



Title	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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1 **Article**

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

4  
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31

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33

34 **Abstract**

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

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

43 **Findings:** For 157 861 omicron-infected symptomatic individuals, cough was the most common  
44 symptom (99 032/62.7%), followed by sore throat (95 838/60.7%), nasal discharge (69 968/44.3%),  
45 and fever (61 218/38.8%). Omicron BA.5 infection was associated with a higher systemic symptom  
46 prevalence than BA.2 in vaccinated and unvaccinated individuals (adjusted odds ratio for fever: 2.18  
47 [95% CI 2.12 - 2.25]). Omicron breakthrough-infected individuals with  $\geq 3$  vaccinations or previous  
48 infection were less likely to exhibit systemic symptoms (fever: 0.50 [0.49-0.51]), but more likely to  
49 exhibit upper respiratory symptoms (sore throat: 1.33 [1.29-1.36], nasal discharge: 1.84 [1.80-1.89]).  
50 Infected elderly individuals had lower odds for all symptoms. However, when symptoms were manifest,  
51 systemic symptoms were associated with an increased odds (dyspnea: 3.01 [1.84-4.91], fever: 2.93  
52 [1.89-4.52]), whereas upper respiratory symptoms with a decreased odds (sore throat: 0.38 [0.24-0.63],

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

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

61 **Funding:** Japan Agency for Medical Research and Development.

62

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

64

65

66 **Research in context**

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

85 of these variants.

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

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

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

108

109



110 **Introduction**

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

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

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

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

136

## 137 **Methods**

### 138 **Study population and data sources**

139 This registry-based observational study was based on the Sapporo population. Data from  
140 treatment decision sites (TDS) and registration centres for test-positive patients (RCPP) were utilized  
141 for analyses (**Fig. S1**). Individuals residing in Sapporo were eligible to register for TDS and RCPP if  
142 they met the following criteria: 1) symptomatic individuals who tested positive for SARS-CoV-2  
143 (polymerase chain reaction or antigen test); 2) individuals who were not tested for SARS-CoV-2 but  
144 developed new symptoms after a household member tested positive for SARS-CoV-2. Those  
145 diagnosed with COVID-19 were requested to immediately register clinical information with the TDS  
146 through a web device, including the presence/absence of 12 preselected specific symptoms at the time  
147 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**

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

172

### 173 **Statistical analysis**

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

186 16.2.0 and SAS<sup>®</sup> Version 9.4 (SAS Institute Inc., Cary, NC, USA). The detailed statistical methods for  
187 the results presented in the figures or tables are described in **Supplementary methods**.

188

### 189 **Role of the funding source**

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

192

## 193 **Results**

### 194 **Study population**

195 Data collected from the TDS and RCPP systems were analysed between April 25, 2022, and  
196 September 25, 2022. The epidemic period for the omicron subvariant BA.2 spanned April 25 to June  
197 26, and that for BA.5 spanned July 18 to September 25 (**Fig. 1**). After individuals who met the  
198 exclusion criteria were excluded (< 5.6%), a total of 157 861 symptomatic COVID-19 cases (34 336  
199 and 123 525 for the BA.2 and BA.5 groups, respectively) were analysed (**Fig. 1**).

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

205 cardiovascular diseases (1620 [1.0%]). SARS-CoV-2 vaccination status of the cohort was: 60 033  
206 (38.0%) unvaccinated, 1052 (0.7%) one dose, 38 304 (24.3%) two doses, 53 389 (33.8%) three doses,  
207 and 5083 (3.2%) four doses. The vast majority (99.3%) of vaccinations administered were mRNA  
208 vaccines (BNT162b2 or mRNA-1273) (**Table S1**). Additionally, 5767 individuals (3.7%) had a history  
209 of previous SARS-CoV-2 infection.

210 Coughing was the most prevalent symptom per individual (99 032 [62.7%]), followed by sore  
211 throat (95 838 [60.7%]), nasal discharge (69 968 [44.3%]), headache (66 425 [42.1%]), and fever (61  
212 218 [38.8%]) (**Fig. 2A, Table S2**). Mild positive correlations were observed amongst systemic or upper  
213 airway symptoms whereas no correlation was observed between systemic and upper airway symptoms  
214 (**Fig. S2**). A total of 142 (0.1%) individuals developed severe disease (31 [0.02%] for individuals  
215 younger than 65 years of age and 111 [1.01%] for those 65 years of age or older), including four  
216 individuals who died within 30 days after onset (**Table 1**).

217

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

219 The clinical features of symptomatic individuals with BA.2 vs. BA.5 infections were  
220 compared (**Table 1**). The BA.2 group had a lower median age, BMI, history of cerebrovascular disease,  
221 and a higher proportion of unvaccinated and  $\leq 2$  dose-vaccinated individuals. The BA.5 group  
222 exhibited higher proportions of other comorbidities, e.g., malignancy, immunodeficiency,  
223 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:

243 1372 [33.8%] vs. 1571 (38.7%), Phlegm: 905 [22.3%] vs. 1088 [26.8%]) symptoms (**Table 2**). Odds  
244 ratios for each symptom demonstrated specific associations between higher odds for systemic  
245 symptoms with BA.5 vs. BA.2 (**Fig. 2C**), consistent with data observed in the unmatched analysis.  
246 These findings were similarly observed in matched subgroup analyses of unvaccinated, two-dose, or  
247 three-dose vaccinated individuals with BA.2 vs. BA.5 infection (**Fig. S4, Table S6**).

