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COVID-19 symptoms at hospital admission vary with age and sex: results from the ISARIC prospective multinational observational study

ISARIC Clinical Characterisation Group¹

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Abstract

Background The ISARIC prospective multinational observational study is the largest cohort of hospitalized patients with COVID-19. We present relationships of age, sex, and nationality to presenting symptoms.

Methods International, prospective observational study of 60 109 hospitalized symptomatic patients with laboratory-confirmed COVID-19 recruited from 43 countries between 30 January and 3 August 2020. Logistic regression was performed to evaluate relationships of age and sex to published COVID-19 case definitions and the most commonly reported symptoms.

Results ‘Typical’ symptoms of fever (69%), cough (68%) and shortness of breath (66%) were the most commonly reported. 92% of patients experienced at least one of these. Prevalence of typical symptoms was greatest in 30- to 60-year-olds (respectively 80, 79, 69%; at least one 95%). They were reported less frequently in children (≤ 18 years: 69, 48, 23; 85%), older adults (≥ 70 years: 61, 62, 65; 90%), and women (66, 66, 64; 90%; vs. men 71, 70, 67; 93%, each $P < 0.001$). The most common atypical presentations under 60 years of age were nausea and vomiting and abdominal pain, and over 60 years was confusion. Regression models showed significant differences in symptoms with sex, age and country.

Interpretation This international collaboration has allowed us to report reliable symptom data from the largest cohort of patients admitted to hospital with COVID-19. Adults over 60 and children admitted to hospital with COVID-19 are less likely to present with typical symptoms. Nausea and vomiting are common atypical presentations under 30 years. Confusion is a frequent atypical presentation of COVID-19 in adults over 60 years. Women are less likely to experience typical symptoms than men.

Keywords COVID-19 · SARS-CoV-2 · Symptoms · Diagnosis · Case definition

Background

Despite the pandemic’s immense human cost, enormous economic toll, and extensive research response, the precise clinical characteristics of COVID-19 remain unclear [1]. At the start of the outbreak, COVID-19 was broadly characterised as a severe respiratory illness presenting with fever, cough and an atypical pneumonia [2–5]. Altered sense of

taste and smell have since been found to be strongly associated with the disease [6, 7]. However, a review of 77 observational studies found substantial proportions of patients presenting with less typical symptoms [8].

Different sets of clinical criteria for suspected COVID-19 have been produced by the World Health Organization (WHO) [9], Centers for Disease Control and Prevention in the United States [10], Public Health England [11], and the European Centre for Disease Prevention and Control [12] (Table 1). Defining presenting symptoms of COVID-19 is further complicated by clinical experience suggesting that patients frequently present with atypical symptoms other than cough, fever and shortness of breath. This variation in the clinical characterisation of COVID-19 is problematic, as case definitions are used to guide clinical diagnosis, disease surveillance, and public health interventions.

The International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) cohort study is an

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Members of the "ISARIC Clinical Characterisation Group" are listed in Acknowledgement section.

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Table 1 Clinical case descriptions in use

Source	Symptoms
World Health Organization [9]	A combination of acute fever and cough or A combination of three or more of: Fever Cough General weakness and fatigue Headache Myalgia Sore Throat Coryza Dyspnoea Anorexia Nausea and vomiting Diarrhoea Altered mental status
Centers for Disease Control, United States [10]	At least two of: Fever Chills Rigors Myalgia Headache Sore throat New olfactory and taste disorder or At least one of: Cough Shortness of breath Difficulty breathing
Public Health England [11]	New cough, or temperature ≥ 37.8 °C, or a loss or change in sense of smell or taste
European Centre for Disease Prevention and Control [12]	At least one of Cough Fever Shortness of breath Sudden onset anosmia, ageusia or dys- geusia

international collaboration to gather reliable observational data about patients admitted to hospital with COVID-19 [13]. Here, we present an analysis of how symptoms of patients admitted to hospital with confirmed COVID-19 vary by age and sex. Secondly, we investigated how sensitivity of clinical case definitions varied among these populations, and explored heterogeneity among countries.

Methods

Study design and setting

This analysis used international observational data of clinical features of patients admitted to hospital with COVID-19 between 30 January and 3 August 2020. The ISARIC/

WHO Clinical Characterisation Protocol for Severe Emerging Infections is a standardized protocol for investigation of severe acute infections by pathogens of public health interest [14]. ISARIC case report forms [15] allow standardized data collection from the start of an outbreak and rapid dissemination of clinical information [3, 16–20]. Different tiers of data collection exist to allow sites to collect data to the highest possible standards while recognising varying levels of resource for data collection during epidemics. Details of symptoms at admission were included on the case report forms for all tiers. Data were collected via electronic ‘Core’ and ‘Rapid’ forms, and through aligned forms by ISARIC-4C Coronavirus Clinical Characterisation Consortium in the United Kingdom [21] and the COVID-19 Critical Care Consortium [22]. Investigators from 41 countries are using Research Electronic Data Capture (REDCap, version

8.11.11, Vanderbilt University, Nashville, Tenn.) to contribute their data to a central database hosted by the University of Oxford. Additional data were submitted by investigators from Malaysia, Russia [23] and Spain, who had used alternative data collection forms and databases. This observational study required no change to clinical management and permitted enrolment in other research. The study was approved by the World Health Organization Ethics Review Committee (RPC571 and RPC572). Local ethics approval was obtained for each participating country and site according to local requirements. All investigators retained full rights to their data.

Study population

Patients of any age admitted to hospital with suspected or confirmed COVID-19 were eligible for recruitment. Some versions of the case report form included specific criteria such as fever and cough, but investigators were able to include patients with a clinical suspicion of COVID-19 even if these criteria were not met. This analysis was limited to patients who were admitted to hospital with symptomatic laboratory-confirmed COVID-19: laboratory confirmation was classified according to sites' local diagnostic methods. We excluded asymptomatic patients who had been admitted to hospital for isolation and patients admitted for other conditions who subsequently developed COVID-19 symptoms.

