Article

Associations of COVID-19 symptoms with omicron subvariants BA.2 and BA.5, host status, and clinical outcomes in Japan: a registry-based observational study

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Abstract

Background: Previous SARS-CoV-2 infection and vaccination, coupled to rapid evolution of SARS-CoV-2 variants, have modified COVID-19 clinical manifestations. We characterized the clinical symptoms of COVID-19 individuals in omicron BA.2 and BA.5 Japanese pandemic periods to identify omicron and subvariant associations between symptoms, immune status, and clinical outcomes.

Methods: Individuals registered in Sapporo's web-based COVID-19 information system entered 12 pre-selected symptoms, days since symptom onset, vaccination history, SARS-CoV-2 infection history, and background. Symptom prevalence, variables associated with symptoms, and symptoms associated with progression to severe disease were analysed.

Findings: For 157 861 omicron-infected symptomatic individuals, cough was the most common symptom (99 032/62.7%), followed by sore throat (95 838/60.7%), nasal discharge (69 968/44.3%), and fever (61 218/38.8%). Omicron BA.5 infection was associated with a higher systemic symptom prevalence than BA.2 in vaccinated and unvaccinated individuals (adjusted odds ratio for fever: 2.18 [95% CI 2.12 - 2.25]). Omicron breakthrough-infected individuals with ≥ 3 vaccinations or previous infection were less likely to exhibit systemic symptoms (fever: 0.50 [0.49-0.51]), but more likely to exhibit upper respiratory symptoms (sore throat: 1.33 [1.29-1.36], nasal discharge: 1.84 [1.80-1.89]]. Infected elderly individuals had lower odds for all symptoms. However, when symptoms were manifest, systemic symptoms were associated with an increased odds (dyspnea: 3.01 [1.84-4.91], fever: 2.93 [1.89-4.52]), whereas upper respiratory symptoms with a decreased odds (sore throat: 0.38 [0.24-0.63],

nasal discharge: 0.48 [0.28-0.81]), for severe disease.

Interpretation: Host immunological status, omicron subvariant, and age were associated with a spectrum of COVID-19 symptoms and outcomes. BA.5 produced a higher systemic symptom prevalence than BA.2. Vaccination and prior infection reduced systemic symptom prevalence and improved outcomes but increased upper respiratory tract symptom prevalence. Systemic, but not upper respiratory, symptoms in the elderly heralded severe disease. Our findings may serve as a practical guide to utilize COVID-19 symptoms to appropriately modify healthcare strategies and predict clinical outcomes for elderly patients with omicron infections.

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Keywords: COVID-19, omicron subvariant, vaccination, upper respiratory symptoms, older age.

Research in context

Evidence before this study: COVID-19 clinical symptoms and disease severity have evolved over the COVID-19 pandemic as host immunity has become more widespread through vaccination and natural infection and the transition to mutant strains. Data linking patient clinical presentations to viral, host factor, and disease outcomes must be continuously updated to guide healthcare responses to successive SARS-CoV-2 mutant strains. We searched PubMed up to November 2022, using terms ("COVID-19" or "SARS-CoV-2") AND "symptom" AND ("vaccination" or "natural infection" or "age") AND "omicron". Multiple studies of the original Wuhan strain have described associations between COVID-19 symptoms and viral loads, vaccination status, and clinical outcomes. To the best of our knowledge, the most up-to-date report relating COVID-19 symptoms and outcomes with SARS-CoV-2 mutant strains focused on delta vs. the original dominant omicron strain BA.1. This United Kingdom self-reporting prospective observational study of 63 002 individuals infected with SARS-CoV-2 delta or omicron described a shorter symptom interval and a lower risk of hospitalization with the omicron vs. delta variant. Another prospective cohort study of 1119 United States essential and frontline workers with SARS-CoV-2 delta or omicron infections reported similar findings but also an unexplained increase in total symptom burden in individuals with breakthrough infections for the omicron variant after vaccination (≥ three doses). Notably, no large-scale epidemiological studies describing the relative COVID-19 symptoms and outcomes in the newer BA.2 and BA.5 omicron subvariants, nor relationships to host immune status, are available despite the widespread prevalence

of these variants.

Added value of this study: Using a highly integrated large-scale web-based healthcare registry system in Sapporo, Japan, we enrolled 157 861 individuals with symptomatic COVID-19 BA.2 and BA.5 omicron infections into this study. We report comprehensive and updated data describing BA.2 vs BA.5 clinical manifestations, linked to individual background, vaccination status, history of previous SARS-CoV-2 infection, and clinical outcomes. The large study population, the focus on COVID-19 clinical symptoms, and recent period (from April 25, 2022 to September 25, 2022) for data acquisition, allowed us to: 1) compare the relative symptom prevalence for BA.2 vs. BA.5 infections; and 2) identify novel associations between mutant omicron strains, specific symptoms, host immune status, as modified by vaccination or previous infection, and clinical outcomes.

Implications of all the available evidence: We found that individuals infected with BA.5 exhibited a higher risk for systemic symptoms than BA.2, independent of host factors, including vaccination status. Individuals infected with BA.2 or BA.5, who were vaccinated with ≥ three doses or had a history of previous infection, were less likely to develop systemic symptoms, but more likely to develop upper respiratory symptoms, than unvaccinated, vaccinated with ≤ two doses, or previously uninfected individuals. Our study also found that older individuals were less likely to develop clinical symptoms with omicron infection. However, when symptoms were manifest, systemic symptoms were associated with an increased risk, whereas upper respiratory symptoms were associated with a decreased risk, of severe disease. In summary, our study provides the most up-to-date characterization of clinical

manifestations of COVID-19 in the omicron BA.2 and BA.5 pandemic periods. Our findings may serve as a practical guide to utilize COVID-19 symptoms to broadly modify healthcare strategies and predict clinical outcomes for elderly patients with omicron infections. Continuous updates for our observations are needed as newer SARS-CoV-2 variants emerge.

Introduction

The coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome 2 (SARS-CoV-2), has caused more than 759 million infections worldwide[1]. Since early in the pandemic, multifaceted host factors, e.g., age and underlying disease, have been reported to impact the clinical course of individuals infected with SARS-CoV-2[2-5]. Associated with the widespread implementation of SARS-CoV-2 vaccines and previous infections, the severity and mortality rates of the COVID-19 syndrome have decreased[5-7]. The emergence of mutant strains likely has also modified the clinical manifestations of COVID-19[8,9]. A challenge for healthcare providers/public health officials is appropriately advising individuals with breakthrough infections and implementing healthcare strategies in the current omicron pandemic period[10-12].

Patient clinical symptoms are the most accessible information describing the status of individuals with infections in healthcare settings. However, data linking patient manifestations to viral, host factor, and clinical outcomes must be continuously updated to maximize their utility and guide appropriate healthcare strategies[13,14]. Studies designed to compare the symptoms of alpha vs. delta SARS-CoV-2 variants with those of the original Wuhan strain[15], and the original omicron variant compared to the delta variant, helped guide healthcare strategies[8]. However, no large-scale epidemiological studies describing COVID-19 symptoms and outcomes as a function of host factors across newer omicron subvariants are available.

Sapporo, a Japanese metropolitan city with 2 million people, launched a registration system

to automate the acquisition of self-entered personal information from individuals with COVID-19. This unique system, in which individuals enter their current status via the internet, enables the collection of timely data describing COVID-19 symptoms that can be linked to databases representing individuals' backgrounds, vaccination and previous SARS-CoV-2 infection status, and severity outcomes. Our objective was to update the characterization of COVID-19 clinical symptoms during the omicron BA.2-BA.5 variant pandemic period and identify associations between clinical symptoms, host factors, immune status, and clinical outcomes relevant to the patient and healthcare communities.

Methods

Study population and data sources

This registry-based observational study was based on the Sapporo population. Data from treatment decision sites (TDS) and registration centres for test-positive patients (RCPP) were utilized for analyses (**Fig. S1**). Individuals residing in Sapporo were eligible to register for TDS and RCPP if they met the following criteria: 1) symptomatic individuals who tested positive for SARS-CoV-2 (polymerase chain reaction or antigen test); 2) individuals who were not tested for SARS-CoV-2 but developed new symptoms after a household member tested positive for SARS-CoV-2. Those diagnosed with COVID-19 were requested to immediately register clinical information with the TDS through a web device, including the presence/absence of 12 preselected specific symptoms at the time of registration and the date of symptom onset. Details of the two registration systems are given in **Fig.**

148 **S1** and **Supplementary methods**.

149 Individuals were excluded from the study if they: (1) entered the date of onset inappropriately,
150 (2) registered > 5 days after symptom onset, or (3) registered as asymptomatic. Detailed inclusion and
151 exclusion criteria and the treatment of missing values are described in **Supplementary methods**.

152

153 **Data collected**

154 Data from the TDS and the RCPP are integrated and stored at the Sapporo City Public Health
155 Center. The following data were extracted from these systems: 1) date of first symptom onset; 2)
156 dietary intake; 3) presence of 12 predefined symptoms (fever, cough, sore throat, nasal discharge,
157 sputum, headache, joint or muscle pain, severe fatigue, dyspnoea, diarrhoea, and taste or smell
158 disorder) at registration; and 4) demographic information (age, sex, height, weight, and underlying
159 disease). Data describing previous SARS-CoV-2 infection and progression to severe disease, i.e.,
160 requiring oxygenation or mechanical ventilation, or death, were collected from the Health Center Real-
161 time Information-sharing System for COVID-19 operated by the Ministry of Health, Labor, and
162 Welfare, as well as data linked to patient information in the TDS and RCPP. Vaccination history,
163 including the timelines of vaccination, was accessed from the Vaccination Record System operated by
164 the Japan Government Digital Agency (**Fig. S1**).

165

166 **Characterization of SARS-CoV-2 omicron subvariants**

Whole genome analyses were performed at the Sapporo City Institute of Public Health to identify SARS-CoV-2 variants prevalent in Sapporo. Randomly collected specimens with positive SARS-CoV-2 test results were analysed for approximately 50–80 cases per week and the proportions of omicron subvariants calculated. In this study, omicron subvariant epidemic periods were defined as when the percentage of the most predominant subvariants exceeded 80%.