248

### 249 **Associations between vaccine status and COVID-19 symptoms**

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

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



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

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

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

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

284

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

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

293 Multivariable analyses also identified specific COVID-19 symptoms associated with adverse  
294 clinical outcomes in elderly individuals. Dyspnea, fever, decreased food intake, and severe fatigue  
295 were associated with an increased odds of severe disease (3.01 [1.84–4.91], 2.91 [1.89–4.51], 2.41  
296 [1.55–3.74], and 1.93 [1.22–3.07], respectively) (**Fig. 4C, Table S5**). Indeed, the combination of these  
297 four symptoms was associated with progressively increasing odds of severe disease (adjusted OR [95%  
298 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],  
299 14.38 [7.14–28.98], and 40.72 [14.72–112.68], respectively) (**Table S13**). In contrast, sore throat and

300 nasal discharge were associated with a decreased odds of severe disease (0.39 [0.24–0.63] and 0.48  
301 [0.28–0.82], respectively) (**Fig. 4C, Table S5**). The combination of these two upper airway symptoms  
302 was associated with a decreased odds of severe disease (adjusted OR [95% CI] with no upper  
303 respiratory symptom as a reference: 0.20 [0.09–0.46]) (**Table S13**).

304

## 305 **Discussion**

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

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

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

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

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

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

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

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

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

390

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398

### 399 **Ethics Approval**

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

406

### 407 **Contributors**

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



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

415

#### 416 **Declaration of interests**

417 KO reports grants from the National Heart, Lung, and Blood Institute, the Cystic Fibrosis Foundation  
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424

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435

#### 436 **Data sharing statement**

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

439

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- 519

520 **Figure legends**

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

526

527 **Figure 2. Associations of COVID-19 symptoms with the omicron subvariants BA.2 and BA.5.**

528 **A.** Prevalence of COVID-19 symptoms in the total study population and in individuals with BA.2 or  
529 BA.5 infections. Error bars indicate 95% confidence intervals (CIs). **B.** Associations between omicron  
530 subvariants and symptom odds. Multivariable analysis used each symptom as an outcome and mutant  
531 strain, age, body mass index, underlying disease, vaccination history, and history of previous infection  
532 as explanatory variables. The type of omicron subvariant (BA.5 or not) and the adjusted odds ratio  
533 (OR) for each symptom are arranged from highest to lowest. Points indicate ORs, and bars indicate  
534 95% CIs. The detailed results of the multivariable analysis are presented in **Table S4**. **C.** Differences  
535 in symptom odds between omicron subvariants BA.2 and BA.5 identified by a 1:1 propensity score  
536 matching analysis. Individuals infected with omicron subvariant BA.2 or BA.5 were grouped and  
537 matched for background clinical conditions, vaccine status, a history of previous infections, and time  
538 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  $\geq 3$  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



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

561

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

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

575

**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 <sup>2</sup>	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

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

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

579

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<sup>2</sup>); SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SD, standard deviation.

