1   **Original research**

2   **Associations of COVID-19 Symptoms with Omicron Subvariants BA.2 and BA.5, Host Status,**

3   **and Clinical Outcomes: A Registry-Based Observational Study in Sapporo, Japan**

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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 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 frequencies, variables associated with symptoms, and symptoms associated with progression to severe disease were analysed.

Results: For all omicron-infected individuals, cough was the most common symptom (62.7%), followed by sore throat (60.7%), nasal discharge (44.3%), and fever (38.8%). Omicron BA.5 infection was associated with a higher symptom burden than BA.2 in vaccinated and unvaccinated individuals. Omicron breakthrough-infected individuals with ≥ 3 vaccinations or previous infection were less likely to exhibit systemic symptoms, but more likely to exhibit upper respiratory symptoms. Infected elderly individuals had lower odds for all symptoms, but, when symptoms were manifest, systemic symptoms were associated with an increased risk, whereas upper respiratory symptoms with a decreased risk, of severe disease.

Conclusion: Host immunological status, omicron subvariant, and age were associated with a

53 spectrum of COVID-19 symptoms and outcomes. BA.5 produced a greater symptom burden than

54 BA.2. Vaccination and prior infection mitigated systemic symptoms and improved outcomes, but

55 increased upper respiratory tract symptom burden. Systemic, but not upper respiratory, symptoms in

56 the elderly heralded severe disease.

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58 **Keywords:** COVID-19, Omicron subvariant, vaccination, upper respiratory symptoms, older age.

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Introduction

The coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome 2 (SARS-CoV-2), has caused more than 657 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 may have 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 state 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

80   to automate the acquisition of self-entered personal information from individuals with COVID-19.

81   This unique system, in which individuals enter their current status via the internet, enables the

82   collection of timely data describing COVID-19 symptoms that can be linked to databases

83   representing individuals' backgrounds, vaccination and previous SARS-CoV-2 infection status, and

84   severity outcomes. Our objective was to update the characterization of COVID-19 clinical symptoms

85   during the omicron BA.2-BA.5 variant pandemic period and identify associations between clinical

86   symptoms, host factors, immune status, and clinical outcomes relevant to the patient and healthcare

87   communities.

88

89   **Methods**

90   **Study population and data sources**

91   This registry-based observational study was based on the Sapporo population. Data from

92   treatment decision sites (TDS) and registration centres for test-positive patients (RCPP) were utilized

93   for analyses (**Fig. S1**). The TDS is a system launched by the City of Sapporo to notify individuals

94   with a COVID-19 diagnosis of the need for hospitalization and clinical advice. Individuals eligible

95   for enrolment in the TDS were: 1) symptomatic individuals who visited a medical institution and

96   tested positive for SARS-CoV-2 (polymerase chain reaction or antigen test), and 2) individuals who

97   were not tested for SARS-CoV-2 but developed new symptoms after a household member tested

98   positive for SARS-CoV-2. Those diagnosed with COVID-19 were requested to immediately register

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99   clinical information with the TDS through a web device, including the onset of any newly developed

100   symptoms and the presence/absence of 12 preselected specific symptoms. The RCPP is a registration

101   system operated by the City of Sapporo for symptomatic individuals who cannot visit a healthcare

102   provider. The RCPP sends SARS-CoV-2 antigen test kits to symptomatic individuals at home upon

103   request. A self-test is conducted, and information identical to that for the TDS is entered into the

104   RCPP system by test-positive individuals. Data from both systems are integrated and stored at the

105   Sapporo City Public Health Center. Because both systems share identification information assigned

106   to individuals with COVID-19, case duplication is not possible. Data describing previous

107   SARS-CoV-2 infection and progression to severe disease are collected from the Health Center

108   Real-time Information-sharing System on COVID-19 operated by the Ministry of Health, Labor, and

109   Welfare, as well as data linked to patient information in the TDS and RCPP. Vaccination history,

110   including the timeline of vaccination, was accessed from the Vaccination Record System operated by

111   the Japan Government Digital Agency (**Fig. S1**).

112   Individuals were excluded from the study if they: (1) entered the date of onset

113   inappropriately, (2) were registered > 5 days after symptom onset, or (3) were asymptomatic.

114   Detailed inclusion and exclusion criteria and the treatment of missing values are described in

115   **Supplementary methods**.

116

117   **Data collected**

118   The following data were extracted from the TDS and RCPP: 1) date of first symptom onset;

119   2) dietary intake; 3) presence of 12 predefined symptoms (fever, cough, sore throat, nasal discharge,

120   sputum, headache, joint or muscle pain, severe fatigue, dyspnoea, diarrhoea, and taste or smell

121   disorder) at registration; and 4) demographic information (age, sex, height, weight, and underlying

122   disease). Outcomes defining severe disease, i.e., requiring oxygenation, mechanical ventilation, or

123   death, were collected as above.

124

Characterization of SARS-CoV-2 omicron subvariants

126   Whole genome analysis was performed at the Sapporo City Institute of Public Health to

127   identify SARS-CoV-2 variants prevalent in Sapporo. Randomly collected specimens with positive

128   SARS-CoV-2 test results were analysed for approximately 50–80 cases per week, and the proportions

129   of omicron subvariants were calculated. In this study, omicron subvariant epidemic periods were

130   defined as when the percentage of the most predominant subvariants exceeded 80%.

131

Statistical analysis

133   Continuous and categorical data were expressed as median (interquartile range [IQR]) and

134   proportions, respectively. A 95% confidence interval (CI) was calculated for symptom frequency,

135   odds ratio (OR), and hazard ratio. Multivariate logistic regression analyses were performed, using

136   days from symptom onset, age, sex, body mass index (BMI), underlying diseases, omicron

137   subvariants, vaccination status, and previous SARS-CoV-2 infection as explanatory variables, with

138   the development of each symptom as the outcome. To estimate symptom time courses, frequencies of

139   the 12 predefined symptoms were calculated from individuals aligned by days from the first

140   symptom onset and plotted on a day 0-5 scale. Estimates of the relative rates of symptom

141   accumulation were analysed using a Cox regression model. Regarding logistic regression analysis for

142   progression to severe disease, all symptoms were incorporated in addition to the factors included in

143   the above-mentioned multivariable symptoms analysis. All statistical analyses were performed using

144   JMP® Pro Version 16.2.0 (SAS Institute Inc., Cary, NC, USA).

145

146   **Results**

147   **Study population**

148   Data collected from the TDS and RCPP systems were analysed between April 25, 2022, and

149   September 25, 2022. The epidemic period for the omicron subvariant BA.2 spanned April 25 to June

150   26, and that for BA.5 spanned July 18 to September 25 (**Fig. 1**). After individuals who met the

151   exclusion criteria were excluded ($< 5.6\%$), a total of 157,861 symptomatic COVID-19 cases (34,336

152   and 123,525 for the BA.2 and BA.5 groups, respectively) were analysed (**Fig. 1**).