Variables and measurement

Variables used in this analysis were age, sex at birth, symptoms, date of symptom onset, SARS-CoV-2 confirmation, and country of recruitment. To allow proportions to be calculated with a reliable denominator, only symptoms specified on the case report forms [15, 21, 22] were included in this analysis. The list of symptoms collected is presented with the results.

Statistical methods

Data were converted to Study Data Tabulation Model (version 1.7, Clinical Data Interchange Standards Consortium, Austin, Tex.) to allow inclusion of data submitted not using the ISARIC case report forms. We excluded patients with all symptoms recorded as missing or unknown, and those with missing age, sex or country.

Continuous variables were expressed as median with interquartile range (IQR), and categorical variables as counts with percentages. We tested for differences between female and male patients using Wilcoxon rank-sum tests for continuous variables and chi-square tests for categorical variables. We grouped patients into ten-year age bands (with a single group for age ≥ 90 years). We plotted the most frequently reported

symptoms by age group, presenting missing data as a third category. We collated symptoms according to four sets of clinical criteria. These were based on published criteria [9–12] but modified to omit symptoms with large numbers of missing data due to being added to the case report form part way through the data collection period (altered sense of taste and smell) or not being collected in all datasets (anorexia):

1. Fever plus cough; or any three of fever, cough, fatigue, headache, myalgia, sore throat, rhinorrhoea, shortness of breath, nausea and vomiting, diarrhoea, and confusion;
2. Cough or shortness of breath; or any two of fever, myalgia, headache, and sore throat;
3. Cough or fever;
4. At least one of cough, fever, and shortness of breath.

Patients with missing details of cough, fever or shortness of breath were omitted from the composite groups; patients missing details of symptoms included in the lists of criteria 1 and 2 were included, and were classified according to the non-missing symptoms. We plotted proportions of patients meeting each set of criteria by ten-year age group, with 95% confidence intervals (CI) calculated using the Clopper–Pearson method.

We used logistic regression to identify associations of age and sex with the twelve most prevalent symptoms. Age group and sex were included as fixed effects, with country as a random intercept. To display heterogeneity between countries on the same scale as the fixed effects, we calculated median odds ratios (MOR) [24]. This quantifies variation between countries by comparing odds of an outcome between randomly chosen persons in different clusters who share the same covariates [24]. MORs are defined as a comparison of the group with greater propensity to the group with lower propensity, so lie in the range 1 to infinity [24]. We plotted the MOR to show the magnitude of the effect of heterogeneity and allow comparison with the fixed effects in our data.

79% of patients were recruited in a single country (United Kingdom). As a sensitivity analysis, we repeated the analysis excluding patients from this country to see if results substantially changed. Finally, we plotted age-stratified symptom frequencies for each country with at least 250 patients.

No minimum sample size was calculated. All significance tests were two-tailed. Analyses were performed using R (version 3.6.2, R Foundation for Statistical Computing, Vienna, Austria) with packages including *binom*, *Epi*, *ggplot2*, *lme4*, *sjstats*, *tableone*, and *tidyverse*.

Results

Data were available for 99 623 patients. We excluded 24 336 who did not have documented SARS-CoV-2 confirmation, 3290 with missing data, and 5794 who developed COVID-19 after admission to hospital. 6094 patients were admitted to hospital with asymptomatic COVID-19, with the greatest proportion in the age band 10–20 years (46% of patients admitted in that age group). The greatest proportion of asymptomatic patients was in Malaysia (49%), where hospitalization was compulsory throughout the data collection period for people with COVID-19. We included 60 109 patients in the analysis (Fig. 1), recruited from 394 sites in 43 countries (Supplementary Table 1), in this analysis. The median age of included patients was 70 years (IQR 54–82; Table 2). 929 (1.5%) were 18 years old or younger. Age distribution of patients varied among countries, between a median of 10 years in Poland, and 73 years in the United Kingdom (Supplementary Figure 1). 34 641 (58%) patients were male.

The most frequently reported symptoms were fever, cough and shortness of breath (Table 3). These symptoms were each more prevalent in male patients, whereas less typical symptoms such as confusion, nausea and vomiting,

diarrhoea, chest pain, headache and abdominal pain were more prevalent in female patients. The greatest sex-related difference was for nausea and vomiting, reported by 23% of female patients but only 16% of male patients. For most symptoms, the greatest prevalence was reported in adults aged between 30 and 60 years, decreasing toward extremities of age (Fig. 2). Frequency of confusion increased with age. Large numbers of patients had missing data for anorexia, severe dehydration, altered sense of taste and smell, and inability to walk, as these were not included on all case report forms. Altered sense of taste and smell, which we had excluded from the composite criteria, were experienced by only 7.4 and 6.2% respectively of patients with non-missing data.

Data on cough, fever or shortness of breath were missing for 3446 patients. The composite clinical criteria were calculated for the remaining 56 663 patients. Each set of criteria was met by a greater proportion of patients aged 30–60 years than those toward either extreme of age (Fig. 3). The criteria based on WHO's clinical criteria [9] (fever plus cough; or any three of fever, cough, fatigue, headache, myalgia, sore throat, rhinorrhoea, shortness of breath, nausea and vomiting, diarrhoea, and confusion) were met by 40 911 (72%) patients, but only 51% of those aged 18 years and under, and 67% of those aged 70 years