585

Figure 1

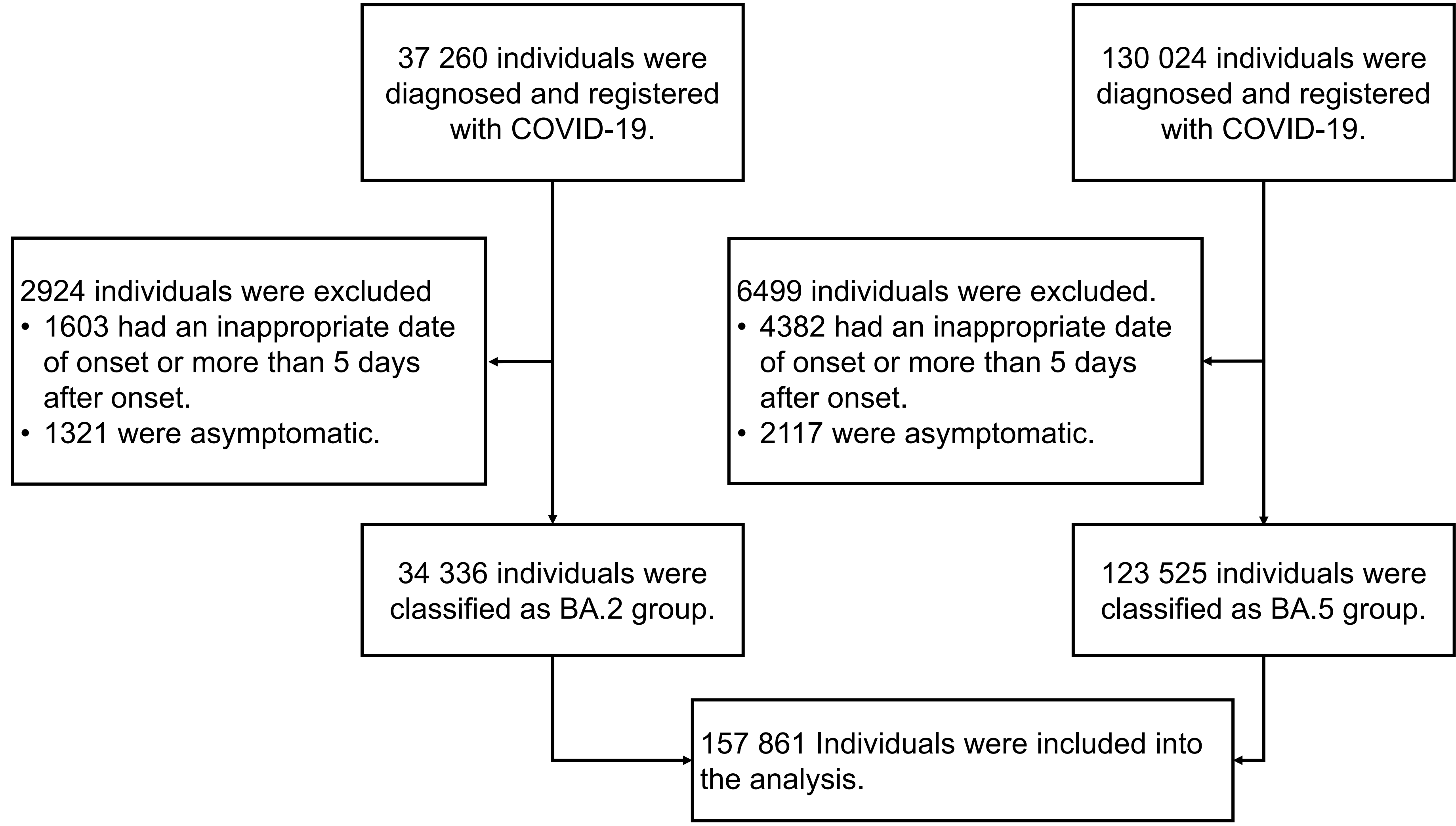