153   The median age of all individuals included in the study was 33 years (range 0–104) (**Table**

154   **1**). The most prevalent age group was the 30-year-old group, and those aged $\geq$ 65 years accounted for

155   9·3% of the total. Forty-eight percent were men, and the median BMI was 21·1 (IQR 18·6–24·0). The

156   proportion of patients with an underlying disease was highest for hypertension (5·6%), followed by

157   chronic respiratory (3·6%) and cardiovascular diseases (1·0%). SARS-CoV-2 vaccination status was:

158   38·0% unvaccinated, 0·7% one dose, 24·3% two doses, 33·8% three doses, and 3·2% four doses.

159   Additionally, 3·7% had a history of previous SARS-CoV-2 infection. Coughing was the most

160   prevalent symptom (62·7%), followed by sore throat (60·7%), nasal discharge (44·3%), headache

161   (42·1%), and fever (38·8%) (**Fig. 2A, Table S1**). A total of 142 individuals developed severe disease,

162   and four died within 30 days after onset. The risk of progression to severe disease was 0·02% for

163   individuals younger than 65 years of age and 1·01% for those at this age or over (**Table 1).**

164

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

166   The clinical features of symptomatic individuals with BA.2 vs. BA.5 infections were also

167   compared (**Table 1**). The BA.2 group had a lower median age, BMI, history of cerebrovascular

168   disease, and a higher proportion of unvaccinated and ≤ 2 dose-vaccinated individuals. The BA.5

169   group exhibited higher proportions of other comorbidities, e.g., malignancy, immunodeficiency,

170   cardiovascular disease, hypertension, and diabetes, previous SARS-CoV-2 infection, and contained

171   all individuals with a fourth vaccine dose.

172   All 12 predefined symptoms, except for nasal discharge and phlegm, were more prevalent in

173   the BA.5 vs. BA.2 populations (**Fig. 2B, Table S1**), findings that were replicated in the unvaccinated

174   BA.5 vs. BA.2 subgroups (**Fig. S2, Table S2**). Multivariate analyses of the BA.5 and BA.2

175   population data identified associations that predicted an increased risk, for BA.5-infected populations,

176   of fever (adjusted OR [95% CI]: 2·18 [2·12–2·25]), decreased food intake (1·80 [1·75–1·86]), severe

177   fatigue (1·64 [1·59–1·69]), joint or muscle pain, smell or taste disorders, headache, dyspnoea,

178   diarrhoea, and sore throat, juxtaposed to a decreased risk of nasal discharge and phlegm (**Fig. 2C,**

179   **Table S3**). Logistic regression analysis demonstrated comparable odds for progression to severe

180   disease between the two subvariants (**Table S4**).

181

182   **Associations between vaccine status and COVID-19 symptoms**

183   Individuals were divided into two subgroups to determine the effects of the modification of

184   host immune status by vaccination on the prevalence of COVID-19 symptoms. The boundary

185   between the two subgroups was set at three vaccinations, a number clinically effective for omicron

186   variants[16-18]. The group with ≥ 3 vaccinations exhibited breakthrough infections, and a lower

187   frequency of fever, decreased food intake, severe fatigue, joint or muscle pain, and diarrhoea than the

188   group with ≤ 2 vaccinations (**Fig. 3A, Table S1**). In contrast, cough, sore throat, nasal discharge, and

189   phlegm were more common with breakthrough infections in the ≥ 3 vaccination group.

190   Logistic regression analysis demonstrated that individuals with breakthrough infections and

191   ≥ 3 vaccinations had a decreased risk of systemic symptoms, including fever (0·50 [0·49–0·51]),

192   decreased food intake (0·39 [0·37–0·40]), severe fatigue (0·59 [0·58–0·61]), joint or muscle pain,

193   headache, diarrhoea, smell or taste disorders, and dyspnoea, as compared to individuals with ≤ 2

194 vaccinations (**Fig. 3B, Table S3**). In contrast, the likelihood of upper airway symptoms, including

195 nasal discharge (1·84 [1·80–1·89]), cough (1·49 [1·45–1·52]), sore throat (1·33 [1·29–1·36]), and

196 phlegm, were higher in individuals who received ≥ 3 vaccinations than those who received ≤ 2

197 vaccinations. Similar analyses performed on the ≥ 3 vaccine dose group, incorporating the time

198 elapsed since the last vaccination date as a variable, revealed that longer periods from the last

199 vaccination date were associated with: 1) an increased risk of fever, headache, joint or muscle pain,

200 decreased food intake, and severe fatigue; and 2) a decreased risk of coughing, nasal discharge, sore

201 throat, and dyspnoea (**Table S5**).

202   The estimated temporal course of breakthrough omicron symptoms differed with

203 vaccination status for upper respiratory but not systemic symptoms (**Fig. 3C, S3, Table S6**). Cox

204 regression analyses, using the presence of symptoms as the occurrence of an event, revealed that the

205 appearance of coughing, sore throat, nasal discharge, and phlegm, but not systemic symptoms, were

206 significantly accelerated in the ≥ 3 vs. ≤ 2 vaccination groups (**Table S7**).

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

208 SARS-CoV-2 infection. The individuals with previous SARS-CoV-2 infection exhibited associations

209 similar to vaccination status, including a higher likelihood of upper respiratory symptoms and a

210 lower likelihood of systemic symptoms (**Fig. S4, Table S3, S6, S7**).

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

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213   The frequency of each symptom by age group was calculated (**Fig. 4A, Table S8**). Fever

214   and decreased food intake were most frequent in individuals under 10 years of age and decreased

215   with age. Cough frequency exhibited bimodal peaks in the 20s and 70s age groups. Other symptoms

216   were most frequent in individuals in their 20s and 30s, with frequencies decreasing with increasing

217   age throughout the 70s. Consistent with these data, multivariate analysis identified advanced age ($\geq$

218   65 years) as an independent factor associated with a lower likelihood of development of any

219   symptom than younger ages (**Fig. 4B, Table S9**).

