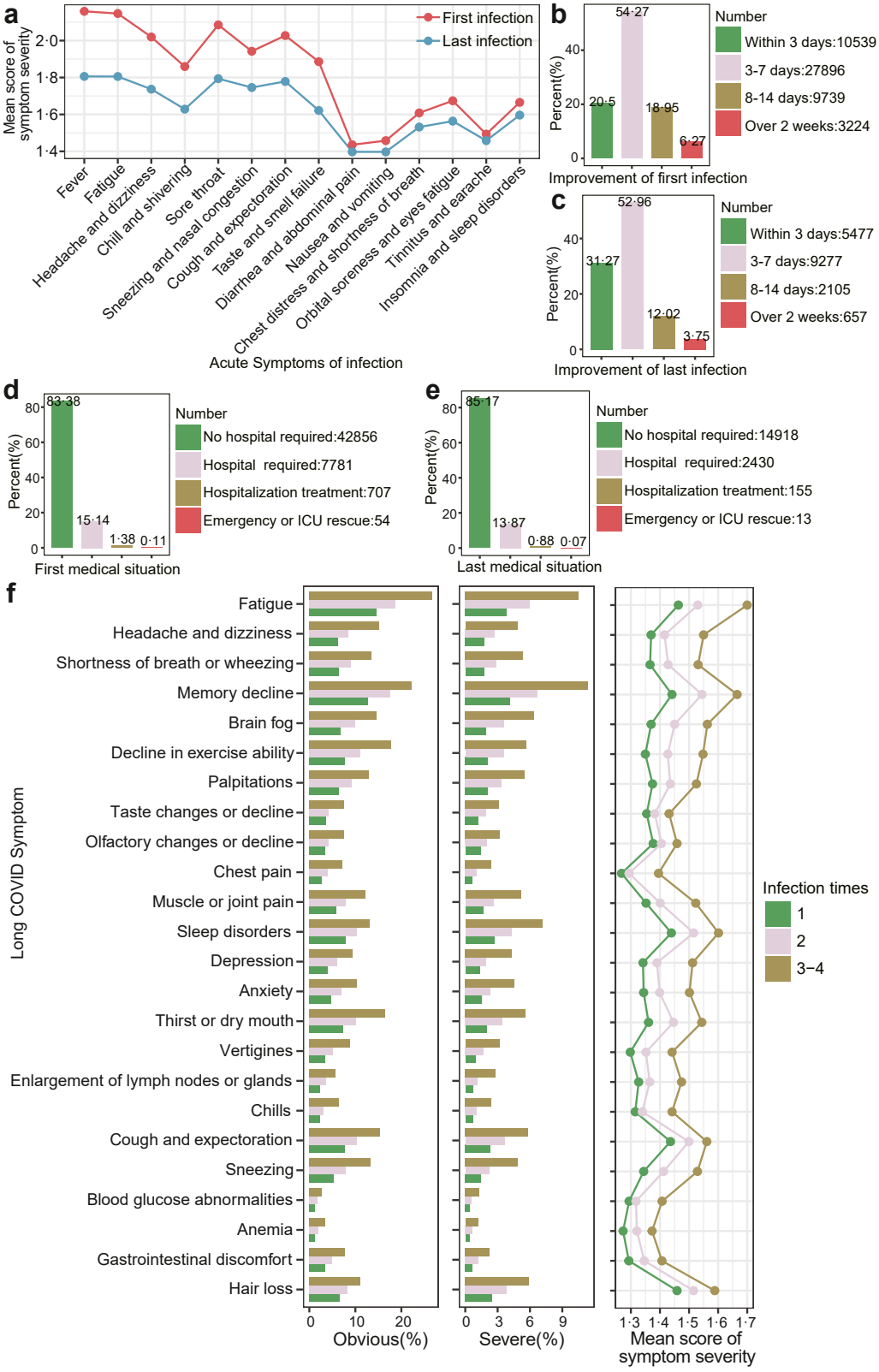