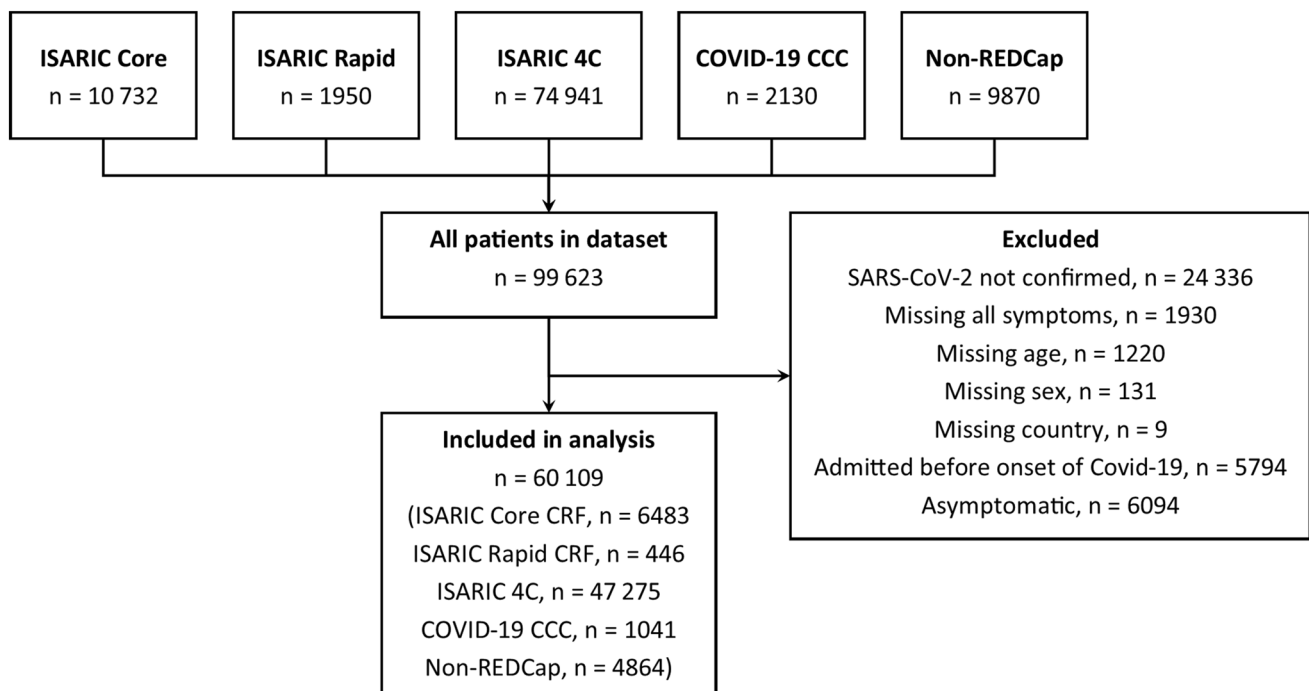


Fig. 1 Flow of participants in this analysis. ISARIC Core and ISARIC Rapid represent data collected internationally via two sets of case report forms; ISARIC 4C and COVID-19 CCC data were collected on separate databases using aligned case report forms; Non-REDCap data were submitted from additional sites and were

collected with different case report forms. 4C, Coronavirus Clinical Characterisation Consortium; CCC, Critical Care Consortium; ISARIC, International Severe Acute Respiratory and emerging Infection Consortium; REDCap, Research Electronic Data Capture; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2.

Table 2 Patient demographics

Variable ^a	Overall <i>n</i> = 60 109	Sex		<i>P</i> value
		Female <i>n</i> = 25 468	Male <i>n</i> = 34 641	
Age (years): median [IQR]	70 [54, 82]	72 [55, 83]	68 [54, 80]	<0.001
Age bands (years)				<0.001
0–10	514 (0.9)	221 (0.9)	293 (0.8)	
10–20	522 (0.9)	221 (0.9)	301 (0.9)	
20–30	1972 (3.3)	872 (3.4)	1100 (3.2)	
30–40	3209 (5.3)	1450 (5.7)	1759 (5.1)	
40–50	5013 (8.3)	1966 (7.7)	3047 (8.8)	
50–60	8581 (14.3)	3280 (12.9)	5301 (15.3)	
60–70	9874 (16.4)	3701 (14.5)	6173 (17.8)	
70–80	12,333 (20.5)	4916 (19.3)	7417 (21.4)	
80–90	13,483 (22.4)	6196 (24.3)	7287 (21.0)	
≥90	4608 (7.7)	2645 (10.4)	1963 (5.7)	
Region				<0.001
East Asia and Pacific	3252 (5.4)	1117 (4.4)	2135 (6.2)	
Europe and Central Asia	55,401 (92.2)	23,749 (93.3)	31,652 (91.4)	
Latin America and Caribbean	162 (0.3)	67 (0.3)	95 (0.3)	
Middle East and North Africa	91 (0.2)	35 (0.1)	56 (0.2)	
North America	926 (1.5)	413 (1.6)	513 (1.5)	
South Asia	267 (0.4)	83 (0.3)	184 (0.5)	
Sub-Saharan Africa	10 (0.0)	4 (0.0)	6 (0.0)	
Country income classification ^b				<0.001
High income	54,836 (91.2)	23,420 (92.0)	31,416 (90.7)	
Upper middle income	5003 (8.3)	1964 (7.7)	3039 (8.8)	
Lower middle or low income	270 (0.4)	84 (0.3)	185 (0.5)	

IQR interquartile range

^aData are number (percent within columns) unless specified otherwise

^bAccording to World Bank classification [25]

or over. The most sensitive criteria were at least one of cough, fever and shortness of breath, met by 52 041 (92%) participants. These criteria were met by 85% aged 18 years and under, and 90% of those aged 70 years or over. Each set of criteria were met by a greater proportion of male than female patients (Table 3).

For the 4622 patients whose symptoms did not meet any assessed case definitions, the most frequent symptom was confusion (47%; Table 4). This increased with age to 66% of those aged 90 years or older. Nausea and vomiting, and abdominal pain were the most common symptoms for people less than 60 years old who had not met any of the case definitions.

In the logistic regression models (Fig. 4 and 5), similar associations between age and symptoms were seen after adjustment for sex as in the unadjusted bar charts. Confusion increased with age. Nausea and vomiting, headache, abdominal pain, and sore throat were each more frequent in younger age groups, decreasing with age. Male patients had greater odds of fever, cough and shortness of breath, and lower odds of gastrointestinal symptoms of nausea and vomiting, diarrhoea,

abdominal pain, chest pain, headache and sore throat. However, in each case except diarrhoea, the magnitude of the difference according to sex was much less than the effect of age. The MOR for heterogeneity between countries was greater than the relationship with sex in all symptoms (Fig. 4). It was of similar magnitude to the relationship with age for most symptoms. For each symptom, heterogeneity between countries was of a similar magnitude to the effect of age, and a greater magnitude than sex.