220   Multivariate analyses identified specific COVID-19 symptoms associated with adverse

221   clinical outcomes in elderly individuals. Dyspnoea, fever, decreased food intake, and severe fatigue

222   were associated with an increased risk of severe disease (3·01 [1·84–4·91], 2·91 [1·89–4·51], 2·41

223   [1·55–3·74], and 1·93 [1·22–3·07], respectively). The combination of these four symptoms was

224   associated with an increased risk of severe disease (adjusted OR [95% CI] for the number of

225   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],

226   and 40·72 [14·72–112·68], respectively) (**Fig. 4C, Table S10**). In contrast, sore throat and nasal

227   discharge were associated with a decreased risk of severe disease (0·39 [0·24–0·63] and 0·48

228   [0·28–0·82], respectively). The combination of these two upper airway symptoms was associated

229   with a decreased risk of severe disease (adjusted OR [95% CI] with no upper respiratory symptom as

230   a reference: 0·20 [0·09–0·46]) (**Fig. 4C, Table S10**).

231

Discussion

232

233   The registry-based self-entry COVID-19 symptom study was conducted over an interval

234   when two omicron subvariants were prevalent. Collectively, individuals with omicron infections

235   exhibited more commonly upper respiratory symptoms, e.g., cough, sore throat, and nasal discharge,

236   than systemic symptoms (**Fig. 2A**). The clinical features of individuals with omicron breakthrough

237   infections differed from those in the early Wuhan strain-dominated pandemic period, which was

238   characterized by a higher frequency of fever, cough, dyspnoea, and fatigue and a lower frequency of

239   upper airway symptoms[19-21]. The pattern of a higher incidence of upper respiratory symptoms and a

240   lower incidence of systemic symptoms was replicated in unvaccinated individuals with omicron

241   infections (**Fig. S2**), suggesting that the viral strain is a variable causing difference in clinical

242   manifestations between individuals with the Wuhan strain and omicron breakthrough infection.

243   The omicron subvariants themselves also differed concerning symptom frequencies.

244   Although emerging later in the pandemic, BA.5 was associated with a higher prevalence of

245   symptoms than BA.2 (**Fig. 2B**). The increased BA.5 symptom prevalence may reflect greater escape

246   from humoral immunity with increased upper airway viral loads as compared to BA.2[22,23]. Notably,

247   the risk of progression to severe disease did not significantly differ between BA.2 vs. BA.5 (**Table

248   S4**).

249   Significant associations between vaccination status or previous COVID-19 infection and

250   specific symptoms following omicron breakthrough infection were also identified. For example, a

251   reduced risk of systemic symptoms, including fever, fatigue, and headache, was observed in

252   individuals with omicron infections and ≥ 3 vaccinations or a history of previous infection. In

253   contrast, a strong correlation was observed between a history of ≥ 3 vaccinations or previous

254   infection and increased upper airway symptom prevalence (**Fig. 3B, S4**). These contrasting

255   post-vaccination symptom-based observations may reflect: 1) vaccine-mediated reductions in viral

256   load, reduced cytokine release into the systemic circulation, and, hence, reduced systemic

257   symptoms[24-26], and 2) vaccine-mediated amplification of local host antiviral responses to upper

258   respiratory tract SARS-CoV-2 infection, the consequences being increased symptom prevalence but

259   shorter symptom duration (**Fig. 3**)[27,28]. The increased prevalence of post-breakthrough upper

260   respiratory symptoms after vaccinations likely accounts for the unexplained increase in total

261   symptom burden, but reduced systemic symptoms (fever and chills), recently reported in a cohort of

262   vaccinated United States Essential and Frontline workers after SARS-CoV-2 breakthrough

263   infections[24].

264   We observed a decreasing frequency of COVID-19 symptoms with age (**Fig. 4B**). These

265   findings are consistent with an earlier study showing that typical COVID-19 symptoms were less

266   commonly reported in adult groups with advanced age[29,30]. Importantly, if systemic symptoms were

267   present in the elderly (≥ 65-year-old group), strong associations with severe disease were observed

268   (**Fig. 4C**), consistent with reports on pre-vaccinated United States veterans[3]. Unexpectedly, our data

269   suggest that upper respiratory tract symptoms are associated with a reduced risk of severe disease in

270   the elderly.

271   Our study had several limitations, starting with symptom data being entered directly by

272   individuals without the assistance of healthcare providers. This is a significant limitation as

273   self-reported symptoms are inherently subjective, leading to increased variability. However, these

274   are the data frequently provided in clinical encounters. Second, since symptom data were analysed

275   for 12 predefined questions, COVID-19 symptoms other than the predefined items, including

276   neurological and psychological symptoms, were not evaluated. Third, the reporting of clinical

277   symptom intensity was not collected; thus, quantitative assessments of symptom intensity were not

278   performed. Fourth, asymptomatic individuals were not enrolled in the TDS or RCPP and were

279   excluded from the study. Thus, it is unknown how vaccination and previous infection may have

280   affected the presence of symptoms in the overall population. Fifth, our study was a retrospective

281   observational study and did not provide prospective information describing the duration of

282   COVID-19 symptoms. However, our system, entering symptoms singly at the time of diagnosis

283   with data describing the onset of symptoms, juxtaposed to the large sample size, allowed us to

284   estimate the dynamics of COVID-19 symptoms. Finally, the small number of individuals with

285   severe disease may have resulted in a statistically underpowered detection of factors potentially

286   associated with severe COVID-19 outcomes. Nevertheless, the significance of the specific

287   symptoms identified as independent factors associated with severe outcomes was statistically

288   robust.

289   In conclusion, our symptom-based description of the clinical manifestations of COVID-19

290   during the BA.2- and BA.5-dominated COVID-19 pandemic periods provides practical insights into

291   clinical features of the current COVID-19 pandemic. First, BA.5 infections were associated with

292   more prevalent symptoms than BA.2 infections in both vaccinated and unvaccinated individuals.

293   These data suggest that BA.5 emerged as a more troublesome variant than the BA.2 antecedent.

294   Second, an increased prevalence of local upper respiratory tract symptoms, but reduced systemic

295   symptom prevalence, was observed post-vaccination (or previous infection) following omicron

296   breakthrough infections. Thus, it might be appropriate to counsel individuals contemplating

297   vaccination that post-vaccination breakthrough COVID-19 infections may be associated with an

298   increased likelihood of upper airway symptoms, with offsetting benefits being a shorter symptom

299   interval and a reduced risk of severe outcomes. Third, individuals with advanced age experienced, on

300   average, fewer omicron-induced symptoms, but when present, systemic but not upper respiratory

301   symptoms heralded worsened outcomes. These observations may serve as a practical guide to utilize

302   COVID-19 symptoms to predict clinical outcomes for elderly patients with omicron infections.

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308   the Sapporo City Institute of Public Health for providing genomic information on Sapporo's

309   prevalent SARS-CoV-2 mutant strains.

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311   **Ethical Approval Statement**

312   The research protocol was approved by the Ethics Committee of Hokkaido University Hospital

313   (Research No. 022-0225). Analysis was performed using database in Sapporo city, with no additional

314   risks to the patients. Therefore, the requirement for informed consent from individual participants

315   was waived by the ethics committee. All methods were performed in accordance with the relevant

316   guidelines and regulations of the Ethics Committee of Hokkaido University Hospital. All patient data

317   were anonymized.