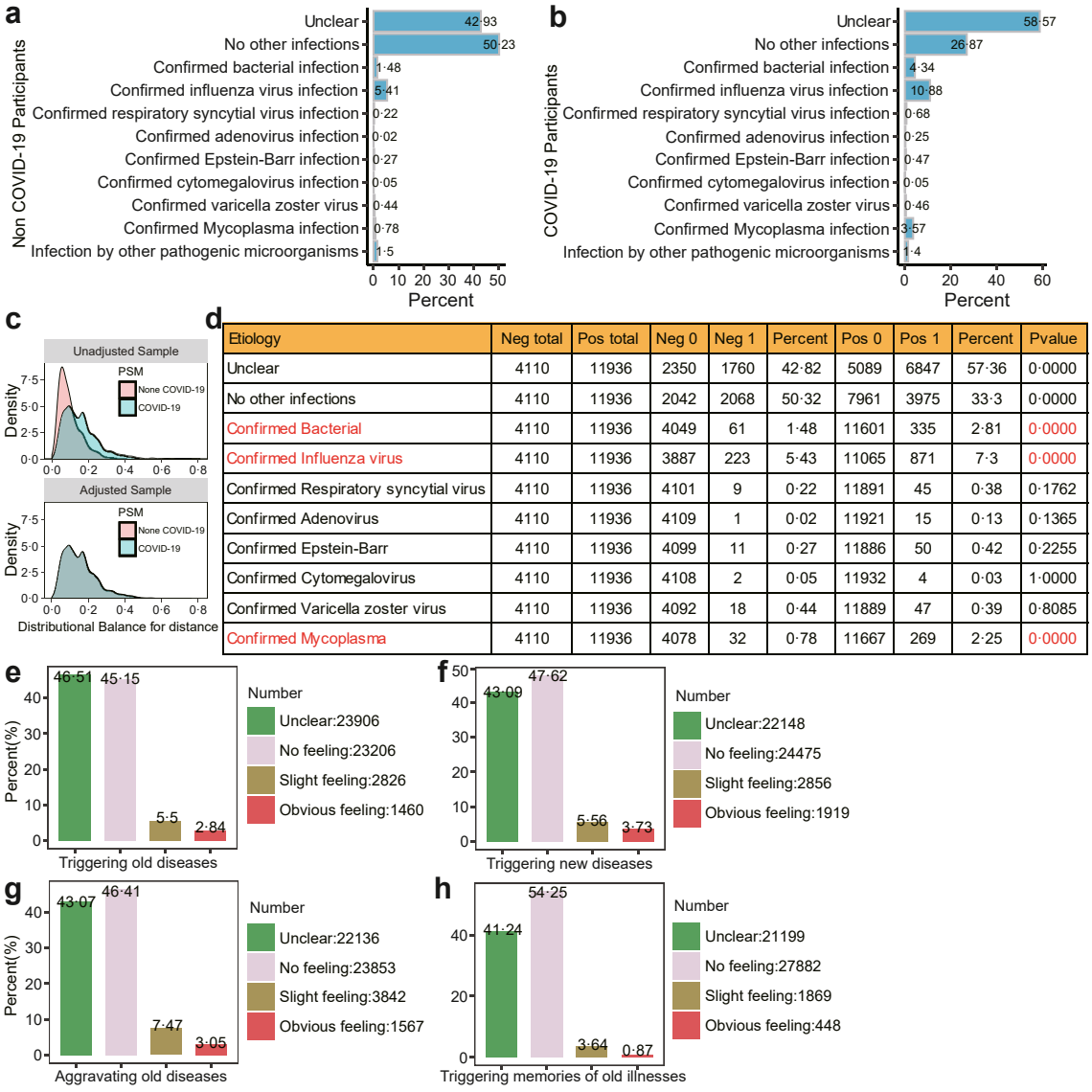