Statistical analysis

Continuous data were presented as medians (interquartile range [IQR]) and categorical data were presented as numbers and percentages. A 95% confidence interval (CI) for symptom prevalence, odds ratio (OR) and hazard ratio (HR) was calculated by the score method and Wald test, respectively. Multivariable analyses were performed to identify factors associated with the prevalence of each symptom and to test the association between each symptom and progression to severe disease. All available variables from the registry system that have been reported as predictors of COVID-19 outcomes were incorporated[3,8,16]. Vaccination status was divided into two groups with more vs. less than three vaccinations as the boundary, a number clinically relevant to omicron variants[17-19]. Propensity score matching was performed using a 1:1 nearest available matching algorithm without replacement and a caliper of 0.05. The propensity score for each variable was calculated by logistic regression analysis with the variables. Absolute value of standardized difference greater than 0.1 was considered as a sign of imbalance. All statistical analyses were performed using JMP® Pro Version

16.2.0 and SAS® Version 9.4 (SAS Institute Inc., Cary, NC, USA). The detailed statistical methods for the results presented in the figures or tables are described in **Supplementary methods**.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Study population

Data collected from the TDS and RCPP systems were analysed between April 25, 2022, and September 25, 2022. The epidemic period for the omicron subvariant BA.2 spanned April 25 to June 26, and that for BA.5 spanned July 18 to September 25 (**Fig. 1**). After individuals who met the exclusion criteria were excluded (< 5.6%), a total of 157 861 symptomatic COVID-19 cases (34 336 and 123 525 for the BA.2 and BA.5 groups, respectively) were analysed (**Fig. 1**).

The median age of all individuals included in the study was 33 years (IQR 17-47) (**Table 1**). The most prevalent age group was the 30-year-old group (27 665 individuals [17.6%]). Those aged ≥ 65 years accounted for 10 874 (6.9%) of the total. Forty-eight percent were men, and the median BMI was 21.1 kg/m^2 (IQR 18.6–24.0). The proportion of individuals with an underlying disease was highest for hypertension (8781 [5.6%]), followed by chronic respiratory (5652 [3.6%]) and

cardiovascular diseases (1620 [1.0%]). SARS-CoV-2 vaccination status of the cohort was: 60 033 (38.0%) unvaccinated, 1052 (0.7%) one dose, 38 304 (24.3%) two doses, 53 389 (33.8%) three doses, and 5083 (3.2%) four doses. The vast majority (99.3%) of vaccinations administered were mRNA vaccines (BNT162b2 or mRNA-1273) (**Table S1**). Additionally, 5767 individuals (3.7%) had a history of previous SARS-CoV-2 infection.

Coughing was the most prevalent symptom per individual (99 032 [62.7%]), followed by sore throat (95 838 [60.7%]), nasal discharge (69 968 [44.3%]), headache (66 425 [42.1%]), and fever (61 218 [38.8%]) (**Fig. 2A, Table S2**). Mild positive correlations were observed amongst systemic or upper airway symptoms whereas no correlation was observed between systemic and upper airway symptoms (**Fig. S2**). A total of 142 (0.1%) individuals developed severe disease (31 [0.02%] for individuals younger than 65 years of age and 111 [1.01%] for those 65 years of age or older), including four individuals who died within 30 days after onset (**Table 1).**

Clinical manifestations of individuals infected with omicron BA.2 or BA.5

The clinical features of symptomatic individuals with BA.2 vs. BA.5 infections were compared (**Table 1**). The BA.2 group had a lower median age, BMI, history of cerebrovascular disease, and a higher proportion of unvaccinated and ≤ 2 dose-vaccinated individuals. The BA.5 group exhibited higher proportions of other comorbidities, e.g., malignancy, immunodeficiency, cardiovascular disease, hypertension, and diabetes, previous SARS-CoV-2 infection, and contained all

224 individuals with a fourth vaccine dose.

225 All 12 predefined symptoms, except for nasal discharge and phlegm, were more prevalent in
226 the BA.5 vs. BA.2 populations (**Fig. 2A, Table S2**), findings that were replicated in the unvaccinated
227 BA.5 vs. BA.2 subgroups (**Fig. S3, Table S3**). Multivariable logistic regression analyses of the BA.5
228 and BA.2 population data identified associations that predicted an increased odds for BA.5-infected
229 populations of fever (adjusted OR [95% CI]: 2.18 [2.12–2.25]), decreased food intake (1.80 [1.75–
230 1.86]), severe fatigue (1.64 [1.59–1.69]), joint or muscle pain, smell or taste disorders, headache,
231 dyspnoea, diarrhoea, and sore throat, juxtaposed to a decreased odds of nasal discharge and phlegm
232 (**Fig. 2B, Table S4)**. Logistic regression analysis demonstrated comparable odds for progression to
233 severe disease between the two subvariant groups **(Table S5**).

234 As a sensitivity analysis, we performed propensity score matching on backgrounds between
235 BA.2 and BA.5-infected individuals, including the duration from last vaccination date to symptom
236 development. For this matched analysis, we focused on unvaccinated, two-dose, and three-dose
237 vaccinated and included BA.2 or BA.5-infected individuals who registered COVID-19 symptoms in
238 the system on the same day as symptom onset, i.e., day 0 after the first symptom onset. The BA.2 and
239 BA.5 groups each were matched for 4063 individuals. This analysis reproduced data obtained from the
240 unmatched symptom comparison between BA.2 vs. BA.5-infected individuals, including a higher
241 proportion in the BA.5 vs. BA.2 groups of systemic (fever: 2606 [64.1%] vs. 2040 [50.2%], decreased
242 food intake: 1533 [37.7%] vs. 1219 [30%]) vs. a lower proportion of upper airway (nasal discharge:

1372 [33.8%] vs. 1571 (38.7%), Phlegm: 905 [22.3%] vs. 1088 [26.8%]) symptoms (**Table 2**). Odds ratios for each symptom demonstrated specific associations between higher odds for systemic symptoms with BA.5 vs. BA.2 (**Fig. 2C**), consistent with data observed in the unmatched analysis. These findings were similarly observed in matched subgroup analyses of unvaccinated, two-dose, or three-dose vaccinated individuals with BA.2 vs. BA.5 infection (**Fig. S4, Table S6**).

Associations between vaccine status and COVID-19 symptoms

Individuals were divided into two subgroups to determine the effects of the modification of host immune status by vaccination on the prevalence of COVID-19 symptoms. The group with ≥ 3 vaccinations exhibited breakthrough infections with a lower proportion of fever, decreased food intake, severe fatigue, joint or muscle pain, and diarrhoea than the group with ≤ 2 vaccinations (**Fig. S5A, Table S2**). In contrast, cough, sore throat, nasal discharge, and phlegm were more common with breakthrough infections in the ≥ 3 vaccination group. The relative frequencies of 12 preselected omicron symptoms were calculated on each day after symptom onset (**Table S7**). Cox regression analyses, using the presence of symptoms as the occurrence of an event, revealed that the appearance of coughing, sore throat, nasal discharge, and phlegm, but not systemic symptoms, was accelerated in the ≥ 3 vs. ≤ 2 vaccination groups (**Fig. S5B, Table S8**).

Logistic regression analyses also demonstrated that individuals with breakthrough infections after ≥ 3 vaccinations had a decreased odds of systemic symptoms, including fever (0.50 [0.49–0.51]),

decreased food intake (0.39 [0.37–0.40]), severe fatigue (0.59 [0.58–0.61]), joint or muscle pain, headache, diarrhoea, smell or taste disorders, and dyspnoea, as compared to individuals with ≤ 2 vaccinations (**Fig. 3A, Table S4**). In contrast, the likelihood of upper airway symptoms, including nasal discharge (1.84 [1.80–1.89]), cough (1.49 [1.45–1.52]), sore throat (1.33 [1.29–1.36]), and phlegm, were higher in individuals who received ≥ 3 vaccinations than those who received ≤ 2 vaccinations. These findings were replicated in a 1:1 matched analysis of individuals who registered COVID-19 symptoms in the system on the same day as symptom onset (**Figure 3B, Table S9**).

In individuals with two or three vaccinations, we also analysed for associations between time that passed since last vaccination and symptom prevalence, referenced to unvaccinated individuals. Consistent with the logistic regression analyses in the unmatched population groups with ≥ 3 vs. ≤ 2 vaccinations, individuals with three vaccinations had lower odds of systemic symptoms (fever, headache, severe fatigue, decreased food intake, and joint and muscle pain), but a higher odd of nasal discharge, as compared to individuals with two vaccinations throughout the period since last vaccination. For individuals with both two- and three-dose vaccinations, the ORs of systemic symptoms increased, whereas the ORs of sore throat and nasal discharge decreased, over time since last vaccination (**Fig. 3C**, **Table S10**). These data indicate that the effects of vaccine on reducing systemic, but increasing upper respiratory, symptoms waned over time after last vaccination in individuals with omicron breakthrough infection.

The study population was also divided into subgroups based on a history of previous SARS-

CoV-2 infection. The individuals with previous SARS-CoV-2 infection exhibited associations similar to vaccination status, including a higher likelihood of upper respiratory symptoms and a lower likelihood of systemic symptoms (**Fig. S6, Table S2, S4, and S7**).

Associations between COVID-19 symptoms and clinical outcomes in elderly individuals

The proportion of each symptom by age group was calculated (**Fig. 4A, Table S11**). Fever and decreased food intake were most prevalent in individuals under 10 years of age and decreased with age. Cough prevalence exhibited bimodal peaks in the 20s and 70s age groups. Other symptoms were most prevalent in individuals in their 20s and 30s, with proportions decreasing with increasing age throughout the 70s. Consistent with these data, multivariable analyses identified advanced age (≥ 65 years) as an independent factor associated with a lower likelihood of development of any of the 12 preselected symptoms than younger ages (**Fig. 4B, Table S12**).

Multivariable analyses also identified specific COVID-19 symptoms associated with adverse clinical outcomes in elderly individuals. Dyspnea, fever, decreased food intake, and severe fatigue were associated with an increased odds of severe disease (3.01 [1.84–4.91], 2.91 [1.89–4.51], 2.41 [1.55–3.74], and 1.93 [1.22–3.07], respectively) (**Fig. 4C, Table S5**). Indeed, the combination of these four symptoms was associated with progressively increasing odds of severe disease (adjusted OR [95% CI] for the number of symptoms 1–4, with none as a reference: 2.98 [1.73–5.14], 7.46 [4.15–13.41], 14.38 [7.14–28.98], and 40.72 [14.72–112.68], respectively) (**Table S13**). In contrast, sore throat and

nasal discharge were associated with a decreased odds of severe disease (0.39 [0.24–0.63] and 0.48 [0.28–0.82], respectively) (**Fig. 4C, Table S5**). The combination of these two upper airway symptoms was associated with a decreased odds of severe disease (adjusted OR [95% CI] with no upper respiratory symptom as a reference: 0.20 [0.09–0.46]) (**Table S13**).