318

319   **Author contributions**

320   This study was designed by SN, NK, and KO. The underlying data were verified by SN, NK, MI,

321   and YI, and data analyses were performed by SN, YI, and IY. SN wrote the first draft of the

322   manuscript, which was revised by KO, KK, MS, RCB, and KS. All authors interpreted the data,

323   provided a critical review and revision of the text, and approved the final version of the manuscript.

324

325   **Declaration of interests**

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328   Pharmaceutical Co., and AstraZeneca, outside the submitted work. The other authors declare that

329   they have no conflict of interest.

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418   **Figure legends**

419   **Figure 1. Schematic representations of the study period and eligibility determination.** The bars

420   indicate the number of persons with new infections per day in Sapporo. The stacked area graph

421   shows the detection rate of mutant strains in Sapporo. The BA.2 period was defined as when the

422   detection rate of omicron subvariant BA.2 exceeded 80%, and the BA.5 period was defined as when

423   the detection rate of BA.5 exceeded 80% and until the end of notifiable disease surveillance in

424   Sapporo.

425

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

427   **A.** Frequency of COVID-19 symptoms in the total study population. **B.** Frequency of COVID-19

428   symptoms in individuals with BA.2 and BA.5 infections. Error bars indicate 95% confidence

429   intervals (CIs). **C.** Associations between omicron subvariants and symptom likelihood. Multivariate

430   analysis used each symptom as an outcome and mutant strain, age, body mass index, underlying

431   disease, vaccination history, and history of spontaneous infection as explanatory variables. The type

432   of omicron subvariant (BA.5 or not) and the adjusted odds ratio (OR) for each symptom are arranged

433   from highest to lowest. Points indicate ORs, and bars indicate 95% CIs. The detailed results of the

434   multivariate analysis are presented in **Table S3**.

435

436   **Figure 3. Associations between vaccine status and COVID-19 symptoms.**

23

437   **A.** Symptom frequency is shown in two groups divided by vaccination status. **B.** Associations

438   between vaccination and symptom likelihood. Multivariate analysis used each symptom as an

439   outcome and mutant strain, age, body mass index, underlying disease, vaccination history, and

440   history of spontaneous infection as explanatory variables. The detailed results of the multivariate

441   analysis are presented in **Table S3**. Three or more vaccinations and the adjusted odds ratio (OR) for

442   each symptom are arranged from highest to lowest. Points indicate ORs, and bars indicate 95%

443   confidence intervals (CIs). **C.** Symptom frequency by day since symptom onset in the two groups

444   divided by vaccination status. Error bars indicate 95% CIs.

445

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

447   **A.** Frequency of COVID-19 symptoms according to age. The shade colour of the cells is linked to

448   the high and low percentage values. **B.** Associations between age and symptom likelihood.

449   Multivariate analysis used each symptom as an outcome and mutant strain, age (elderly or

450   non-elderly), body mass index, underlying disease, vaccination history, and history of spontaneous

451   infection as explanatory variables. Elderly individuals (age $\geq$ 65 years) and the adjusted odds ratio

452   (OR) for each symptom are arranged from highest to lowest. **C.** OR for COVID-19 symptoms and

453   progression to severe disease. Multivariate analysis was performed using progression to severe

454   disease as an outcome and mutant strain, age, body mass index, underlying disease, vaccination

455   history, history of previous infection, and all symptoms as explanatory variables. Symptoms are

456   sorted in descending order of OR for progression to severe disease. Points indicate ORs, and bars

457   indicate 95% confidence intervals. The detailed results of the multivariate analysis are presented in

458   **Table S4**.

459

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

	Total (N=157,861)	BA.2 (n=34,336)	BA.5 (n=123,525)
Median age (range)-yr	33 (0-104)	28 (0-102)	34 (0-104)
Age * – no. (%)			
< 10	23,219 (14·7)	6,427 (18·8)	16,792 (13·6)
10s	21,165 (13·4)	6,012 (17·6)	15,153 (12·3)
20s	26,259 (16·7)	5,667 (16·6)	20,592 (16·7)
30s	27,665 (17·6)	6,093 (17·8)	21,572 (17·5)
40s	26,536 (16·8)	5,465 (16·)	21,071 (17·1)
50s	16,629 (10·6)	2,434 (7·1)	14,195 (11·5)
60s	8,881 (5·6)	1,156 (3·4)	7,725 (6·3)
70s	4,839 (3·1)	647 (1·9)	4,192 (3·4)
≥ 80	2,359 (1·5)	310 (0·9)	2,049 (1·7)
Elderly (Age ≥ 65) – no. (%)	10,874 (9·3)	1,441 (9·6)	9,433 (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)	21·1 (18·6-24·0)	20·7 (18·1-23·5)	21·2 (18·7-24·1)
Obesity (BMI ≥ 30) – no. (%)	6,729 (4·3)	1,241 (3·6)	5,488 (4·4)
Comorbidities – no. (%)			
Malignancy	1,284 (0·8)	188 (0·5)	1,096 (0·9)
Immunocompromised	291 (0·2)	44 (0·1)	247 (0·2)
Chronic respiratory diseases	5,652 (3·6)	1,186 (3·5)	4,466 (3·6)
Chronic kidney diseases	88 (0·1)	15 (0·1)	73 (0·0)
Cardiovascular diseases	1,620 (1·0)	229 (0·7)	1,391 (1·1)
Cerebrovascular diseases	102 (0·1)	22 (0·1)	80 (0·1)
Hypertension	8,781 (5·6)	1,270 (3·7)	7,511 (6·1)
Diabetes	3,740 (2·4)	550 (1·6)	3,190 (2·6)
SARS-CoV-2 vaccination – no. (%)			
Unvaccinated	60,033 (38·0)	15,339 (44·7)	44,694 (36·2)
One dose	1,052 (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)	7,424 (21·6)	45,965 (37·2)
Four doses	5,083 (3·2)	0 (0·0)	5,083 (4·1)
Previous SARS-CoV-2 infection – no. (%)	5,767 (3·7)	732 (2·1)	5,035 (4·1)
Progression to severe disease – no. (%)	142 (0·1)	19 (0·1)	123 (0·1)
Among the elderly (Age ≥ 65 years)	110 (1·01)	12 (0·83)	98 (1·04)

Among individuals aged < 65 years	31 (0·02)	7 (0·02)	24 (0·02)
Death within 30 days – no.	4	2	2