47 280 (79%) patients were included from the United Kingdom. Excluding these patients, the patterns of symptoms were similar to the main analysis (Supplementary Figure 2). The peak prevalence of fever, cough and shortness of breath was in 70- to 80-year olds, and fatigue increased with age. Below the age of 50 years, the clinical case definitions tended to be less sensitive in the analysis excluding the United Kingdom than in the analysis including it; above the age of 70 years each tended to be more sensitive (grey lines in Fig. 3). Within countries, the baseline prevalence of each symptom varied but patterns within countries were broadly similar to the overall results (Supplementary Figures 3–14).

Table 3 Symptoms at presentation to hospital with COVID-19

Variable ^a	Overall, <i>n</i> = 60 109	Sex			Missing data ^b
		Female, <i>n</i> = 25 468	Male, <i>n</i> = 34 641	<i>P</i> value	
Fever	41,067 (68.7)	16,649 (65.7)	24,418 (70.8)	<0.001	291 (0.5)
Cough	40,898 (68.5)	16,683 (65.9)	24,215 (70.4)	<0.001	401 (0.7)
Shortness of breath	37,577 (65.8)	15,450 (64.0)	22,127 (67.2)	<0.001	3024 (5.0)
Fatigue	23,319 (46.4)	9889 (46.3)	13,430 (46.5)	0.622	9893 (16.5)
Confusion	13,732 (27.3)	6108 (28.2)	7624 (26.5)	<0.001	9730 (16.2)
Muscle pains	9472 (20.1)	3952 (19.8)	5520 (20.3)	0.137	12,980 (21.6)
Diarrhoea	10,061 (19.1)	4565 (20.4)	5496 (18.2)	<0.001	7544 (12.6)
Nausea and vomiting	9891 (18.8)	5099 (22.8)	4792 (15.8)	<0.001	7464 (12.4)
Anorexia	613 (15.7)	243 (14.3)	370 (16.8)	0.038	56,202 (93.5)
Severe dehydration	3451 (14.8)	1562 (15.4)	1889 (14.3)	0.027	36,756 (61.1)
Chest pain	6953 (13.6)	3084 (14.2)	3869 (13.1)	0.001	8953 (14.9)
Headache	6154 (13.0)	2830 (14.1)	3324 (12.2)	<0.001	12,796 (21.3)
Sore throat	4880 (10.5)	2135 (10.8)	2745 (10.3)	0.097	13,836 (23.0)
Abdominal pain	5305 (10.4)	2597 (12.0)	2708 (9.2)	<0.001	9015 (15.0)
Wheeze	3845 (7.9)	1790 (8.6)	2055 (7.4)	<0.001	11,390 (18.9)
Altered sense of taste	2011 (7.4)	924 (7.8)	1087 (7.1)	0.023	32,830 (54.6)
Joint pains	3229 (7.1)	1459 (7.5)	1770 (6.8)	0.002	14,587 (24.3)
Altered sense of smell	1733 (6.2)	819 (6.7)	914 (5.7)	0.001	31,969 (53.2)
Rhinorrhoea	2382 (5.2)	1041 (5.3)	1341 (5.1)	0.264	14,403 (24.0)
Unable to walk	220 (5.0)	83 (4.4)	137 (5.4)	0.141	55,668 (92.6)
Skin ulcer	978 (2.3)	489 (2.7)	489 (2.1)	<0.001	18,486 (30.8)
Haemorrhage	993 (2.0)	429 (2.0)	564 (2.0)	0.695	9902 (16.5)
Lower chest wall indrawing	688 (1.6)	235 (1.3)	453 (1.9)	<0.001	17,887 (29.8)
Seizure	775 (1.6)	352 (1.7)	423 (1.5)	0.169	12,055 (20.1)
Rash	694 (1.4)	287 (1.4)	407 (1.5)	0.555	11,400 (19.0)
Lymphadenopathy	307 (0.7)	147 (0.8)	160 (0.6)	0.099	15,267 (25.4)
Conjunctivitis	251 (0.5)	111 (0.5)	140 (0.5)	0.642	12,491 (20.8)
Ear pain	201 (0.5)	107 (0.6)	94 (0.4)	0.003	19,036 (31.7)
Composite categories					3446 (5.7) ^c
Fever and cough; or at least three of fever, cough, fatigue, headache, muscle pains, sore throat, rhinorrhoea, shortness of breath, nausea and vomiting, diarrhoea, and confusion	40,911 (72.2)	17,014 (71.0)	23,897 (73.1)	<0.001	
Cough or shortness of breath; or at least two of fever, muscle pains, headache, or sore throat	48,464 (85.5)	20,103 (83.9)	28,361 (86.7)	<0.001	
Cough or fever	48,494 (85.6)	19,973 (83.3)	28,521 (87.2)	<0.001	
At least one of cough, fever or shortness of breath	52,041 (91.8)	21,607 (90.2)	30,434 (93.1)	<0.001	

^aData are number (percent of patients with non-missing data within columns) unless specified otherwise

^bNumber (percent of all patients)

^cPatients missing any of cough, fever or shortness of breath are omitted from the composite categories

Discussion

The ISARIC prospective multinational cohort study is the largest cohort of patients admitted to hospital with COVID-19 to date. In this report, we confirmed a relationship between patients' symptoms and their age and sex. The 'typical' COVID-19 symptoms occur most frequently in adults

aged 30–60 years. Commonly used case definitions can miss up to half of children and a third of adults over 70 years who are admitted to hospital with COVID-19.