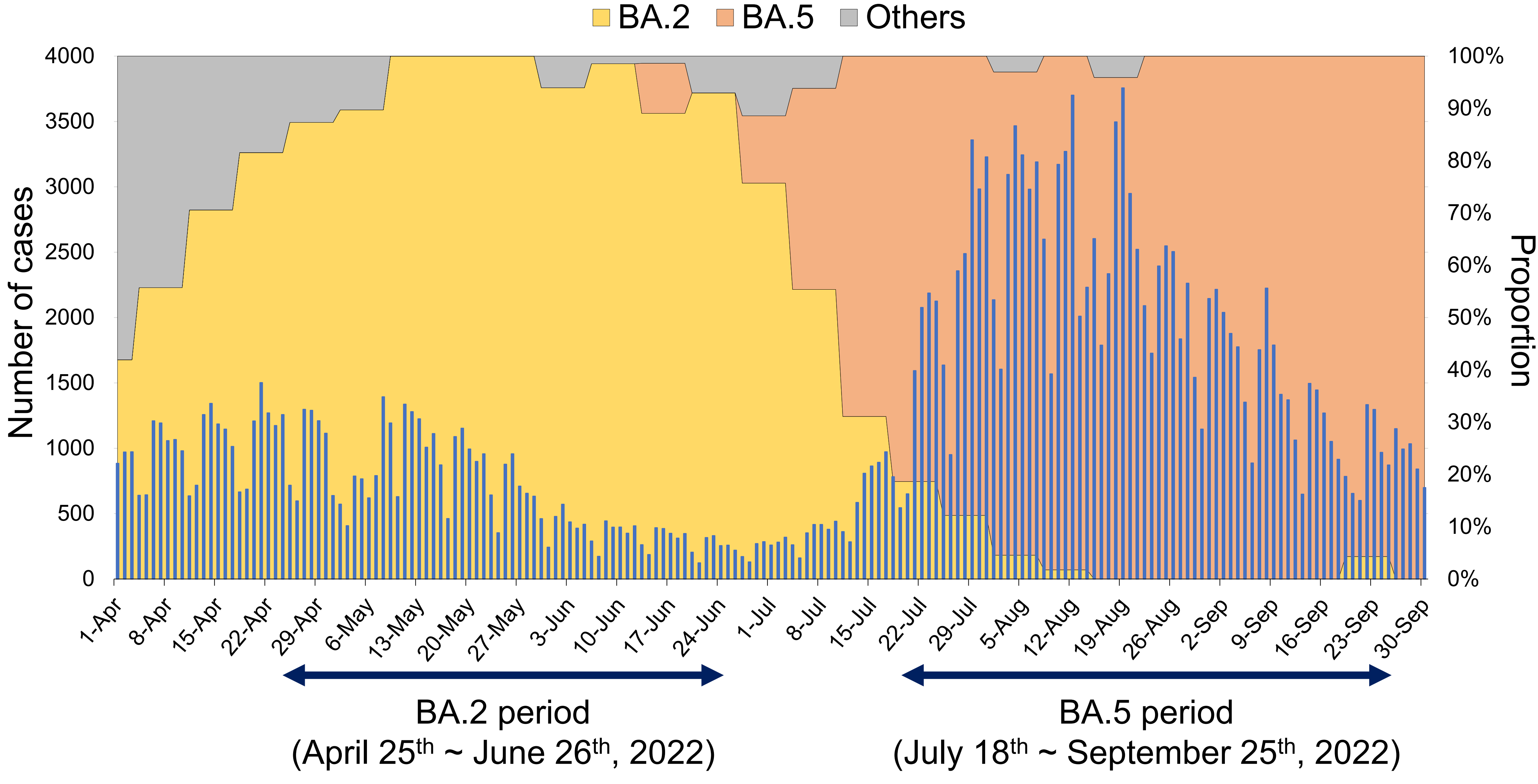
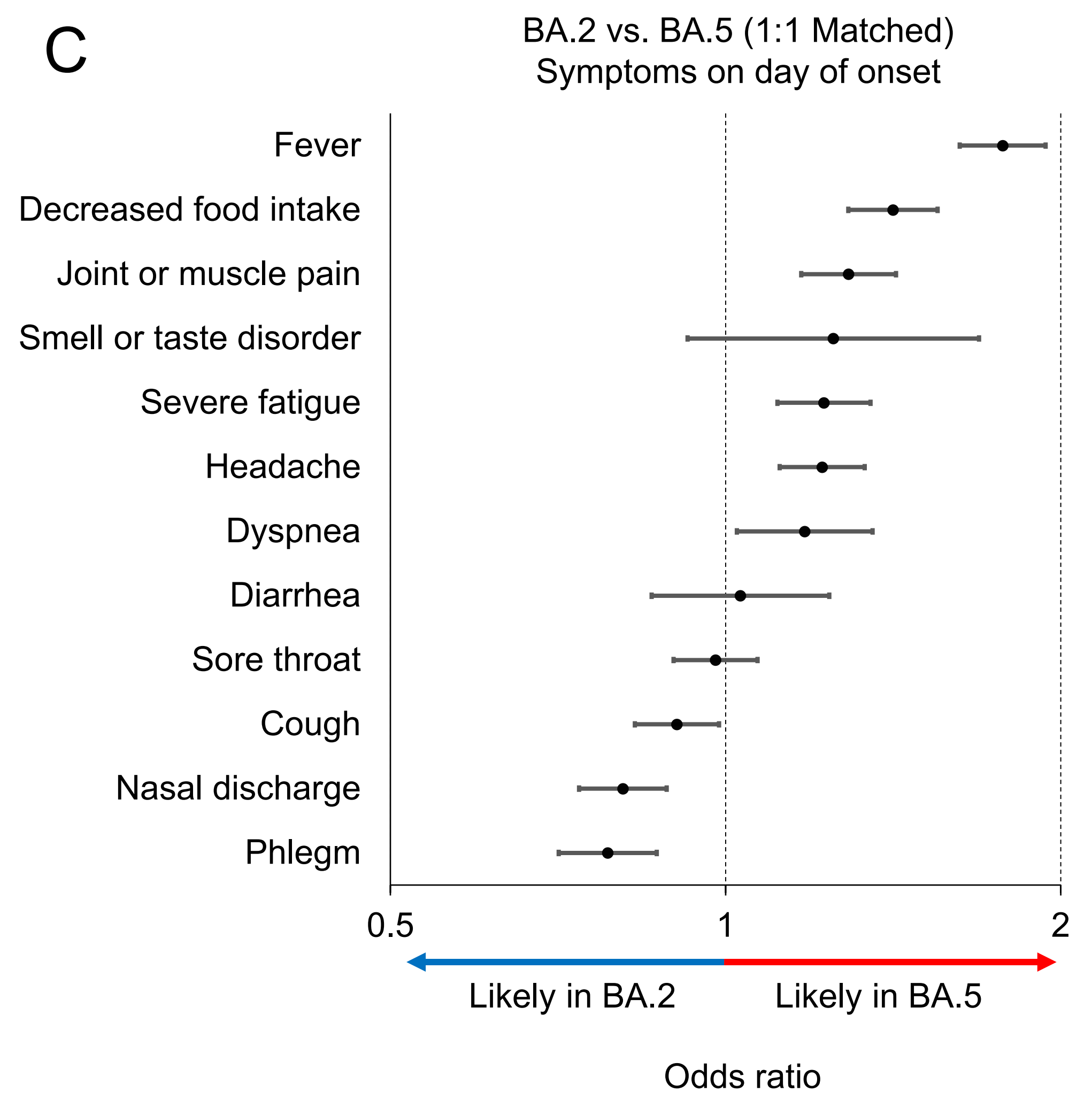