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

462   BMI, body mass index; IQR, interquartile range; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

BA.2 ☐ BA.5 ☐ Others
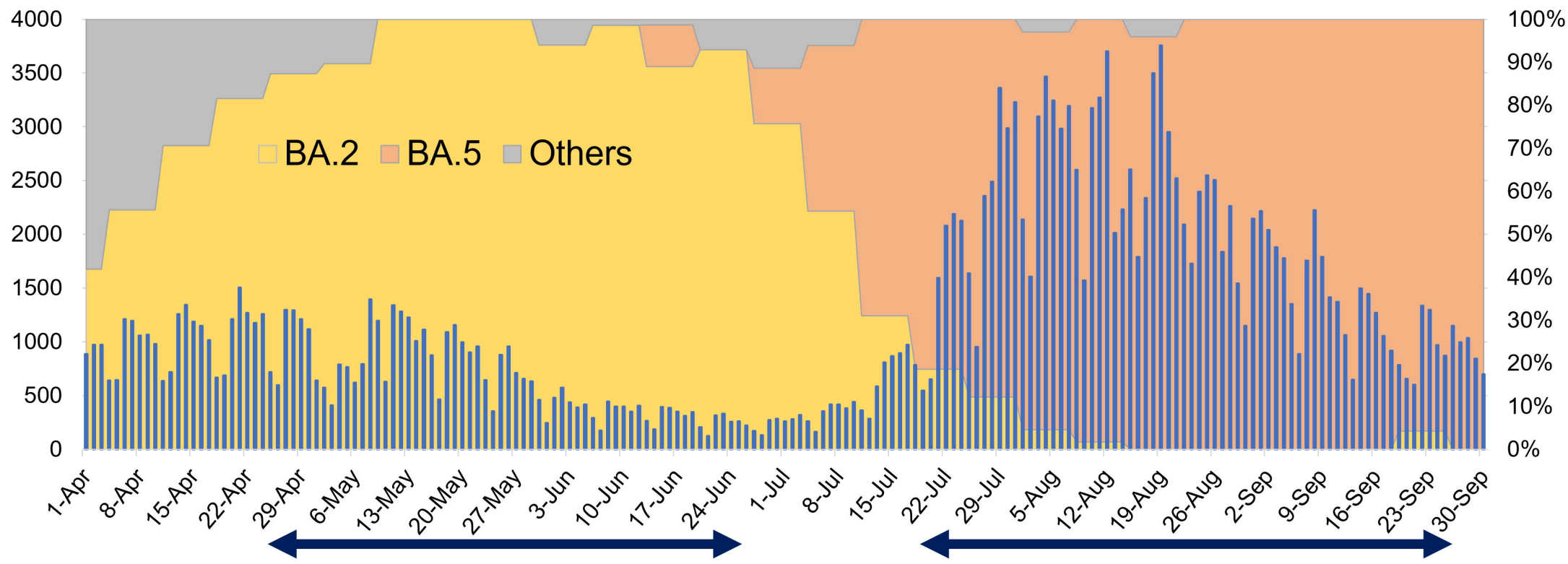
BA.2 period
(April 25th ~ June 26th, 2022)

BA.5 period
(July 18th ~ September 25th, 2022)