Discussion

This registry-based self-entry COVID-19 symptom study was conducted over an interval when two omicron subvariants were prevalent. Collectively, individuals with omicron infections exhibited more commonly upper respiratory symptoms, e.g., cough, sore throat, and nasal discharge, than systemic symptoms (**Fig. 2A**). The clinical features of individuals with omicron breakthrough infections differed from those in the early Wuhan strain-dominated pandemic period, which was characterized by a higher prevalence of fever, cough, dyspnoea, and fatigue and a lower prevalence of upper airway symptoms[20-22]. The pattern of a higher incidence of upper respiratory symptoms and a lower incidence of systemic symptoms was replicated in unvaccinated individuals with omicron infections (**Fig. S3**), suggesting that viral strain is a variable causing differences in clinical manifestations between individuals with the Wuhan strain vs. omicron infections.

The omicron subvariants themselves also differed in symptom prevalence. Although emerging later in the pandemic, BA.5 was associated with a higher prevalence of systemic symptoms than BA.2 (**Fig. 2B**). The increased BA.5 systemic symptom prevalence may reflect greater escape from humoral

immunity as compared to BA.2[23,24] and, as indicated by differences in unvaccinated individuals, intrinsic strain differences (**Fig. S4, Table S6**). Notably, the risk of progression to severe disease did not significantly differ between BA.2 vs. BA.5 (**Table S5**).

Significant associations between vaccination status or previous COVID-19 infection and specific symptoms following omicron breakthrough infection were also identified. For example, a reduced risk of systemic symptoms, including fever, fatigue, and headache, was observed in individuals with omicron infections and ≥ 3 vaccinations or a history of previous infection. In contrast, a strong correlation was observed between a history of ≥ 3 vaccinations or previous infection and increased upper airway symptom prevalence (**Fig. 3A/B, S5, and S6**). Notably, it was shown that these vaccine effects on COVID-19 clinical symptoms waned over time after vaccination (**Fig. 3C**). These contrasting systemic vs. upper respiratory post-vaccination symptom manifestations may reflect: 1) vaccine-mediated reductions in viral load, reduced cytokine release into the systemic circulation, and, hence, reduced systemic symptoms[25-27], and 2) vaccine-mediated amplification of local host antiviral responses to upper respiratory tract SARS-CoV-2 infection, the consequences being increased symptom prevalence with earlier symptom peaks (**Fig. S5B**)[28,29]. The increased prevalence of post-breakthrough upper respiratory symptoms after vaccinations likely accounts for the unexplained increase in total symptom burden, but reduced systemic symptoms (fever and chills), recently reported in a cohort of vaccinated United States Essential and Frontline workers after SARS-CoV-2 breakthrough infections[25].

We observed a decreasing prevalence of COVID-19 symptoms with age (**Fig. 4B**). These findings are consistent with an earlier study showing that typical COVID-19 symptoms were less commonly reported in adult groups with advanced age[30,31]. Importantly, if systemic symptoms were present in the elderly (≥ 65-year-old group), strong associations with severe disease were observed (**Fig. 4C**), consistent with reports of pre-vaccinated United States veterans[3]. Unexpectedly, our data suggest that upper respiratory tract symptoms are associated with a reduced risk of severe disease in the elderly.

The structure of this study of single-queried symptomatic individuals with COVID-19 infection is associated with limitations. First, asymptomatic individuals with COVID-19 were not enrolled in the TDS or RCPP, and those who registered as asymptomatic were excluded from the study. Accordingly, we were unable to capture all COVID-19 cases during the study period in the overall Sapporo population. Our findings, therefore, are limited to symptomatic individuals with omicron infection and do not describe how distinct omicron subvariants, age, vaccination, or previous infection may have affected the prevalence of symptoms in the overall population. While practically challenging, future studies may consider prospective COVID-19 screening of large cohorts to identify all incident infections and characterize clinical symptoms. Second, there may have been differences in testing behaviours of individuals in specific subgroups. For example, given the temporal difference between the omicron subvariant BA.2 vs BA.5 pandemic periods, individual testing behaviours may have differed between the two periods, a potential confounding factor in comparing symptom prevalence

between the two omicron subvariants. It is also possible that elderly individuals may have developed more frequent testing behaviours as compared to younger individuals, which might have contributed to our findings of lower symptom prevalence in elderly individuals. Third, while COVID-19 clinical symptoms generally track the kinetics of SARS-CoV-2 infections, symptom information was collected at a single time point upon registration in our study. Consequently, we were unable to provide longitudinal data describing the evolution of COVID-19 symptoms over a single infection.

Several other limitations exist more generally in our study design. First, since symptom data were entered directly by individuals without the assistance of healthcare providers, the data are subject to individual perception variance. However, these are the data provided in clinical encounters. Second, since symptom data were analysed for 12 predefined questions, COVID-19 symptoms other than the predefined questions, including neurological and psychological symptoms, were not evaluated. Third, the reporting of clinical symptom intensity was not collected, eliminating quantitative assessments of symptom intensity. Fourth, the small number of individuals with severe disease may have resulted in a statistically underpowered detection of factors potentially associated with severe COVID-19 outcomes. Nevertheless, the significance of the specific symptoms identified as independent factors associated with severe outcomes was statistically robust. Finally, our study may represent clinical pictures of omicron infection relatively unique to Sapporo, Japan. Future replication studies are needed to test whether our findings are generalized under different healthcare systems and population demographics.

In conclusion, our symptom-based description of the clinical manifestations of COVID-19 during the BA.2- and BA.5-dominated COVID-19 pandemic periods provides practical insights into clinical features of the current COVID-19 pandemic. First, BA.5 infections were associated with more prevalent systemic symptoms than BA.2 infections in both vaccinated and unvaccinated individuals. These data suggest that BA.5 emerged as a more troublesome variant than the BA.2 antecedent. Second, an increased prevalence of local upper respiratory tract symptoms, but reduced systemic symptom prevalence, was observed post-vaccination (or previous infection) following omicron breakthrough infections. Thus, it might be appropriate to counsel individuals contemplating vaccination that post-vaccination breakthrough COVID-19 infections may be associated with an increased likelihood of upper airway symptoms, with offsetting benefits being a shorter symptom interval and a reduced risk of severe outcomes. Third, individuals with advanced age experienced, on average, fewer omicron-induced symptoms, but when present, systemic but not upper respiratory symptoms heralded worsened outcomes. These observations may serve as a practical guide to utilize COVID-19 symptoms to predict clinical outcomes for elderly patients with omicron infections.

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Ethics Approval

The research protocol was approved by the Ethics Committee of Hokkaido University Hospital (Research No. 022-0225). Analysis was performed using database in Sapporo city, with no additional risks to the patients. Therefore, the requirement for informed consent from individual participants was waived by the ethics committee. All methods were performed in accordance with the relevant guidelines and regulations of the Ethics Committee of Hokkaido University Hospital. All patient data were anonymized.

Contributors

SN, NK, and KO conceptualized the study. NK and MI were responsible for data curation. SN, NK, and MI accessed and verified the underlying data in the study. SN and NK conducted investigation process. SN, KO, KK, MS, IY and YMI were responsible for methodology. SN, IY and YMI analysed the study data. SN wrote the original draft, and it was reviewed and edited by KO, KK, MS, YN, RCB, and SK. YN, RCB, and SK contributed as supervisor. All authors approved the final version of the

manuscript, and the corresponding author (SN) was responsible for the decision to submit for publication.

Declaration of interests

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Data sharing statement

This study is an analysis of confidential data held by the City of Sapporo. The data will not be made publicly available at the request of the City of Sapporo.

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519

Figure legends

Figure 1. Schematic representations of the study period and eligibility determination. The bars indicate the number of cases with new COVID-19 infection per day in Sapporo, Japan. The stacked area graph shows proportions of mutant strains detected. The BA.2 or BA.5 pandemic period was defined as when the detection rate of omicron subvariant BA.2 or BA.5 exceeded 80%, respectively, during the study period.

Figure 2. Associations of COVID-19 symptoms with the omicron subvariants BA.2 and BA.5. **A.** Prevalence of COVID-19 symptoms in the total study population and in individuals with BA.2 or BA.5 infections. Error bars indicate 95% confidence intervals (CIs). **B.** Associations between omicron subvariants and symptom odds. Multivariable analysis used each symptom as an outcome and mutant strain, age, body mass index, underlying disease, vaccination history, and history of previous infection as explanatory variables. The type of omicron subvariant (BA.5 or not) and the adjusted odds ratio (OR) for each symptom are arranged from highest to lowest. Points indicate ORs, and bars indicate 95% CIs. The detailed results of the multivariable analysis are presented in **Table S4**. **C.** Differences in symptom odds between omicron subvariants BA.2 and BA.5 identified by a 1:1 propensity score matching analysis. Individuals infected with omicron subvariant BA.2 or BA.5 were grouped and matched for background clinical conditions, vaccine status, a history of previous infections, and time after last vaccination (N = 4063 per each group). Only individuals, who were registered into the system

539 on the same day as symptom onset, were included in the matched analysis. Odds ratios of symptoms
540 in BA.5 to BA.2 groups are shown in order from highest to lowest. Points indicate ORs, and bars
541 indicate 95% CIs.
542
543 **Figure 3. Associations between vaccine status and COVID-19 symptoms.**
544 **A.** Associations between vaccine status and symptom odds. Multivariable analysis used each symptom
545 as an outcome and mutant strain, age, body mass index, underlying disease, vaccination history, and
546 history of previous infection as explanatory variables. The detailed results of the multivariable analysis
547 are presented in **Table S4**. Three or more vaccinations and the adjusted odds ratio (OR) for each
548 symptom are arranged from highest to lowest. Points indicate ORs, and bars indicate 95% confidence
549 intervals (CIs). **B.** Differences in symptom odds by vaccine status identified by a 1:1 propensity score
550 matching analysis. Individuals, excluding those under 10 years of age, were grouped for individuals
551 with ≥ 3 vaccinations or the others, and background matched between the two groups. Only individuals,
552 who were registered into the system on the same day as symptom onset, were included in the matched
553 analysis. The symptom odds ratios of individuals with 3 vaccinations to the others are shown in order
554 from highest to lowest. Points indicate ORs, and bars indicate 95% CIs. The detailed results of
555 matching analysis are shown in Table S9. **C.** Associations of vaccination dose, times since last
556 vaccination, and symptom odds. Days since last vaccination were included as a variable as 60-days
557 scales in the multivariable analysis. ORs of each symptom in individuals with two- or three-dose

vaccinations were plotted over time as 60-days scales after last vaccination, referenced to unvaccinated individuals. Points indicate ORs, and bars indicate 95% confidence intervals (CIs). The detailed results of the multivariable analysis are presented in **Table S10.**

Figure 4. Associations of COVID-19 symptoms with age and progression to severe disease.