Our results support the findings of smaller cohort studies that atypical symptoms are more common in older adults [26], and correlate with similar findings of atypical presentations for pneumonia, bacteraemia and coronary

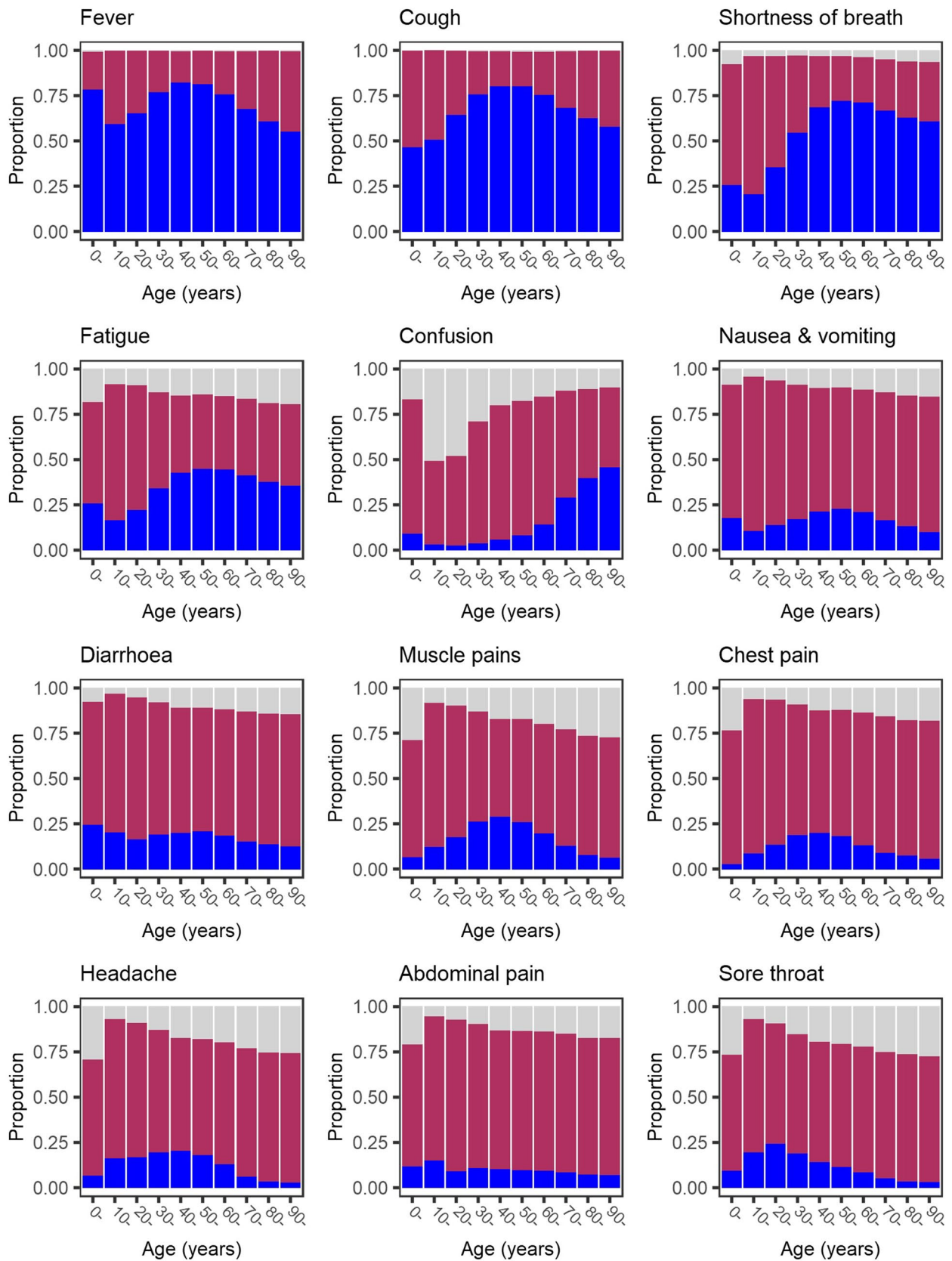


Fig. 2 Age-specific prevalence of symptoms at hospital admission. Dark blue bars show symptom present, maroon bars show symptom absent, pale grey bars show missing data