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

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

2,924 individuals were excluded
• 1,603 had an inappropriate date
  of onset or more than 5 days
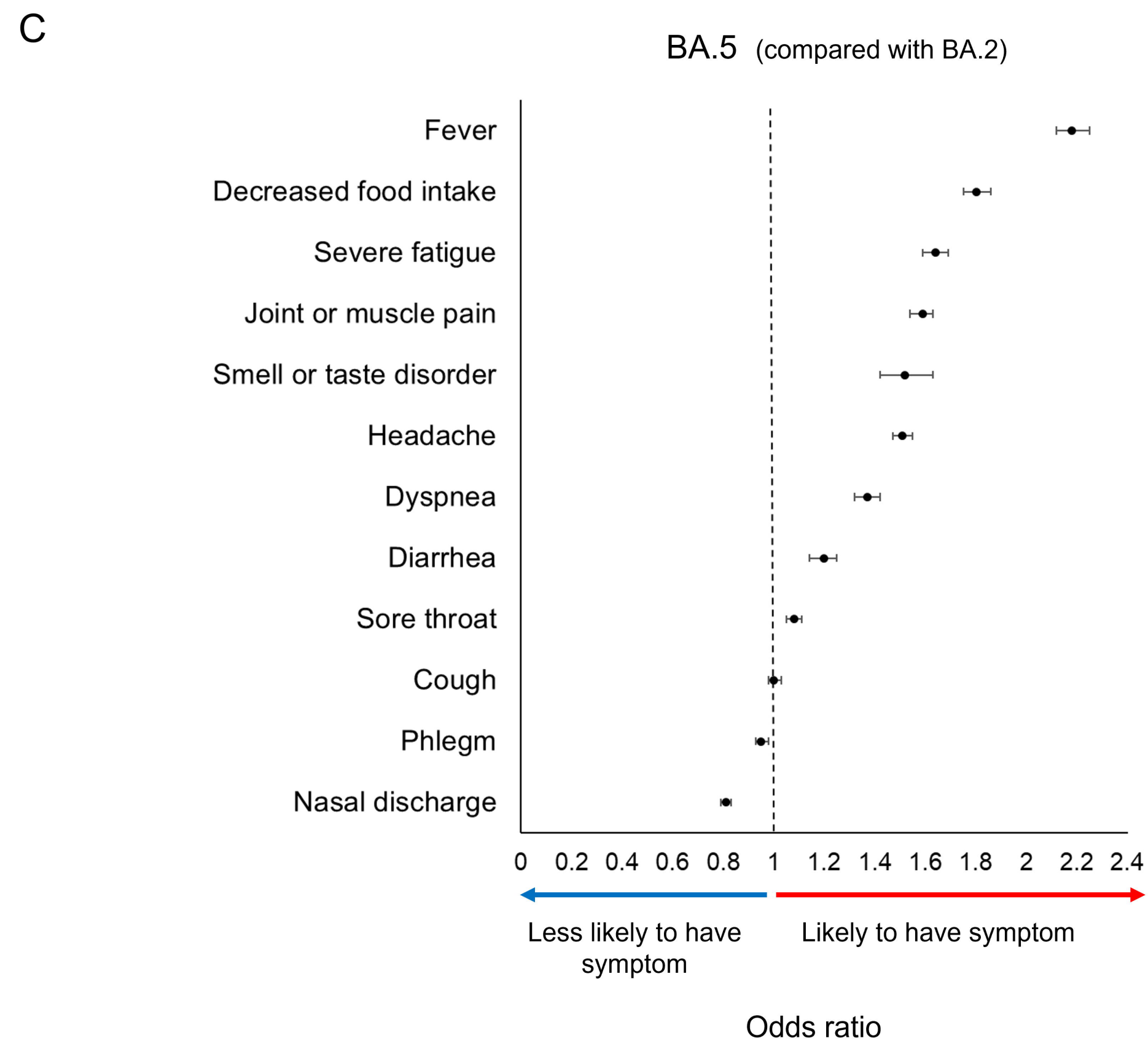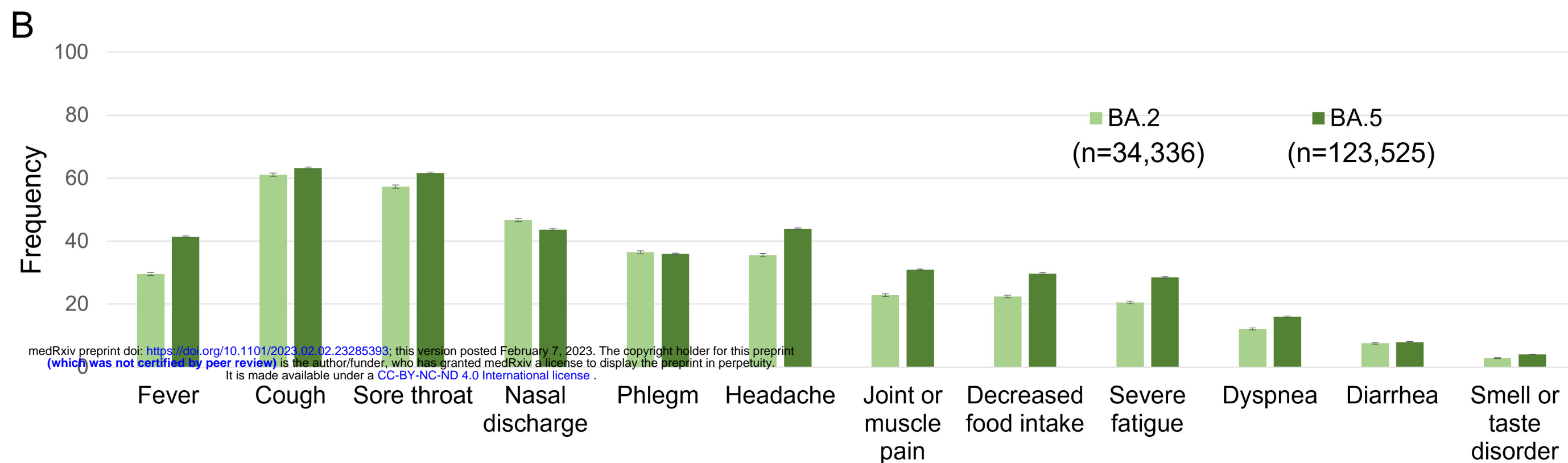 after onset.
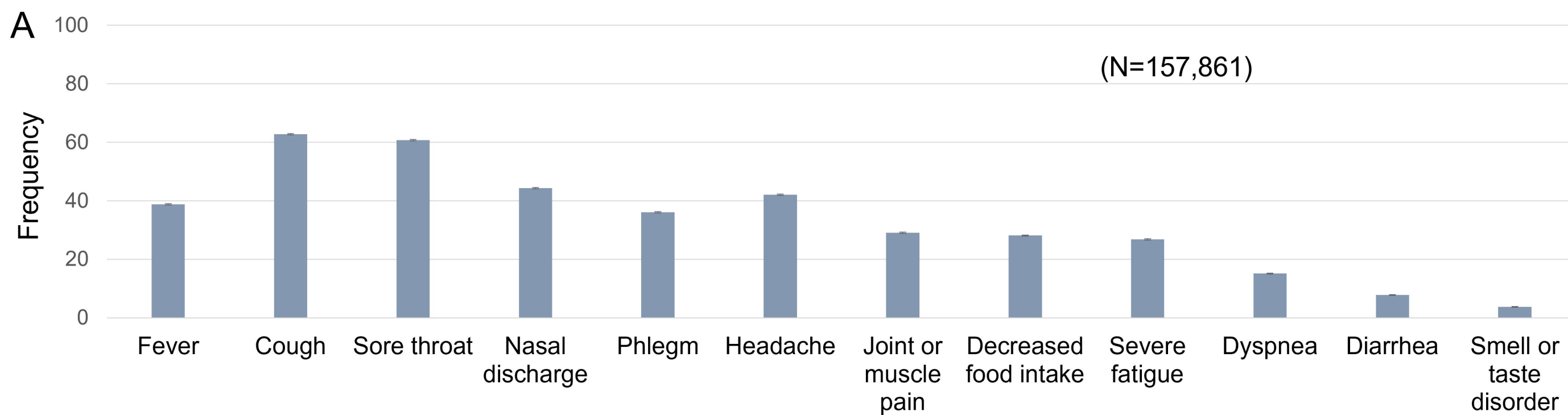• 1,321 were asymptomatic.

6,499 individuals were excluded.
• 4,382 had an inappropriate date
  of onset or more than 5 days
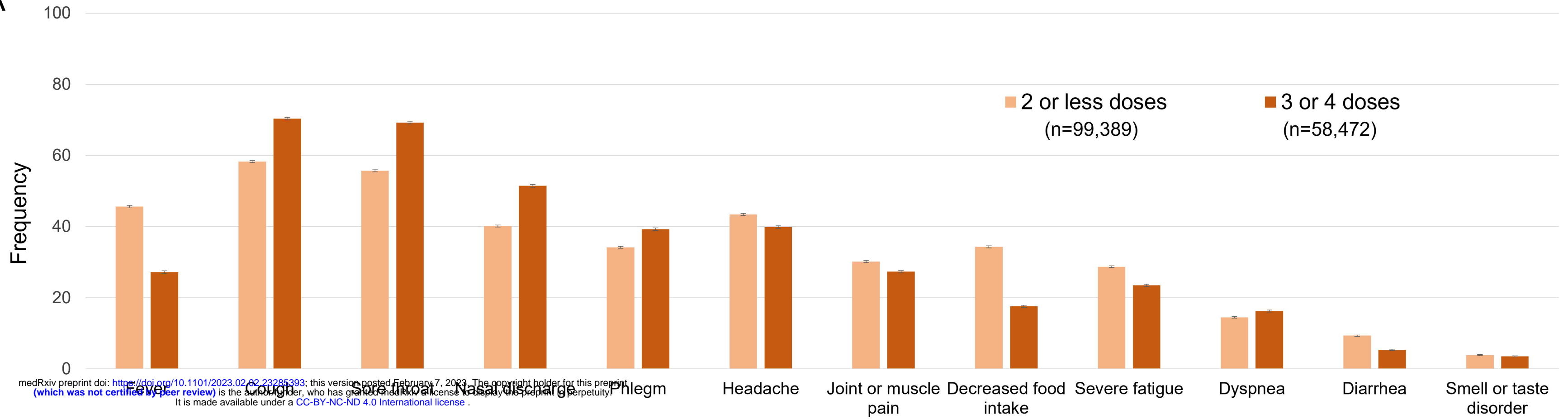 after onset.
• 2,117 were asymptomatic.