A. Prevalence of COVID-19 symptoms according to age. The shade colour of the cells is linked to the high and low percentage values. **B.** Associations between age and symptom odds. Multivariable analysis used each symptom as an outcome and mutant strain, age (elderly or non-elderly), body mass index, underlying disease, vaccination history, and history of spontaneous infection as explanatory variables. Elderly individuals (age ≥ 65 years) and the adjusted odds ratio (OR) for each symptom are arranged from highest to lowest. The detailed results of the multivariable analysis are presented in **Table S12**. **C.** Associations of COVID-19 symptoms with progression to severe disease in elderly subjects. Multivariable analysis was performed using progression to severe disease as an outcome and mutant strain, age, body mass index, underlying disease, vaccination history, history of previous infection, and all symptoms as explanatory variables. Symptoms are sorted in descending order of OR for progression to severe disease. Points indicate ORs, and bars indicate 95% confidence intervals. The detailed results of the multivariable analysis are presented in **Table S5**.

576 **Table 1. Clinical characteristics of the study population.**

	Total (N=15 7861)	BA.2 (n=34 336)	BA.5 (n=123 525)
Median age (IQR) –yr.	33 (17-47)	28 (13-42)	34 (19-48)
Age * – no. (%)			
< 10	23 219 (14.7)	6427 (18.8)	16 792 (13.6)
10s	21 165 (13.4)	6012 (17.6)	15 153 (12.3)
20s	26 259 (16.7)	5667 (16.6)	20 592 (16.7)
30s	27 665 (17.6)	6093 (17.8)	21 572 (17.5)
40s	26 536 (16.8)	5465 (16.0)	21 071 (17.1)
50s	16 629 (10.6)	2434 (7.1)	14 195 (11.5)
60s	8881 (5.6)	1156 (3.4)	7725 (6.3)
70s	4839 (3.1)	647 (1.9)	4192 (3.4)
≥ 80	2359 (1.5)	310 (0.9)	2049 (1.7)
Elderly (Age ≥ 65) – no. (%)	10 874 (6.9)	1441 (4.2)	9433 (7.6)
Sex ** – no. (%)			
Male	75 281 (47.7)	16 292 (47.5)	58 989 (47.8)
Female	82 468 (52.3)	18 012 (52.5)	64 456 (52.2)
Median BMI *** (IQR) –kg/m^2	21.1 (18.6 – 24.0)	20.7 (18.1-23.5)	21·2 (18.7-24.1)
Obesity (BMI ≥ 30) – no. (%)	6729 (4.3)	1241 (3.6)	5488 (4.4)
Comorbidities – no. (%)			
Malignancy	1284 (0.8)	188 (0.5)	1096 (0.9)
Immunocompromised	291 (0.2)	44 (0.1)	247 (0.2)
Chronic respiratory diseases	5652 (3.6)	1186 (3.5)	4466 (3.6)
Chronic kidney diseases	88 (0.1)	15 (0.1)	73 (0.0)
Cardiovascular diseases	1620 (1.0)	229 (0.7)	1391 (1.1)
Cerebrovascular diseases	102 (0.1)	22 (0.1)	80 (0.1)
Hypertension	8781 (5.6)	1270 (3.7)	7511 (6.1)
Diabetes	3740 (2.4)	550 (1.6)	3190 (2.6)
SARS-CoV-2 vaccination – no. (%)			
Unvaccinated	60 033 (38.0)	15 339 (44.7)	44 694 (36.2)
One dose	1052 (0.7)	341 (1.0)	711 (0.6)
Two doses	38 304 (24.3)	11 232 (32.7)	27 072 (21.9)
Three doses	53 389 (33.8)	7424 (21.6)	45 965 (37.2)
Four doses	5083 (3.2)	0 (0.0)	5083 (4.1)
Previous SARS-CoV-2 infection – no. (%)	5767 (3.7)	732 (2.1)	5035 (4.1)
Progression to severe disease – no. (%)	142 (0.1)	19 (0.1)	123 (0.1)
Among the elderly (Age ≥ 65 years)	111 (1.01)	12 (0.83)	99 (1.04)

Among individuals aged < 65 years	31 (0.02)	7 (0.02)	24 (0.02)
Death within 30 days – no.	4	2	2

*N=157 552, **N=157 749, ***N=157 781.

BMI, body mass index (kg/m^2); IQR, interquartile range; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

580 **Table 2. Propensity score matching analysis of day-of-onset symptoms in unvaccinated, two- and three-**
581 **dose populations.**

	Before match			1:1 matched		
	BA.2	BA.5	Std diff	BA.2	BA.5	Std diff
Total	4692	16 995		4063	4063	
Age, mean (SD)	26.7 (19.3)	30.2 (20.3)	-0.173	25.4 (19.7)	24.0 (19.0)	0.073
Age group						
< 10	1191 (25.4)	3643 (21.4)	0.093	1191 (29.3)	1229 (30.2)	-0.020
10s	828 (17.6)	2327 (13.7)	0.109	720 (17.7)	803 (19.8)	-0.052
20s	703 (15.0)	2544 (15.0)	0.000	580 (14.3)	569 (14.0)	0.008
30s	720 (15.3)	2833 (16.7)	-0.036	565 (13.9)	556 (13.7)	0.006
40s	639 (13.6)	2631 (15.5)	-0.053	485 (11.9)	464 (11.4)	0.016
50s	331 (7.1)	1725 (10.2)	-0.111	285 (7.0)	244 (6.0)	0.041
60s	160 (3.4)	709 (4.2)	-0.040	129 (3.2)	116 (2.9)	0.019
70s	80 (1.7)	327 (1.9)	-0.016	69 (1.7)	54 (1.3)	0.030
≥ 80	40 (0.9)	256 (1.5)	-0.061	39 (1.0)	28 (0.7)	0.030
Male	2337 (0.50)	8679 (51.1)	-0.025	2056 (50.6)	2014 (49.6)	0.021
Obesity (BMI ≥ 30)	179 (3.8)	702 (4.1)	-0.016	145 (3.6)	119 (2.9)	0.036
Comorbidities						
Malignancy	24 (0.5)	135 (0.8)	-0.035	22 (0.5)	16 (0.4)	0.022
Immunocompromised	5 (0.1)	35 (0.2)	-0.025	4 (0.1)	1 (0.0)	0.030
Chronic respiratory diseases	176 (3.8)	615 (3.6)	0.007	141 (3.5)	138 (3.4)	0.004
Chronic kidney diseases	5 (0.1)	5 (0.0)	0.030	3 (0.1)	3 (0.1)	0.000
Cardiovascular diseases	30 (0.6)	153 (0.9)	-0.030	22 (0.5)	26 (0.6)	-0.013
Cerebrovascular diseases	4 (0.1)	4 (0.0)	0.026	3 (0.1)	3 (0.1)	0.000
Hypertension	176 (3.8)	821 (4.8)	-0.053	141 (3.5)	135 (3.3)	0.008
Diabetes	73 (1.6)	338 (2.0)	-0.033	61 (1.5)	59 (1.5)	0.004
Unvaccinated	2402 (51.2)	7393 (43.5)	0.155	2402 (59.1)	2452 (60.3)	-0.025
Days since last vaccination						
Two doses						
-60	42 (0.9)	47 (0.3)	0.081	41 (1.0)	46 (1.1)	-0.012
61-120	41 (0.9)	190 (1.1)	-0.025	41 (1.0)	35 (0.9)	0.015
121-180	210 (4.5)	195 (1.1)	0.202	198 (4.9)	177 (4.4)	0.025

180-240	759 (16.2)	225 (1.3)	0.545	221 (5.4)	225 (5.5)	-0.004
241-	200 (4.3)	2770 (16.3)	-0.404	200 (4.9)	197 (4.8)	0.003
Three doses						
-60	347 (7.4)	284 (1.7)	0.278	271 (6.7)	280 (6.9)	-0.009
61-120	455 (9.7)	1504 (8.9)	0.029	453 (11.1)	410 (10.1)	0.034
121-180	228 (4.9)	2890 (17.0)	-0.397	228 (5.6)	233 (5.7)	-0.005
181-240	8 (0.2)	1381 (8.1)	-0.407	8 (0.2)	8 (0.2)	0.000
241-	0 (0.0)	116 (0.7)	-0.117	0 (0.0)	0 (0.0)	0.000
Previous SARS-CoV-2 infection	120 (2.6)	804 (4.7)	-0.116	109 (2.7)	107 (2.6)	0.003
Prevalence of symptoms						
Fever				2040 (50.2)	2606 (64.1)	
Cough				1990 (49.0)	1888 (46.5)	
Sore throat				2039 (50.2)	2018 (49.7)	
Nasal discharge				1571 (38.7)	1372 (33.8)	
Phlegm				1088 (26.8)	905 (22.3)	
Headache				1656 (40.8)	1855 (45.7)	
Joint or muscle pain				1001 (24.6)	1205 (29.7)	
Decreased food intake				1219 (30.0)	1533 (37.7)	
Severe fatigue				1083 (26.7)	1252 (30.8)	
Dyspnea				407 (10.0)	471 (11.6)	
Diarrhea				239 (5.9)	246 (6.1)	
Smell or taste disorder				78 (1.9)	97 (2.4)	
Number of symptoms, median (IQR)				3 (2-5)	3 (2-5)	