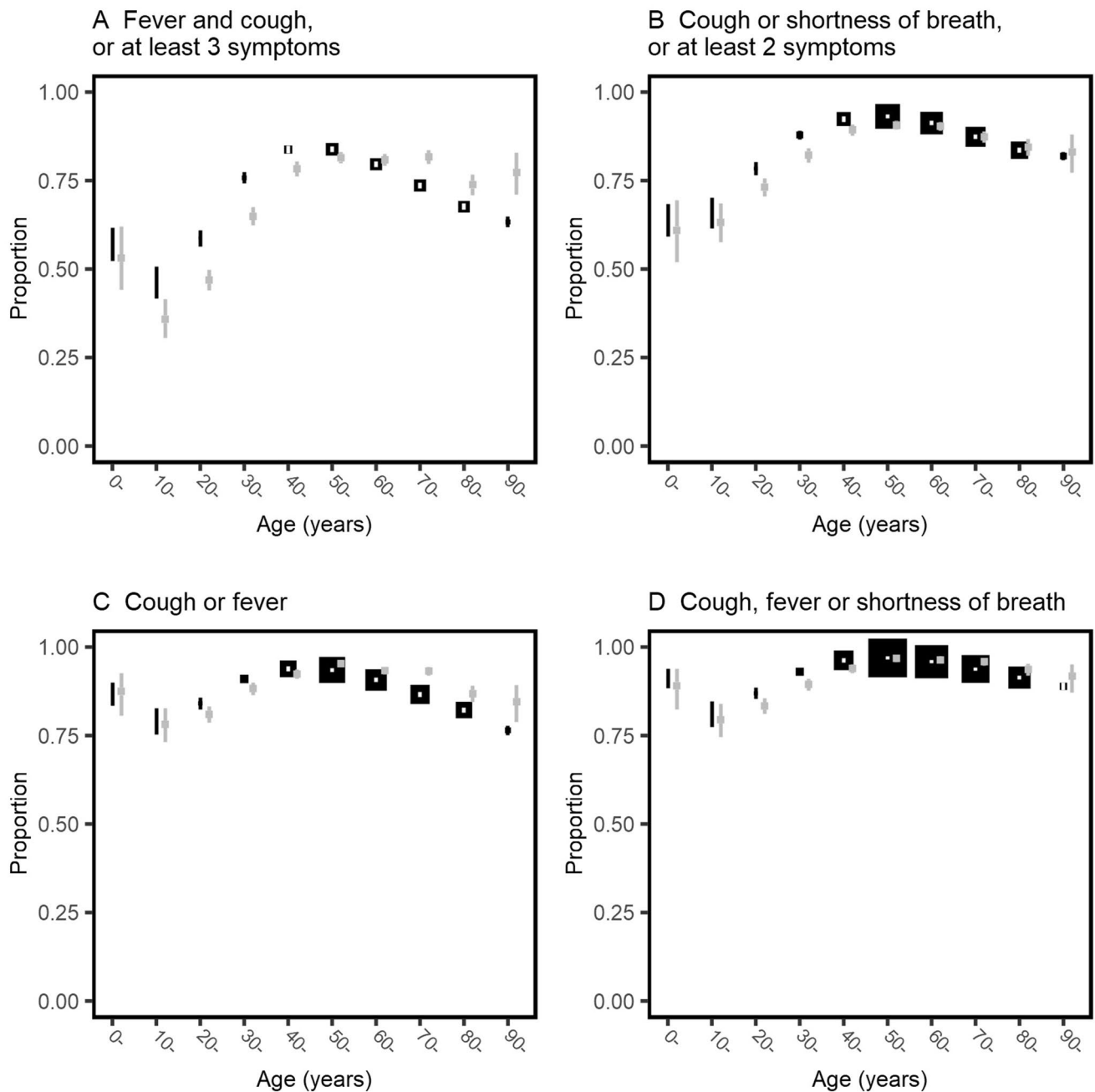


Fig. 3 Proportions meeting clinical criteria at hospital admission stratified by 10-year age band. Black boxes show the proportion of individuals, with error bars showing 95% confidence intervals calculated using the Clopper–Pearson method. The size of each box is inversely proportional to the variance, so larger boxes indicate greater certainty. Grey boxes with 95% confidence intervals show the proportions in the sensitivity analysis excluding patients recruited in the

United Kingdom. In panel A, the three symptoms are from the list of fever, cough, fatigue, headache, myalgia, sore throat, rhinorrhoea, shortness of breath, nausea and vomiting, diarrhoea, and confusion; in panel B the two symptoms are from the list fever, myalgia, headache, and sore throat. Patients with missing data for cough, fever or shortness of breath are excluded from all four plots

artery disease [27, 28]. A lower prevalence of symptoms in children and young people has previously been suggested [29, 30], but this is the first large international cohort to collect data prospectively from both adults and children.

Separate analyses of the ISARIC-4C data have identified fever, cough and shortness of breath as frequently co-occurring clusters of symptoms [31, 32]. In children, the next most frequent cluster consisted of systemic, enteric and

Table 4 Symptoms reported for patients meeting none of the clinical case definitions

Symptom ^a	Age group (years)										Missing data	
	Overall	0	10	20	30	40	50	60	70	80		90
	<i>n</i> = 4622	<i>n</i> = 44	<i>n</i> = 100	<i>n</i> = 269	<i>n</i> = 256	<i>n</i> = 217	<i>n</i> = 309	<i>n</i> = 484	<i>n</i> = 922	<i>n</i> = 1406	<i>n</i> = 615	
Confusion	1917 (46.9)	4 (9.8)	2 (4.2)	7 (6.2)	9 (5.8)	23 (14.1)	57 (21.3)	155 (35.1)	474 (52.8)	785 (57.7)	401 (66.4)	531 (11.5)
Fatigue	1245 (29.1)	9 (23.1)	10 (10.3)	30 (11.3)	37 (15.2)	42 (20.7)	83 (28.1)	148 (33.2)	284 (33.3)	444 (34.4)	158 (28.6)	340 (7.4)
Severe dehydration	472 (22.6)	1 (5.0)	1 (4.3)	4 (8.3)	2 (2.9)	7 (11.3)	18 (13.1)	40 (18.0)	110 (24.8)	201 (27.1)	88 (27.6)	2535 (54.8)
Nausea and vomiting	995 (22.2)	19 (44.2)	24 (24.0)	44 (16.4)	59 (23.4)	77 (36.0)	94 (31.2)	127 (27.1)	210 (23.4)	245 (18.3)	96 (16.2)	145 (3.1)
Abdominal pain	812 (18.5)	9 (22.5)	22 (22.4)	52 (19.5)	67 (26.6)	54 (25.8)	80 (27.0)	107 (23.1)	173 (19.6)	184 (13.9)	64 (11.2)	223 (4.8)
Diarrhoea	612 (13.8)	8 (19.0)	6 (6.1)	26 (9.7)	25 (10.0)	31 (14.8)	46 (15.5)	94 (20.3)	136 (15.2)	177 (13.4)	63 (10.9)	201 (4.3)
Headache	347 (8.3)	2 (6.1)	13 (13.4)	48 (18.4)	39 (16.0)	47 (23.2)	32 (11.0)	45 (10.3)	52 (6.3)	47 (3.8)	22 (4.1)	454 (9.8)
Muscle pains	301 (7.3)	4 (11.8)	5 (5.2)	19 (7.2)	28 (11.5)	24 (12.1)	27 (9.4)	39 (9.0)	54 (6.6)	65 (5.3)	36 (6.8)	482 (10.4)
Joint pains	293 (7.1)	3 (9.1)	4 (4.2)	9 (3.4)	8 (3.3)	13 (6.5)	14 (4.9)	27 (6.2)	49 (6.0)	109 (8.8)	57 (10.7)	473 (10.2)
Chest pain	299 (6.8)	0 (0.0)	1 (1.0)	12 (4.5)	15 (6.0)	21 (9.8)	44 (14.6)	49 (10.6)	51 (5.8)	79 (6.0)	27 (4.7)	209 (4.5)
Sore throat	277 (6.7)	4 (11.1)	24 (25.0)	83 (31.7)	62 (25.1)	39 (19.3)	16 (5.5)	18 (4.1)	17 (2.1)	9 (0.7)	5 (1.0)	460 (10.0)
Haemorrhage	233 (5.5)	0 (0.0)	1 (1.1)	5 (2.1)	10 (4.3)	12 (6.0)	14 (4.8)	22 (4.9)	45 (5.2)	84 (6.5)	40 (7.0)	347 (7.5)
Altered sense of smell	149 (4.9)	1 (4.0)	20 (24.1)	48 (22.7)	30 (16.0)	17 (11.4)	11 (5.1)	9 (2.8)	4 (0.7)	9 (1.0)	0 (0.0)	1584 (34.3)
Rhinorrhoea	188 (4.5)	3 (7.5)	28 (29.2)	58 (22.1)	43 (17.6)	23 (11.4)	14 (4.8)	7 (1.6)	6 (0.7)	2 (0.2)	4 (0.7)	476 (10.3)
Skin ulcer	153 (4.2)	1 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.5)	9 (3.7)	13 (3.3)	43 (5.3)	51 (4.1)	34 (6.2)	982 (21.2)
Seizure	152 (3.8)	5 (11.6)	3 (6.2)	3 (2.7)	6 (3.9)	11 (6.7)	16 (6.1)	22 (5.1)	34 (3.9)	39 (3.0)	13 (2.3)	659 (14.3)
Altered sense of taste	101 (3.3)	1 (4.5)	10 (12.0)	27 (13.0)	15 (8.1)	10 (6.8)	3 (1.4)	7 (2.2)	11 (2.0)	13 (1.5)	4 (1.0)	1602 (34.7)
Rash	78 (1.8)	5 (11.6)	3 (3.0)	2 (0.8)	1 (0.4)	4 (2.0)	5 (1.7)	17 (3.8)	18 (2.2)	15 (1.2)	8 (1.5)	384 (8.3)
Wheeze	53 (1.2)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.4)	0 (0.0)	3 (1.0)	6 (1.3)	8 (0.9)	22 (1.7)	12 (2.1)	296 (6.4)