34,336 individuals were
classified as BA.2 group.

123,525 individuals were
classified as BA.5 group.

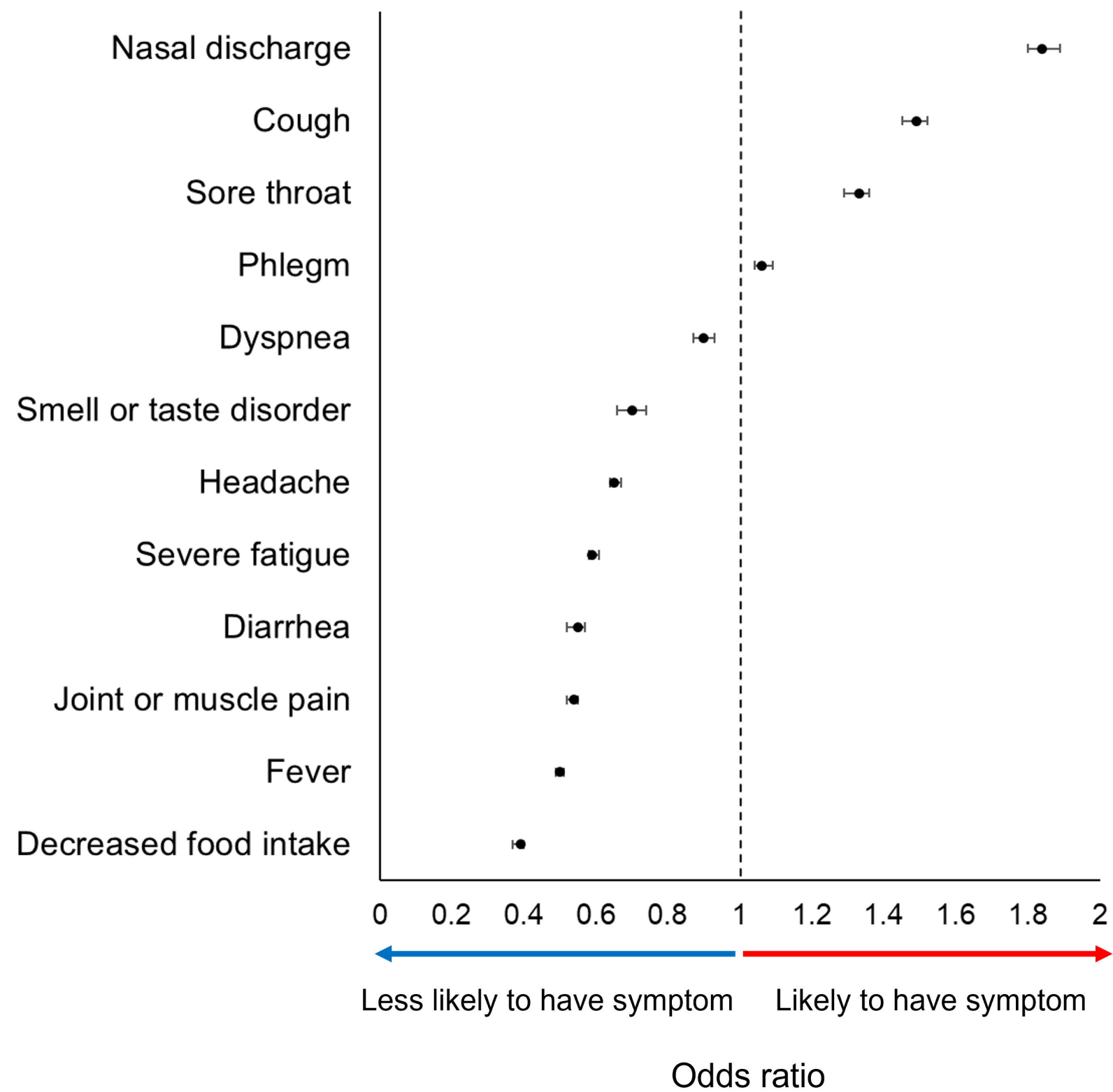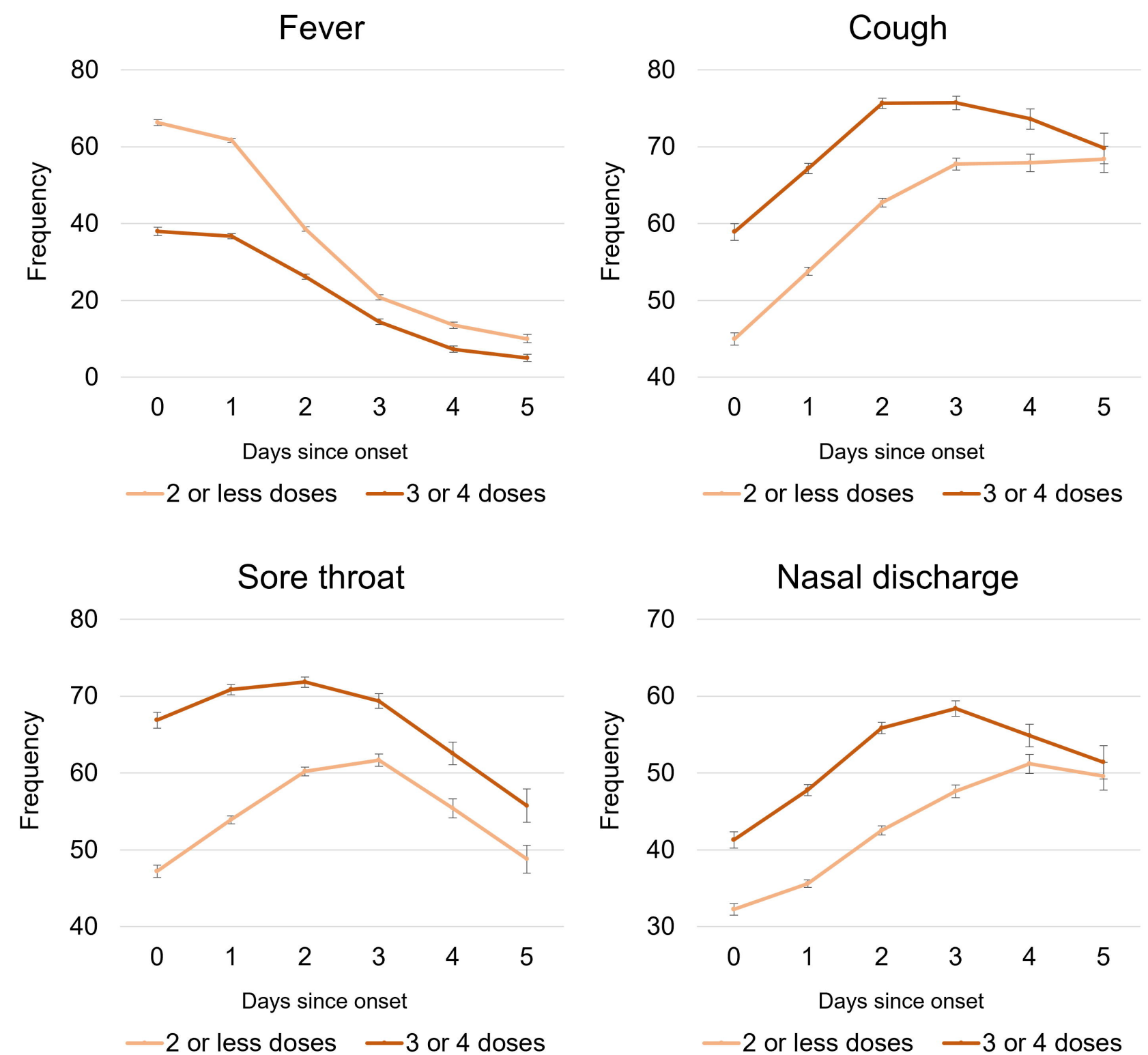157,861 Individuals were included into
the analysis.