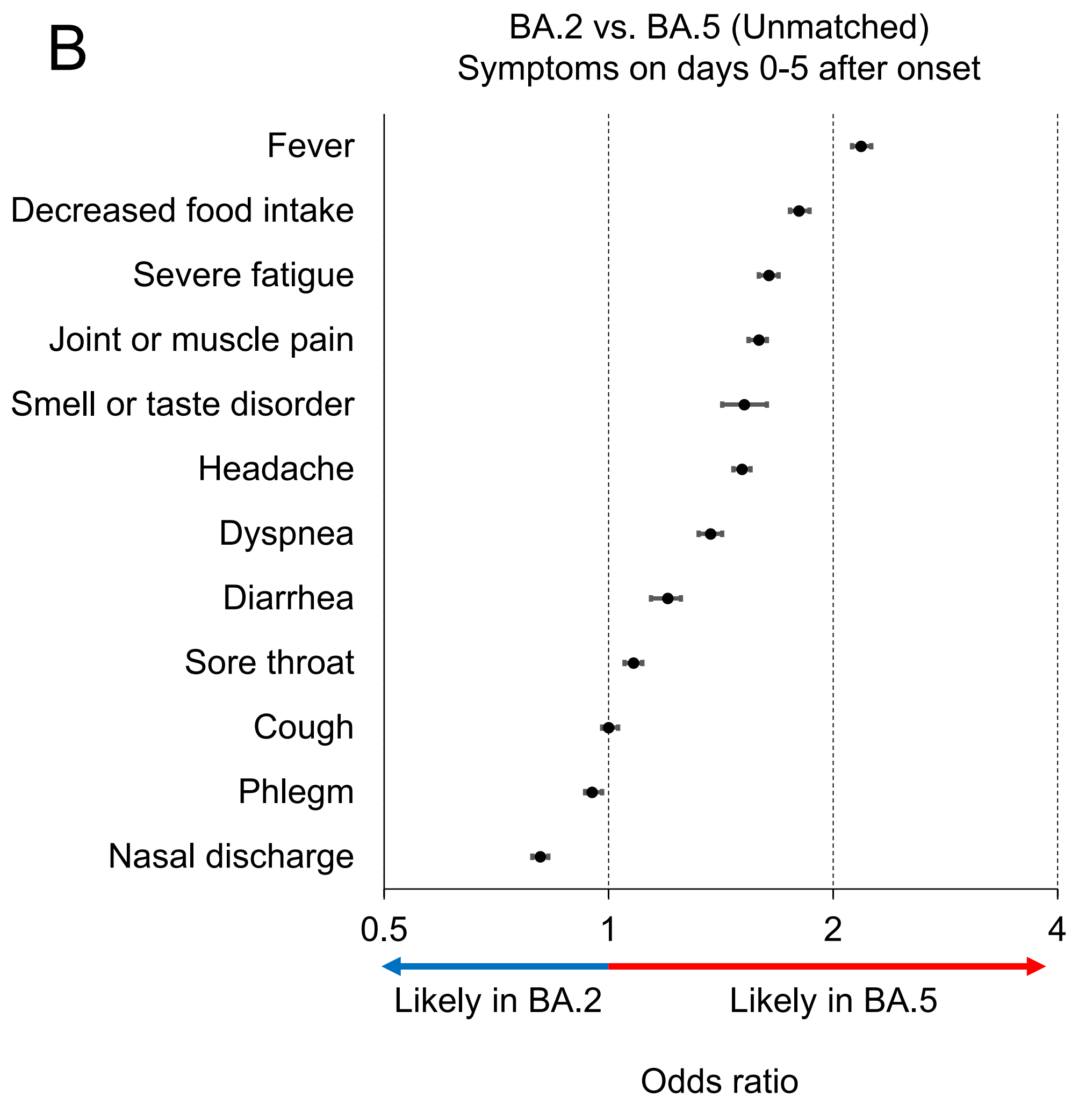
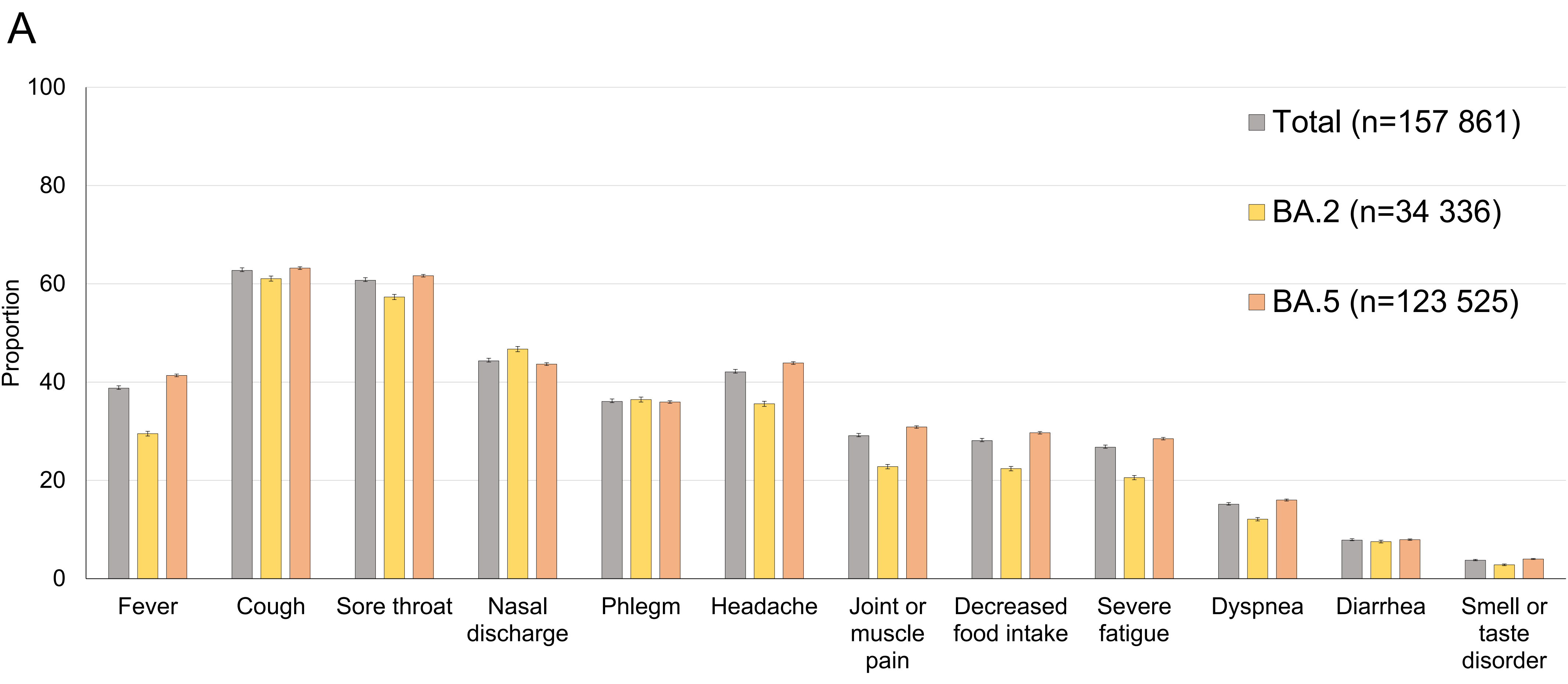