Symptoms experienced by < 25 individuals are omitted

^aData are number (percent of patients with non-missing data within columns)

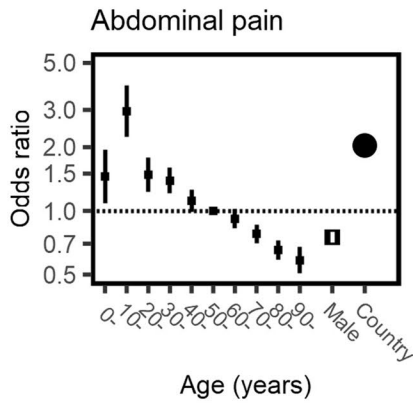
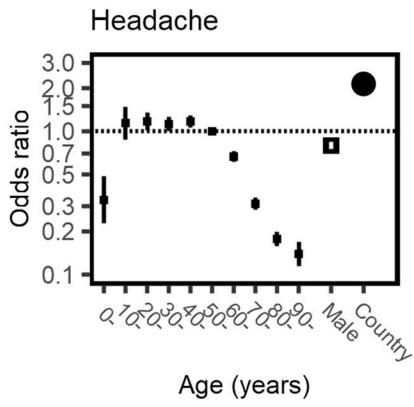
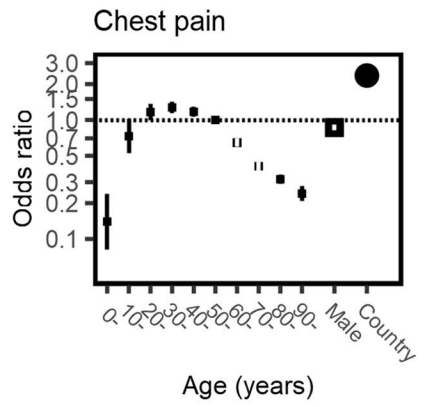
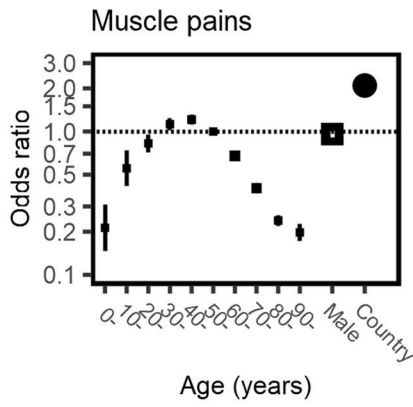
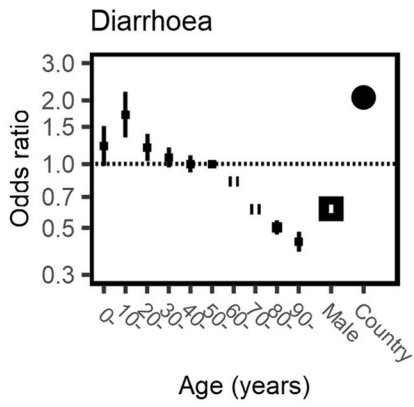
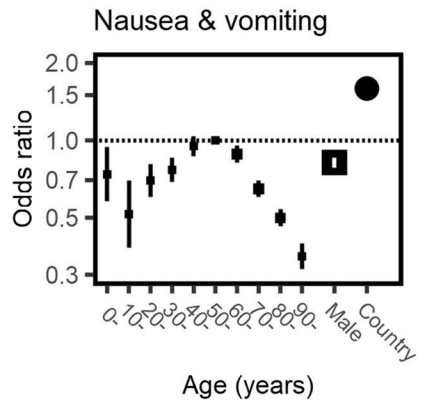
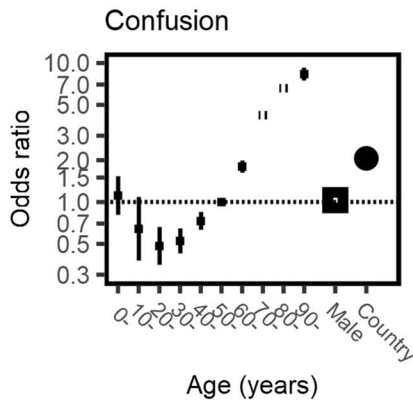
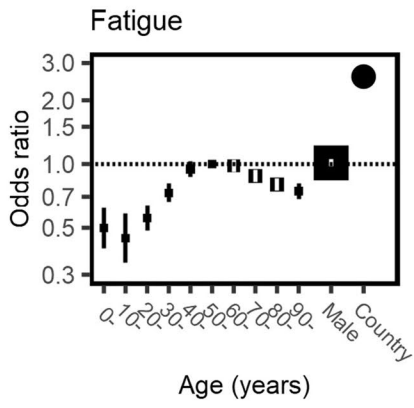
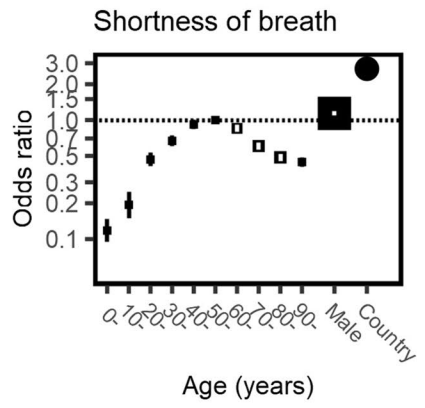
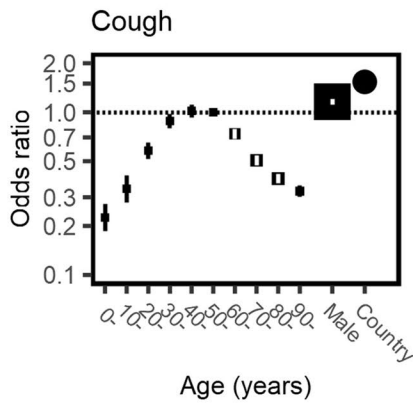
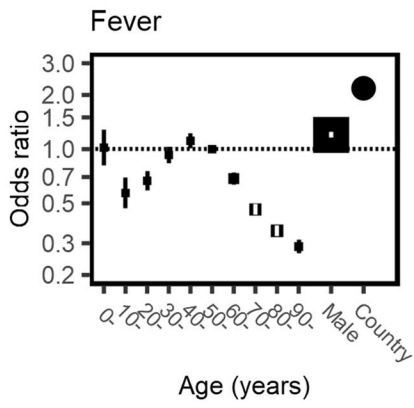