A

B

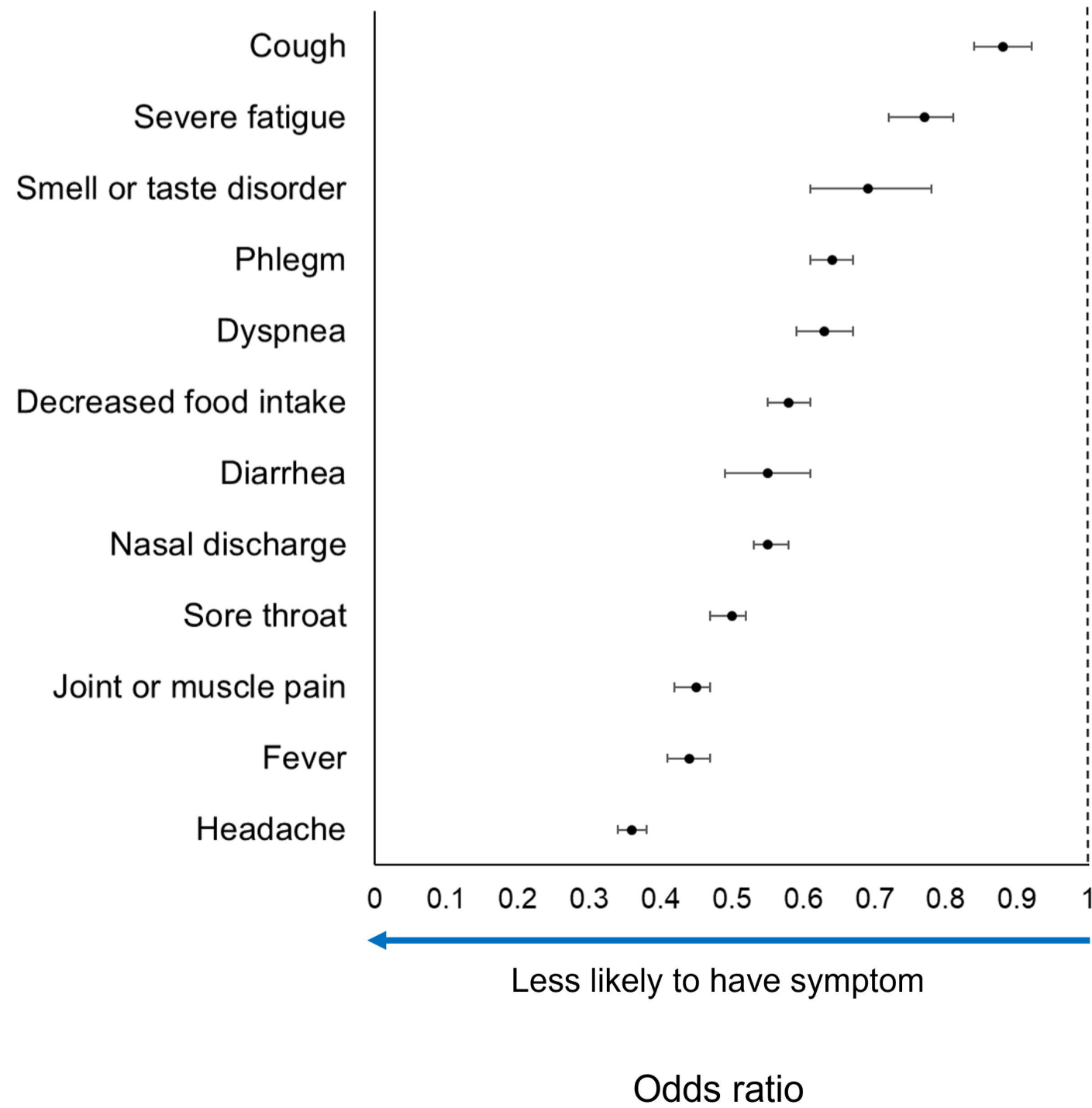3 or 4 doses (compared with 2 or less doses)

Odds ratio

Less likely to have symptom   Likely to have symptom

C

Fever

Cough

Sore throat

Nasal discharge

A

	<10	10s	20s	30s	40s	50s	60s	70s	80 or over		Total
	(n=23219)	(n=21165)	(n=26259)	(n=27665)	(n=26536)	(n=16629)	(n=8881)	(n=4839)	(n=2359)		(N=157552)
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				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%

B

Age ≥ 65 (compared with age < 65)

Cough
Severe fatigue
Smell or taste disorder
Phlegm
Dyspnea
Decreased food intake
Diarrhea
Nasal discharge
Sore throat
Joint or muscle pain
Fever
Headache

Odds ratio

← Less likely to have symptom

C

Progression to severe disease

Dyspnea
Fever
Decreased food intake
Severe fatigue
Cough
Diarrhea
Phlegm
Headache
Joint or muscle pain
Nasal discharge
Sore throat
Smell or taste disorder

Odds ratio

← Less likely to become severe   Likely to become severe →