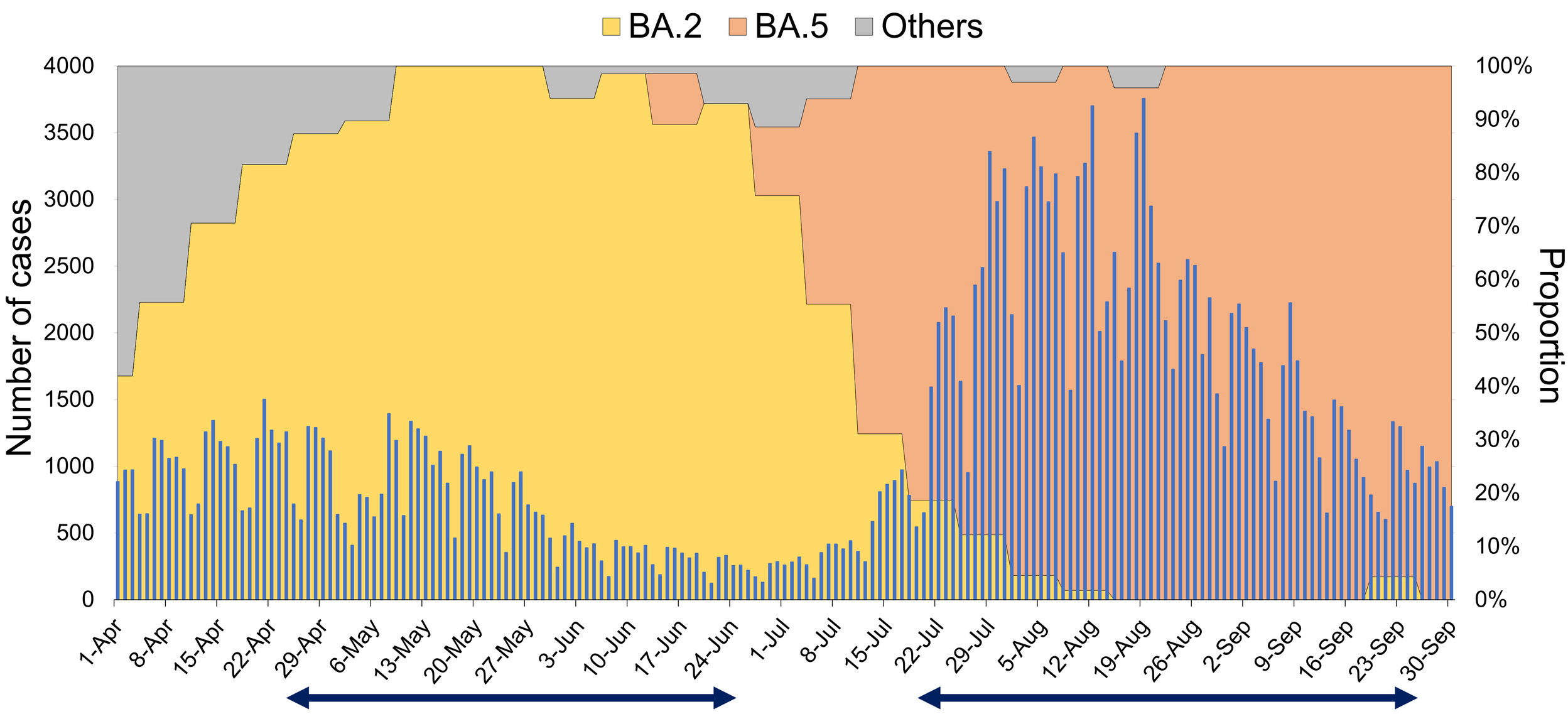
582 Data are n (%) unless otherwise specified.

583 Absolute value of standardized difference (Std diff) greater than 0.1 is considered as a sign of imbalance.

584 BMI, body mass index (kg/m^2); SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SD, standard deviation.

585

Figure 1



37 260 individuals were diagnosed and registered with COVID-19.

130 024 individuals were diagnosed and registered with COVID-19.

2924 individuals were excluded
- 1603 had an inappropriate date of onset or more than 5 days after onset.
- 1321 were asymptomatic.

6499 individuals were excluded.
- 4382 had an inappropriate date of onset or more than 5 days after onset.
- 2117 were asymptomatic.

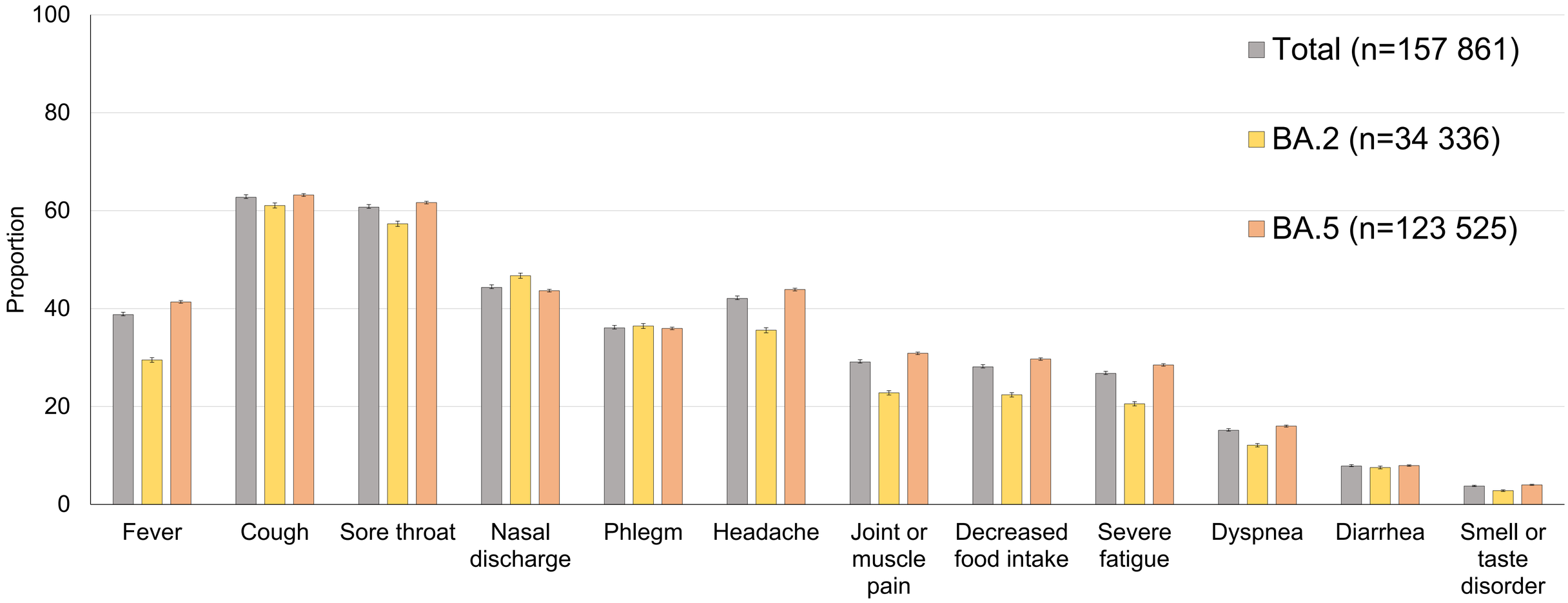
34 336 individuals were classified as BA.2 group.

123 525 individuals were classified as BA.5 group.

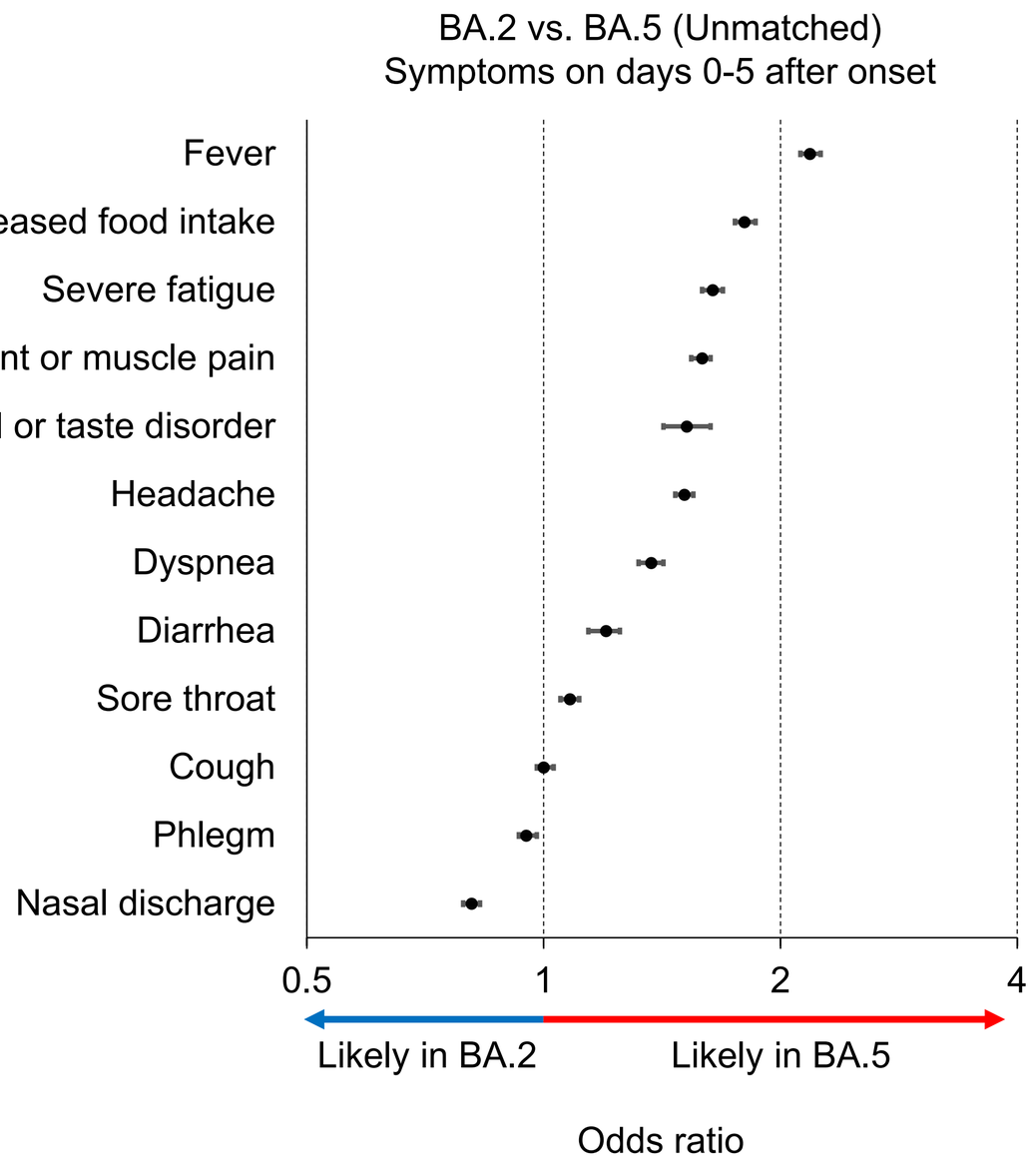
157 861 Individuals were included into the analysis.