Figure 2



**Figure 3**

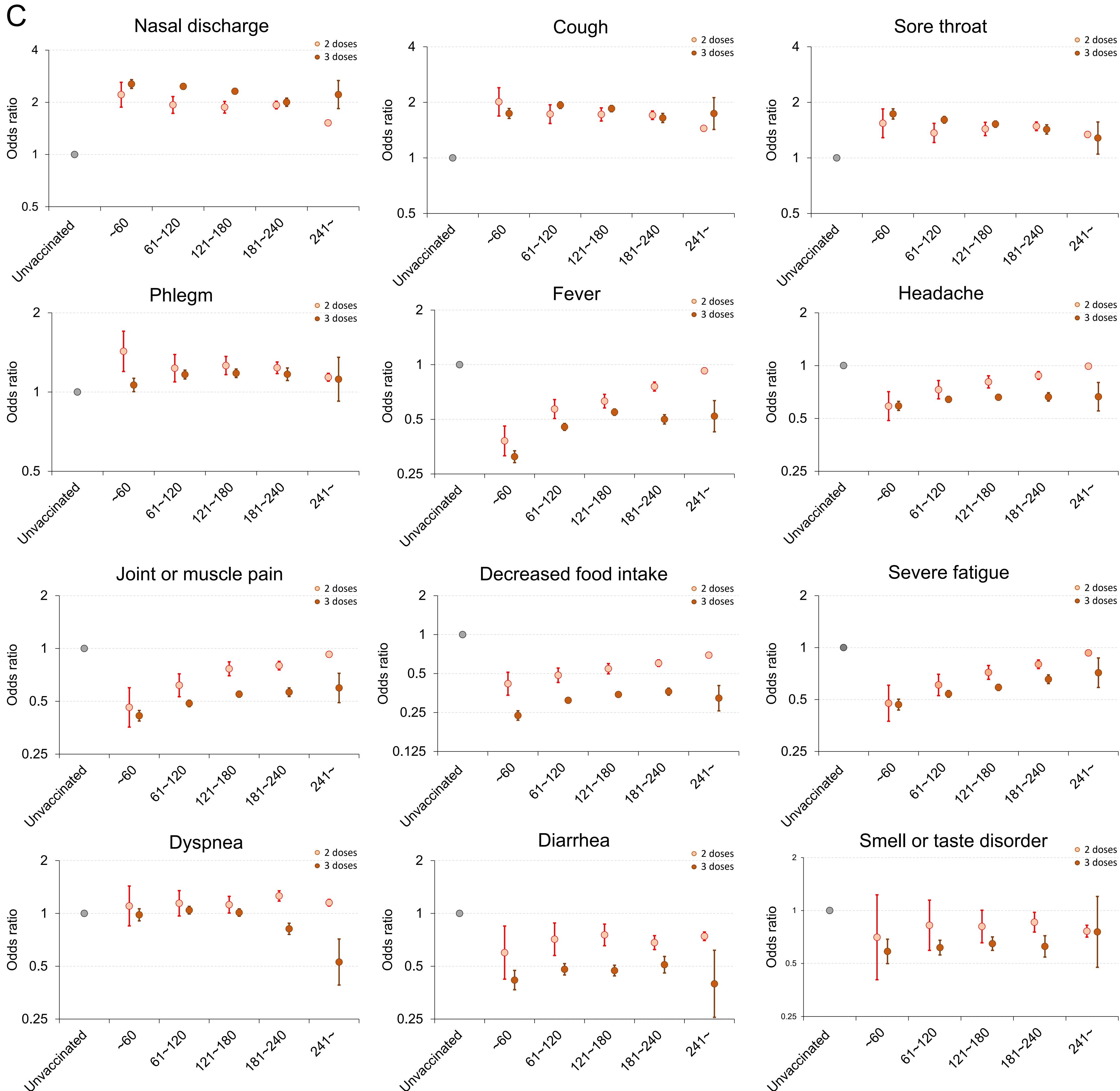