Fig. 4: The association of SARS-CoV-2 reinfection with acute and long COVID symptoms. (a). The difference in severity of acute symptoms between the first and last SARS-CoV-2 infections. (b–c). The proportion of duration of the first and last SARS-CoV-2 infection. Disease duration



Etiology	Neg total	Pos total	Neg 0	Neg 1	Percent	Pos 0	Pos 1	Percent	Pvalue
Unclear	4110	11936	2350	1760	42·82	5089	6847	57·36	0·0000
No other infections	4110	11936	2042	2068	50·32	7961	3975	33·3	0·0000
Confirmed Bacterial	4110	11936	4049	61	1·48	11601	335	2·81	0·0000
Confirmed Influenza virus	4110	11936	3887	223	5·43	11065	871	7·3	0·0000
Confirmed Respiratory syncytial virus	4110	11936	4101	9	0·22	11891	45	0·38	0·1762
Confirmed Adenovirus	4110	11936	4109	1	0·02	11921	15	0·13	0·1365
Confirmed Epstein-Barr	4110	11936	4099	11	0·27	11886	50	0·42	0·2255
Confirmed Cytomegalovirus	4110	11936	4108	2	0·05	11932	4	0·03	1·0000
Confirmed Varicella zoster virus	4110	11936	4092	18	0·44	11889	47	0·39	0·8085
Confirmed Mycoplasma	4110	11936	4078	32	0·78	11667	269	2·25	0·0000

Fig. 5: COVID-19's impact on other pathogenic infections and diseases. (a). Statistics on the percentage of other pathogenic infections in the non-COVID-19 group. (b). Statistics on the percentage of other pathogenic infections in the COVID-19 group. (c). The stacked graph shows the PSM score between the non-COVID-19 group and the COVID-19 group after propensity matching is balanced. Age, gender, region, vaccine status, smoking, drinking and underlying diseases were used as confounding variables for matching and see Table S11 for detailed details. (d). Comparison of other pathogenic infections between the non-COVID-19 and COVID-19 groups after propensity matching. (e). Proportion of SARS-CoV-2 positive patients who feel that COVID-19 can trigger old diseases. (f). Proportion of SARS-CoV-2 positive patients who feel that COVID-19 can trigger new diseases. (g). Proportion of SARS-CoV-2 positive patients who feel that COVID-19 can aggravate old diseases. (h). Proportion of SARS-CoV-2 positive patients who feel that COVID-19 can trigger hallucinations about old diseases but no actual symptoms.

infections from other pathogens than the COVID-19 group (Fig. 5a and b), possibly attributable to strict infection prevention measures or reduced public activities during the pandemic. To ensure more rigorous conclusions, propensity score matching was used to balance the baseline features (age, gender, province,

is defined as the time within which the patient's symptoms significantly improved after infection. (d–e). Proportion of disease severity for the first and last SARS-CoV-2 infections. Disease severity is indirectly reflected by the medical treatment of infected patients. (f). Statistics on the prevalence and severity score of long COVID symptoms in different SARS-CoV-2 infection times.

underlying disease, smoking, drinking, COVID-19 vaccine status) of COVID-19 (n = 11,936) and non-COVID-19 group (n = 4110) (Fig. 5c and Table S11). After matching, bacterial infection ($p < 0.001$), influenza virus infection ($p < 0.001$), and mycoplasma infection ($p < 0.001$) were all significantly higher in the COVID-19 group (Fig. 5d), indicating that COVID-19 may promote susceptibility to these pathogens for unknown reasons.

Additionally, we found that 2.84% and 5.5% of people infected with SARS-CoV-2 had an obvious or slight perception, respectively, that COVID-19 could trigger the re-emergence of old diseases (Fig. 5e). Similarly, 3.73% and 5.56% of COVID-19 patients believed that COVID-19 could cause new diseases (Fig. 5f); 3.05% and 7.47% clearly or slightly felt that COVID-19 would exacerbate an underlying disease (Fig. 5g). Finally, 0.87% and 3.64% of COVID-19 patients, respectively, clearly or slightly believed COVID-19 would cause hallucinations of diseases they were not diagnosed with (Fig. 5h), reflecting potential psychological impacts of COVID-19, particularly in older patients. These findings suggest that COVID-19's side effects include the promotion of other pathogenic infections, as well as old and new disease burdens.