Figure 2

A


Proportion
100
80
60
40
20
0
Total (n=157 861)
BA.2 (n=34 336)
BA.5 (n=123 525)
Fever
Cough
Sore throat
Nasal discharge
Phlegm
Headache
Joint or muscle pain
Decreased food intake
Severe fatigue
Dyspnea
Diarrhea
Smell or taste disorder

B


BA.2 vs. BA.5 (Unmatched)
Symptoms on days 0-5 after onset
Fever
Decreased food intake
Severe fatigue
Joint or muscle pain
Smell or taste disorder
Headache
Dyspnea
Diarrhea
Sore throat
Cough
Phlegm
Nasal discharge
0.5
1
2
4
Likely in BA.2
Likely in BA.5
Odds ratio

C

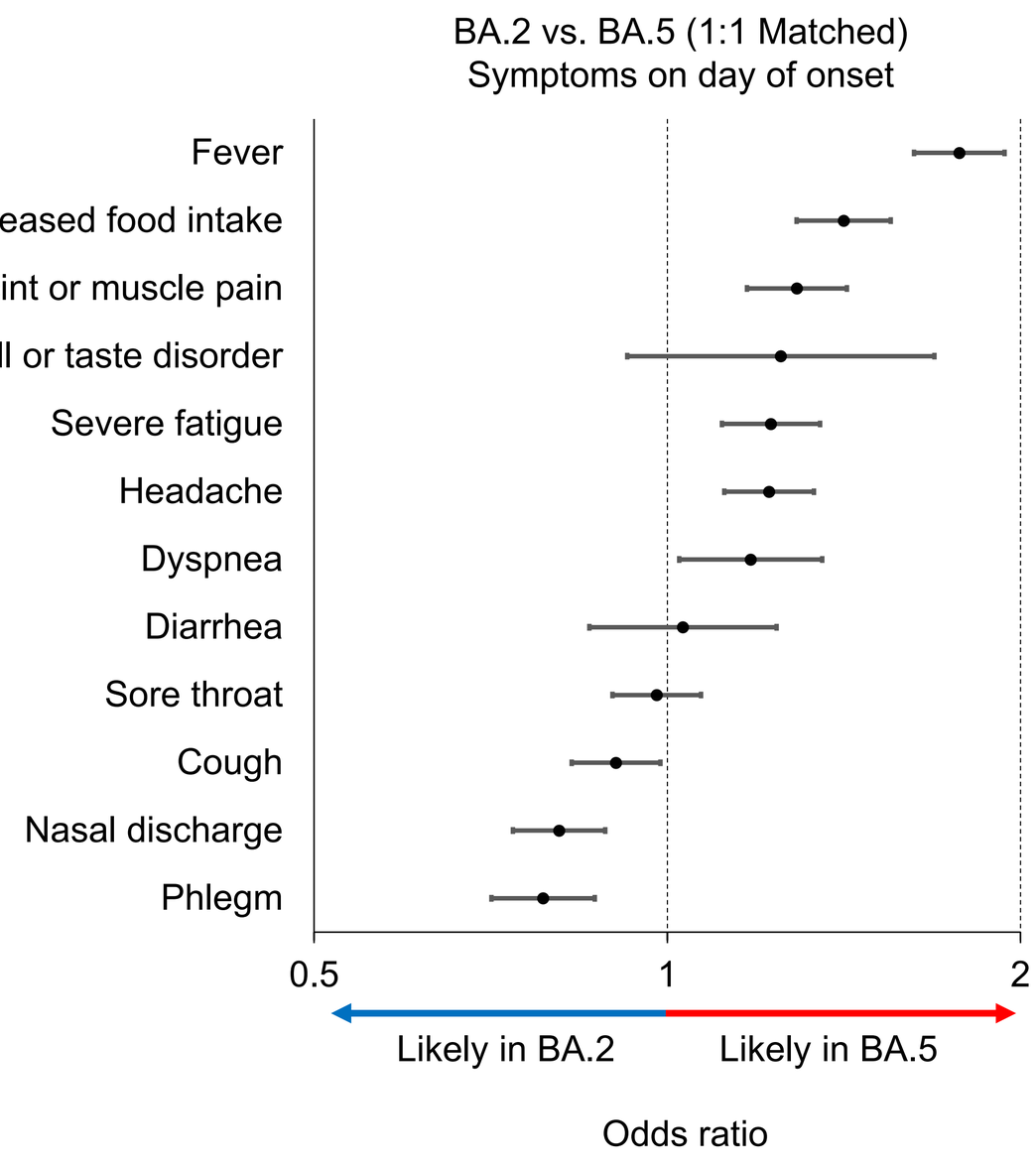
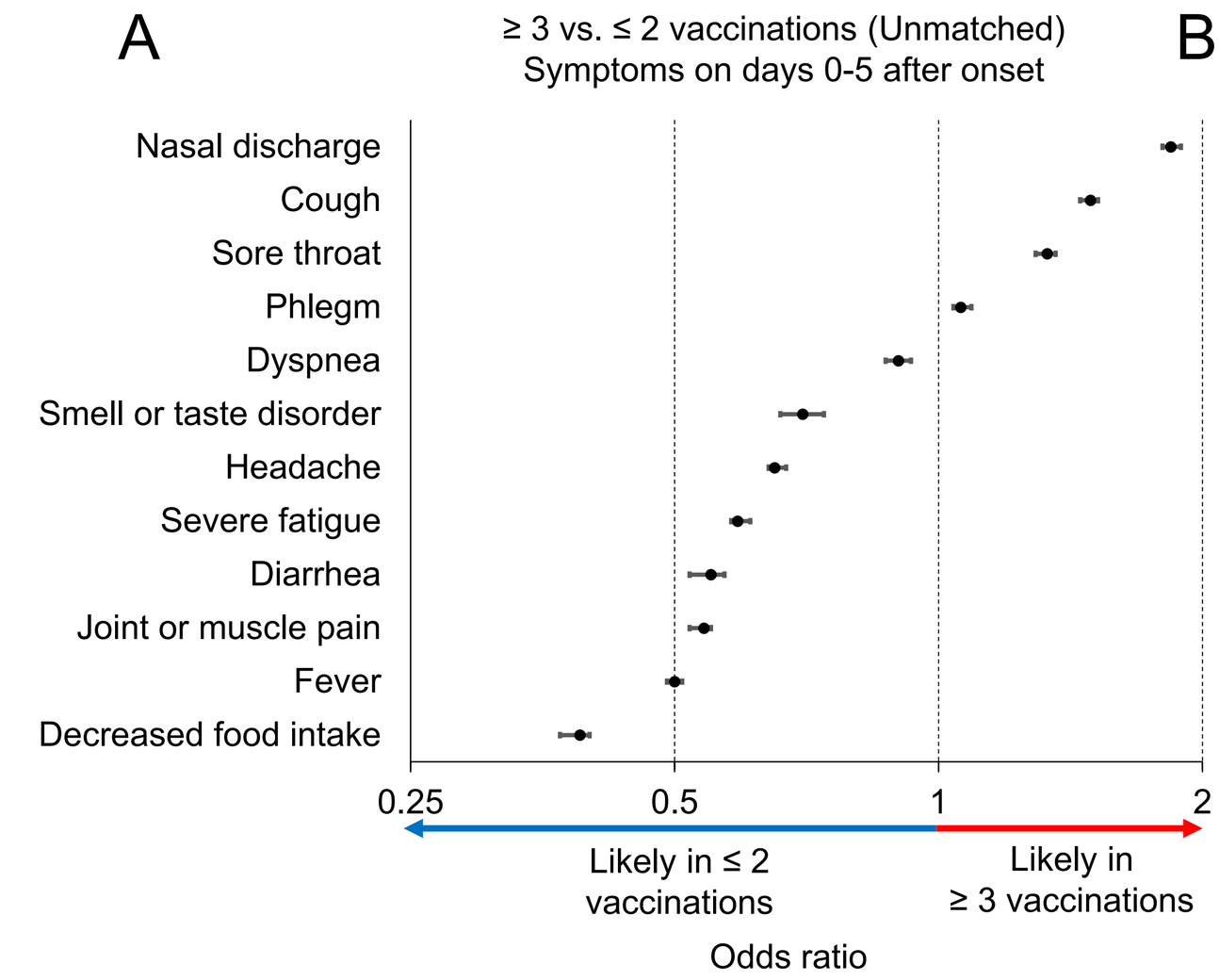
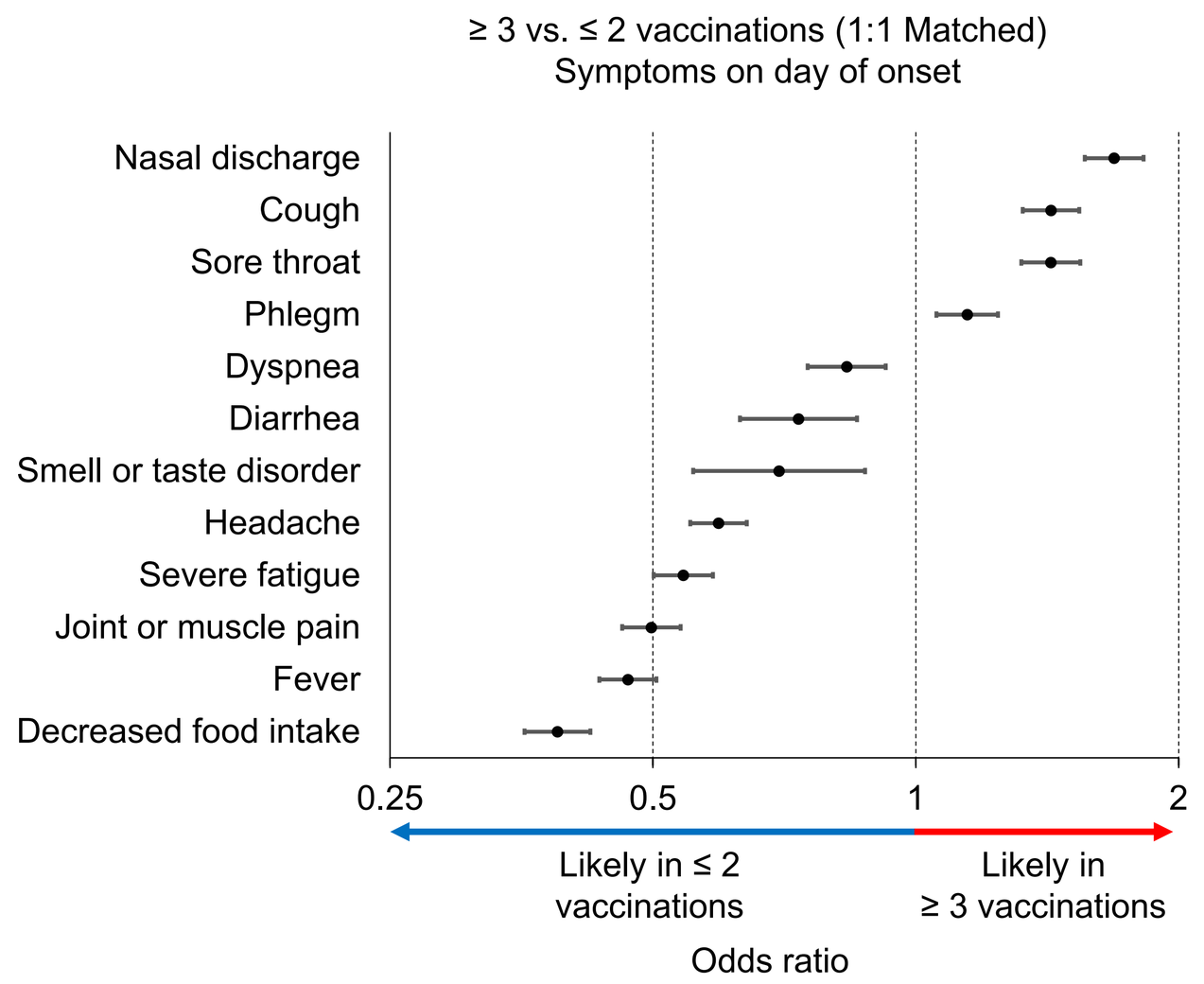