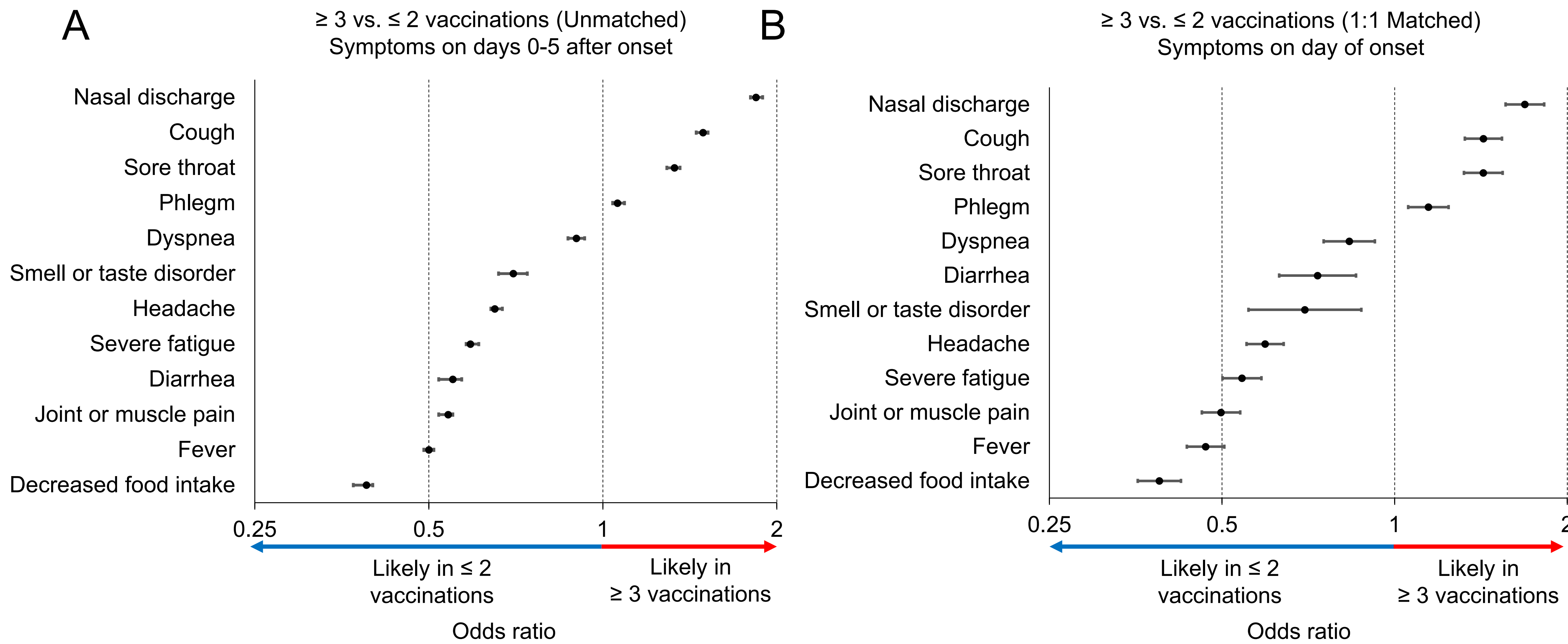
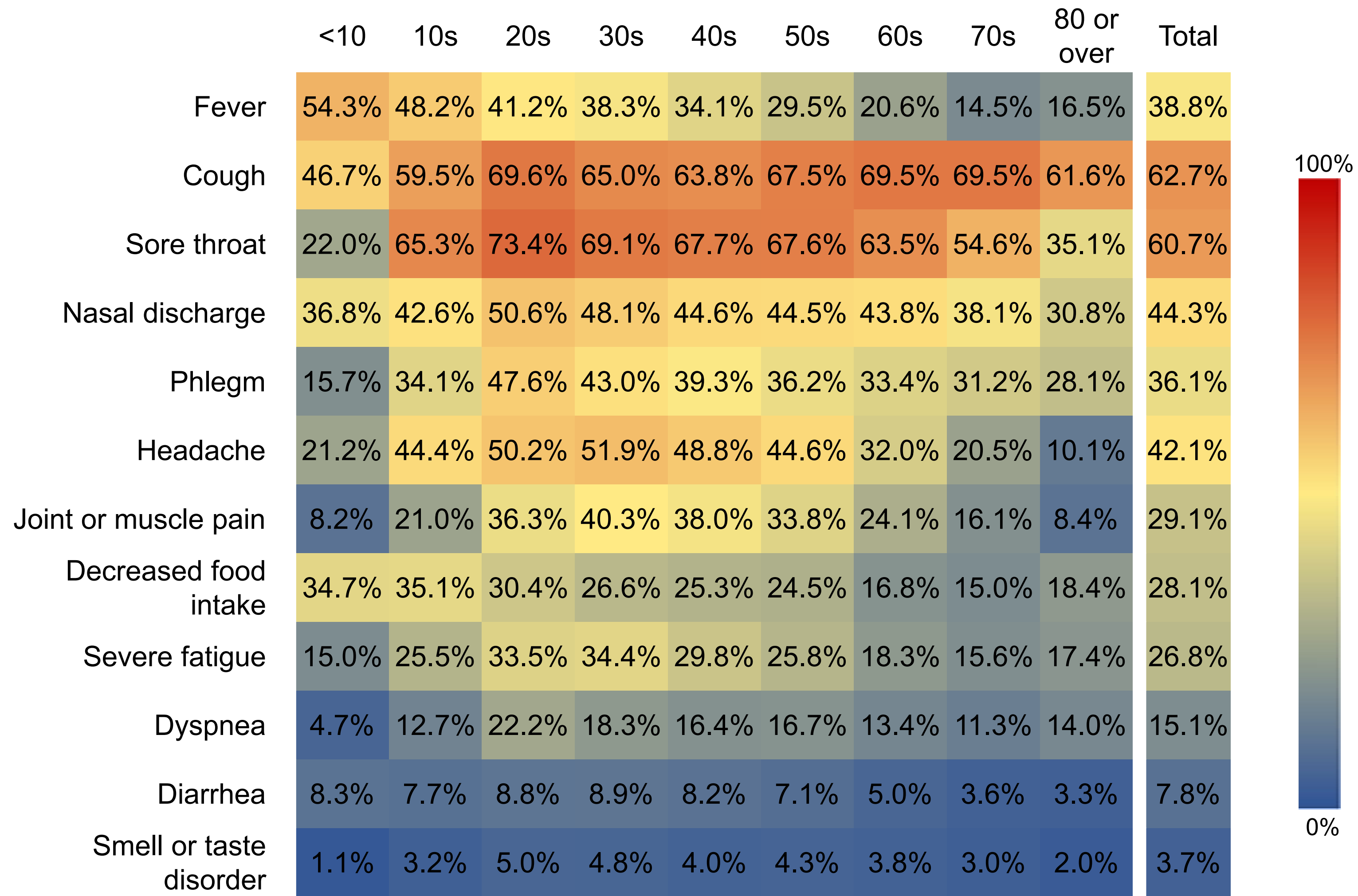