Discussion

An increasing number of empirical studies on long COVID worldwide have summarized the symptom frequencies ranging from 10% to 60%, affecting almost all human body systems.[3,8–12] Extensive long COVID research has been conducted in Europe and America, where national and multinational alliances have been established to address the long COVID diagnosis and treatment.[25,26] However, research on long COVID in China has progressed slowly. One primary reason for this delay is the lack of guidelines or consensus on the treatment and clinical management of long COVID, and a significant gap in key epidemiological data.[27] Although previous studies have provided important insights in long COVID in China, they have not effectively represented the majority of mild COVID-19 cases. Consequently, the characteristics of long COVID remain uncertain for many individuals in China.[10–12]

In a previous study, we investigated the symptoms and influencing factors of COVID-19 among more than 10,000 Chinese.[28] In this study, we expanded our analysis to include long COVID-19 data for over 70,000 participants. Our findings indicate that the prevalence of a single long COVID symptom can be approximately 25%. Moreover, the prevalence of at least one long-term symptom was as high as 49% in this cohort, although this may be overestimated by the total number of symptoms in actual statistics. Therefore, it may be more appropriate to represent the overall prevalence of long COVID through the frequency of top classic long-term symptoms. These results are also comparable to previous long COVID studies reported in China,[10–12] but previous research included more hospitalized patients. The differences observed in prevalence may be attributed to the method of diagnosis and infection of the virus sub-variants.[10–12] Nonetheless, our current findings suggest that even patients with mild COVID-19 are likely to experience long COVID.

Additionally, we identified several factors related to long COVID in this study. Common underlying diseases, along with smoking and alcohol consumption, emerged as significant risk factors for long COVID. Previous studies have shown that underlying diseases such as diabetes and smoking-induced respiratory inflammation and the upregulation of ACE2, etc. can aggravate COVID-19, resulting in prolonged recovery times.[29–31] Furthermore, our findings suggest that women are more susceptible to long COVID than men, although the underlying mechanism is currently unclear. Interestingly, apart from muscle or joint pain and sleep disorders closely related to aging, our multivariate analysis indicates that the increasing age is not a speculated risk factor for long COVID. Healthy middle-aged individuals, free from underlying diseases, may have lower rates of long COVID, owing to better financial support and sufficient rest during recovery,[32] and these factors cannot be ruled out through existing data. The duration and severity of SARS-CoV-2 infection were also risk factors for long COVID, consistent with previous reports, that COVID-19 patients who are critically ill or hospitalized during the acute phase are more likely to develop long COVID.[10–12] Severe COVID-19 can lead to long-term complications, such as pulmonary fibrosis, coagulation system damage, virus residues and other organ damage, which require sufficient time to repair, and are more likely to be affected by the superposition of other diseases during recovery to induce new long COVID symptoms.[18,33] In addition, we also found a higher prevalence of long COVID in the northern China, suggesting a region-related risk factor. Considering that the initial infection period for most participants occurred during winter, we speculate that low temperatures in northern China may contribute to the survival of SARS-CoV-2 and enhance the combined effects of colds and other respiratory illnesses.[34]

Owing to the high variability and strong infectivity of SARS-CoV-2, reinfection is extremely challenging, and its relationship with long COVID is still not fully understood. Our research found that while acute symptoms of reinfection are generally milder, the severity and incidence rate of long COVID increase significantly with the number of reinfections. This extends previous findings that reinfection raises ultimate mortality and the risk of severe illness,[35] while also leading to long COVID. Vaccination is still an effective protective factor in reducing long COVID, particularly the booster shots. Our survey data demonstrated that receiving more than

three doses generally shows stronger protective ranges and effects. Additionally, the results showed that COVID-19 may promote bacterial, influenza virus, and mycoplasma infections, which is consistent with many previous reports of an abnormal wave of multiple pathogenic infections following COVID-19.[23,36] Immune debt has been suggested as a plausible explanation for this phenomenon, but the specific mechanisms require further exploration.[23,36]

Finally, 8%–10% of participants with COVID-19 in this study reported that they felt their infection worsened pre-existing conditions or triggered new complications. This aligns with prior research suggesting that chronic conditions resulting from SARS-CoV-2 infection may persist long-term and contribute to long COVID,[37,38] Importantly, according to the latest long COVID definition from the National Academies of Sciences, Engineering, and Medicine, highlights chronic disease associated with infection as a key feature,[39] supporting our findings.