BA.2 vs. BA.5 (1:1 Matched)
Symptoms on day of onset
Fever
Decreased food intake
Joint or muscle pain
Smell or taste disorder
Severe fatigue
Headache
Dyspnea
Diarrhea
Sore throat
Cough
Nasal discharge
Phlegm
0.5
1
2
Likely in BA.2
Likely in BA.5
Odds ratio

Figure 3


A
≥ 3 vs. ≤ 2 vaccinations (Unmatched)
Symptoms on days 0-5 after onset
Nasal discharge
Cough
Sore throat
Phlegm
Dyspnea
Smell or taste disorder
Headache
Severe fatigue
Diarrhea
Joint or muscle pain
Fever
Decreased food intake
0.25
0.5
1
2
Likely in ≤ 2 vaccinations
Likely in ≥ 3 vaccinations
Odds ratio


B
≥ 3 vs. ≤ 2 vaccinations (1:1 Matched)
Symptoms on day of onset
Nasal discharge
Cough
Sore throat
Phlegm
Dyspnea
Diarrhea
Smell or taste disorder
Headache
Severe fatigue
Joint or muscle pain
Fever
Decreased food intake
0.25
0.5
1
2
Likely in ≤ 2 vaccinations
Likely in ≥ 3 vaccinations
Odds ratio

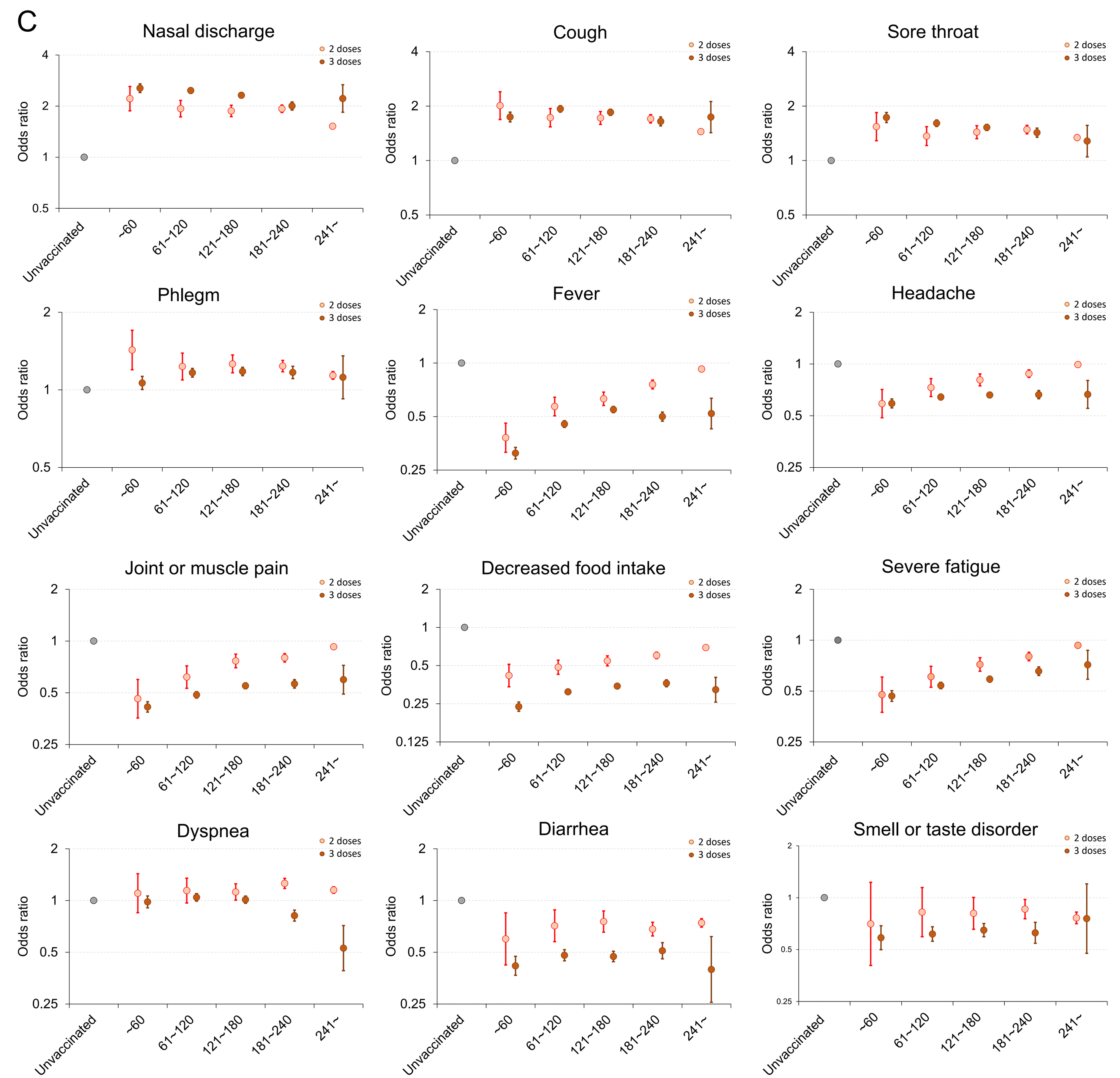
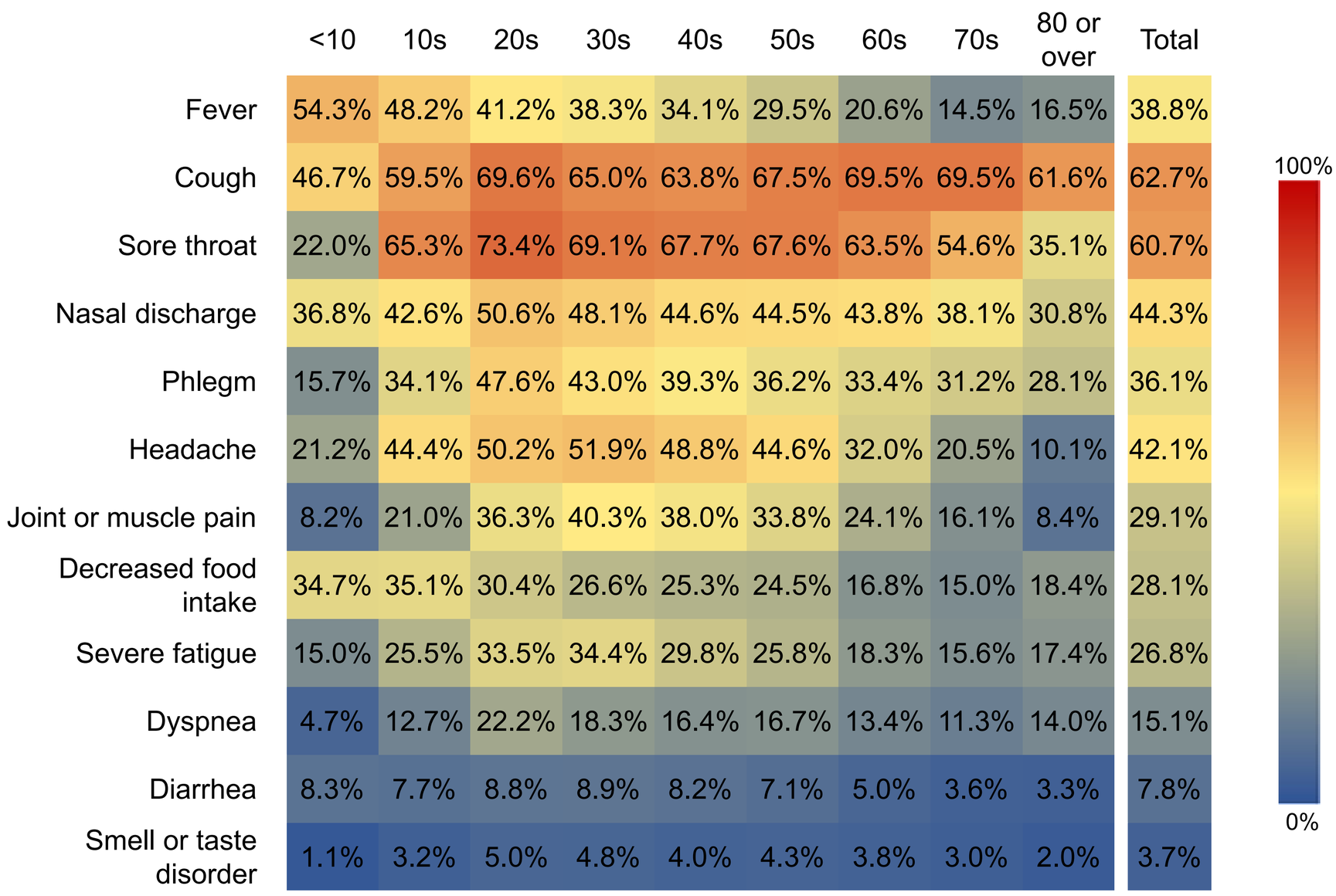
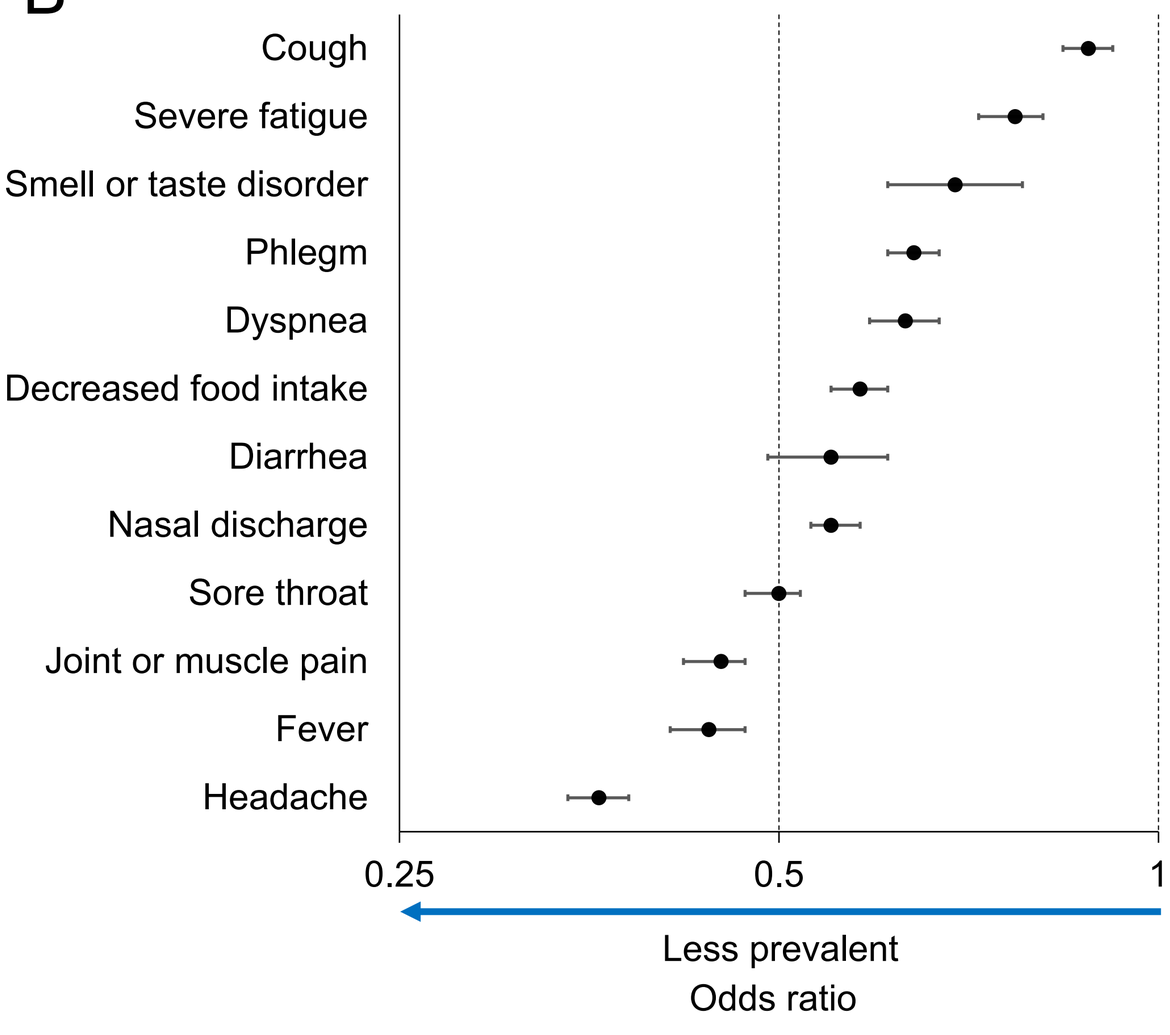