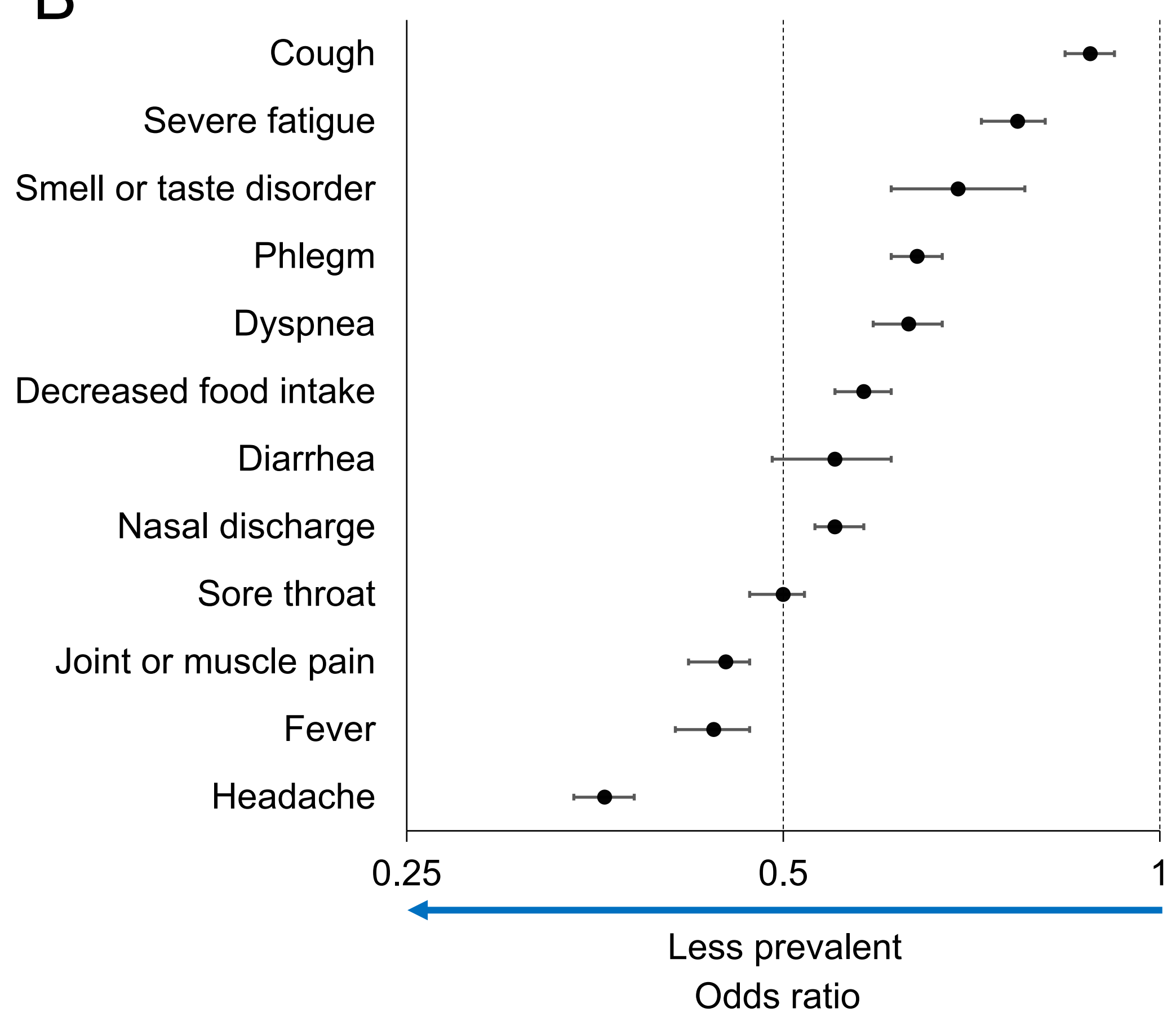


Figure 4

A



B



C