Although we have outlined the long COVID situation above, understanding its pathological mechanisms remains complex and challenging. Currently, several key pathogenic mechanisms have been reported. For example, Klein et al. found that long COVID patients exhibit abnormal T cell activity, latent virus reactivation, and downregulation of cortisol.[18] Gu et al. identified 23 long COVID-related protein markers and proposed four biological recovery processes for COVID-19.[40] Hasler et al. discovered that long COVID patients had significant abnormalities in the coagulation complement system, thrombosis, and inflammation, and suggested biomarkers such as C5bC6/C7 ratio, vWF/ADAMTS13 ratio, age and body mass index (BMI).[41] Appelman et al. linked that mitochondrial metabolic disorders and abnormal amyloid protein accumulation in the skeletal muscles to decreased exercise ability and post-exertional malaise in patients with long COVID.[42] Wong et al. demonstrated that reduced serotonin levels could lead to long-term symptoms such as brain fog, fatigue, or decreased memory, identifying serotonin as a potential biomarker.[43] Other mechanisms include the presence of residual viral substances, dysregulated gut microbiota, and neurological inflammation.[44–46] Recently, we discovered COVID-19 patients require more time to restore their coagulation system, and immune and metabolic balance, which may be contributing factors to long COVID.[47]

In conclusion, our survey data indicate that approximately 10%–30% of 68,200 Chinese participants (including repeated infections) have experienced long COVID symptoms in the past year. Based on these reported long COVID symptoms and existing knowledge,[3,39] long-term symptoms such as myalgic emphalomyelitis/chronic fatigue, cognitive decline, etc., and other chronic diseases caused by long COVID may increase the global burden of medical care in the next few years. It is crucial to prioritize the diagnosis and treatment of long COVID and to strengthen the monitoring of infected people by considering the identified risk and protective factors.

Although we have made every effort to obtain and analyze this valuable long COVID data from China, this study has several limitations. First, the questionnaire survey may ignore the elderly unfamiliar with electronic devices and young children with symptoms,[48] potentially affecting long COVID statistics for these age groups. Second, although the questionnaire sample covers the entire country, the distribution of provinces, gender and age, does not fully align with the demographic characteristics of China, which may introduce prevalence bias and limit the generalizability of the findings. Third, while the questionnaire was open to all, some infected individuals with long COVID may have been more inclined to respond, potentially leading to an overestimation of prevalence. Fourth, the survey data were based on the respondents' self-perceptions of the questions, acute and long COVID symptoms, rather than on accurate clinical assessment, which may result in overestimation of fatigue, etc., or underestimation of symptoms that require clinical diagnosis. Fifth, the timing of symptom onset was based on participants' memory, which may not account for the incubation period or diagnostic delays, leading to some inaccuracies in prevalence estimates. Sixth, the additive effects of other diseases, mixed infections or co-infections of the participants were difficult to isolate, which may lead to an overestimation of long COVID prevalence. Seventh, the questionnaire did not cover all long-term symptoms or baseline characteristics such as economic income or employment, etc., which could influence the long COVID results. Eighth, participants primarily received inactivated vaccines, limiting comparisons to long COVID statistics for those vaccinated with protein subunit, adenovirus vector, or mRNA vaccines.[49,50] Ninth, this study lacked long-term symptom data from SARS-CoV-2 negative participants, which could have provided a more comprehensive understanding of long COVID prevalence. Tenth, it was difficult to determine the specific SARS-CoV-2 variants affecting participants, especially those with repeated infections, which may have introduced bias from mixed SARS-CoV-2 variants. Eleventh, variability in participants' willingness and initiative to detect different pathogens, particularly in cases of co infected, may have contributed to higher detection rates of other pathogens in the COVID-19 group. Finally, this study only used questionnaires to study the prevalence and related factors of long COVID, without conducting experiments to explore the underlying biological mechanisms.

Contributors

GFG, SJQ and XZ conceived the questionnaire questions. SJQ created and managed the questionnaire link. YNZ, LH, YHL, TY, XZ, LKW and GFG discussed and improved the questionnaire. GFG, LKW, SJQ and

XPM led all authors to spread the questionnaire. SJQ analyzed the data and generated charts. JHS participated in the discussion of data analysis and manuscript. SJQ and LH wrote the original draft. All authors reviewed and edited the manuscript. GFG and XPM supervised and funded the project. All authors have agreed to publish the manuscript.

Data sharing statement

The original questionnaire data in this study can be accessed upon reasonable request by contacting the corresponding author.

Editor note

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Declaration of interests

All authors declare that there are no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanwpc.2024.101218.

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