C
Nasal discharge
Cough
Sore throat
Phlegm
Fever
Headache
Joint or muscle pain
Decreased food intake
Severe fatigue
Dyspnea
Diarrhea
Smell or taste disorder
2 doses
3 doses
Odds ratio
Unvaccinated
~60
61~120
121~180
181~240
241~

Figure 4

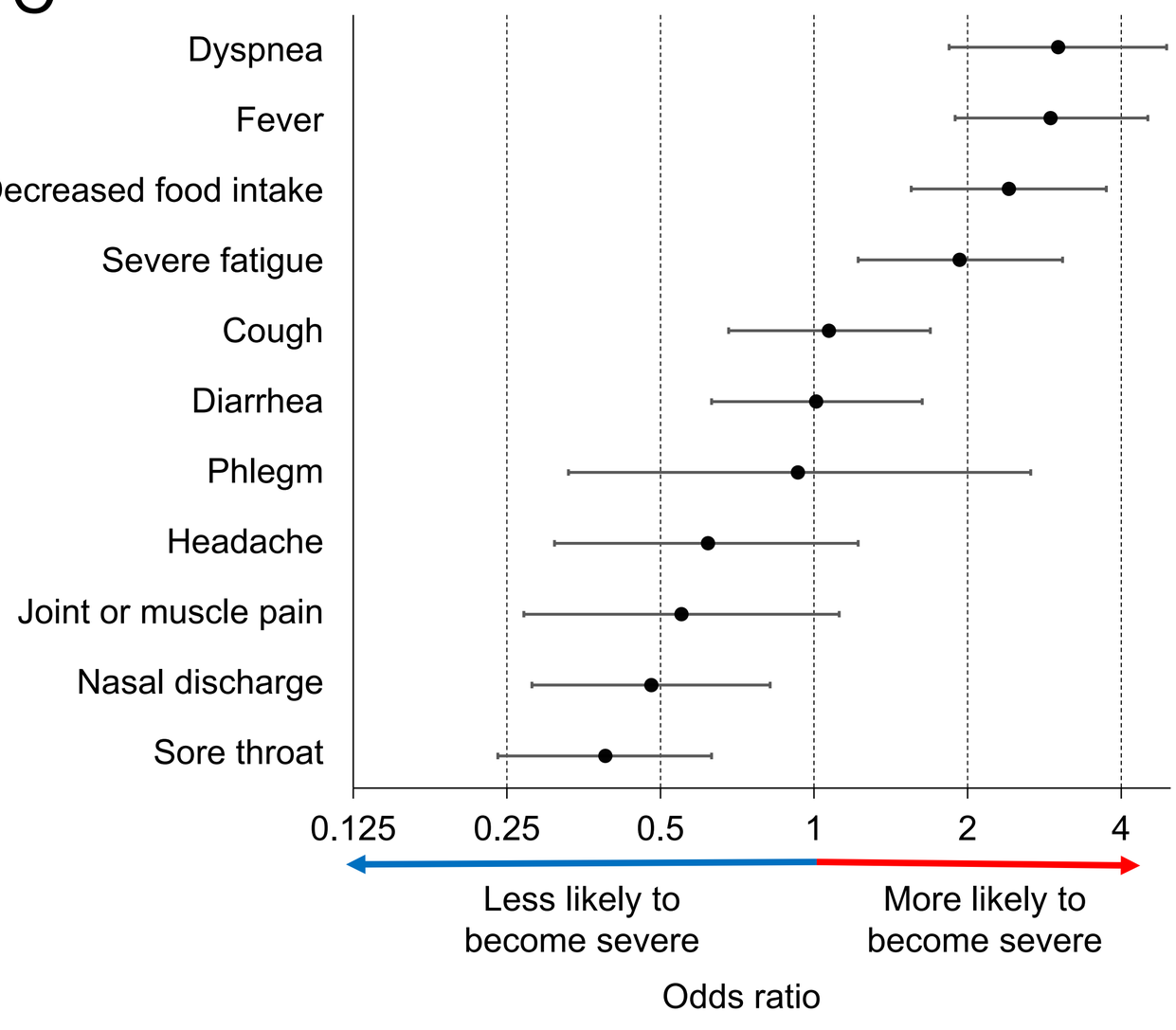
A


<10
10s
20s
30s
40s
50s
60s
70s
80 or over
Total
Fever 54.3% 48.2% 41.2% 38.3% 34.1% 29.5% 20.6% 14.5% 16.5% 38.8%
Cough 46.7% 59.5% 69.6% 65.0% 63.8% 67.5% 69.5% 69.5% 61.6% 62.7%
Sore throat 22.0% 65.3% 73.4% 69.1% 67.7% 67.6% 63.5% 54.6% 35.1% 60.7%
Nasal discharge 36.8% 42.6% 50.6% 48.1% 44.6% 44.5% 43.8% 38.1% 30.8% 44.3%
Phlegm 15.7% 34.1% 47.6% 43.0% 39.3% 36.2% 33.4% 31.2% 28.1% 36.1%
Headache 21.2% 44.4% 50.2% 51.9% 48.8% 44.6% 32.0% 20.5% 10.1% 42.1%
Joint or muscle pain 8.2% 21.0% 36.3% 40.3% 38.0% 33.8% 24.1% 16.1% 8.4% 29.1%
Decreased food intake 34.7% 35.1% 30.4% 26.6% 25.3% 24.5% 16.8% 15.0% 18.4% 28.1%
Severe fatigue 15.0% 25.5% 33.5% 34.4% 29.8% 25.8% 18.3% 15.6% 17.4% 26.8%
Dyspnea 4.7% 12.7% 22.2% 18.3% 16.4% 16.7% 13.4% 11.3% 14.0% 15.1%
Diarrhea 8.3% 7.7% 8.8% 8.9% 8.2% 7.1% 5.0% 3.6% 3.3% 7.8%
Smell or taste disorder 1.1% 3.2% 5.0% 4.8% 4.0% 4.3% 3.8% 3.0% 2.0% 3.7%
100%
0%

B


Cough
Severe fatigue
Smell or taste disorder
Phlegm
Dyspnea
Decreased food intake
Diarrhea
Nasal discharge
Sore throat
Joint or muscle pain
Fever
Headache
0.25
0.5
1
Less prevalent
Odds ratio

C


Dyspnea
Fever
Decreased food intake
Severe fatigue
Cough
Diarrhea
Phlegm
Headache
Joint or muscle pain
Nasal discharge
Sore throat
0.125
0.25
0.5
1
2
4
Less likely to become severe
More likely to become severe
Odds ratio