Fig. 4 Odds of symptoms among patients admitted to hospital with COVID-19, stratified by age and sex. Each plot is the result of a logistic regression with a symptom as an outcome. Fixed effects of age in ten-year bands (baseline group 50–60 years) and sex are shown in black boxes with 95% confidence intervals. The size of each square is inversely proportional to the variance of the log odds ratio, so larger boxes indicate greater certainty. Clustering by country is included as a random intercept and heterogeneity is depicted by circles showing the median odds ratio

mucocutaneous symptoms [31]. For adults, other clusters consisted of non-specific viral symptoms, gastrointestinal symptoms, upper respiratory symptoms, neurological symptoms, and symptoms of bronchospasm [32]. Those data were included in this global dataset so the results of these analyses are not independent of our results.

We found that differences in symptoms by sex were statistically significant but generally of smaller magnitude. Typical symptoms of fever, cough and shortness of breath were more common in men than in women; all other symptoms were equal or more common in female patients. A cohort of non-hospitalized patients with COVID-19 in Poland found greater differences in symptoms of lack of appetite (55% of women, 36% of men) and taste disorder (53% women, 40% men) [33]. We are unable to determine from our data whether these differences reflect differences in health-seeking behaviour between men and women, or physiological differences in their response to the infection. Elaboration of this difference should be a goal of future research.

Our results suggest considerable heterogeneity among countries. We have not attempted to elicit reasons for heterogeneity. Potential reasons include cultural idiosyncrasies in reporting symptoms, and hospitals' criteria for admission and testing. It might also reflect differences in local patient recruitment. Researchers in some countries may be unwilling to recruit confused patients due to requirements for consent, whereas in others, the requirement for consent has been waived or could be obtained from a proxy. We explored the effect of using the country of recruitment as a random effect in regression models and by repeating the analysis excluding the largest country. Each analysis suggested an underlying pattern of lower frequencies of typical symptoms in children and older adults. Therefore, although the prevalence of each symptom reported in this study may not apply to all settings, we have evidence to support the possibility of age-dependent differences internationally.

The size of this cohort is a strength. To our knowledge, it is the largest cohort of hospitalized COVID-19 patients in the world. However, the study has several limitations. First, almost 80% of patients were recruited in a single country. Moreover, less than 1% of patients were recruited from low- or lower-middle-income countries. Second, the cohort overwhelmingly includes older adults, with only 1.8% of the cohort aged 18 years or younger. Third, our analysis includes

only patients who were hospitalized with COVID-19 and who had a laboratory-confirmed diagnosis. This patient population is more likely to be severely unwell and more likely to exhibit symptoms typically associated with COVID-19 than people who were managed in the community or whose disease has not been recognized. Accordingly, the reporting of 'typical' COVID-19 symptoms in this cohort is likely to be an overestimate of the population prevalence. Symptoms are subjective and cannot be externally verified. Some differences for children may reflect that symptoms could only be recorded if a caregiver recognised the symptom or the child had the appropriate vocabulary to describe it. Similarly, some symptoms may be under-reported in elderly patients if there are difficulties in communication, for example due to delirium. As such, the generalizability of estimates of our symptom prevalence is limited. Similarly, there is a shortage of studies conducted outside of high-income countries: a recent scoping review of clinical characteristics of COVID-19 identified no large cohorts in non-high-income countries except China [8].

The absence of a control group of patients without COVID-19 in this dataset prevented estimation of specificity or positive and negative predictive values. We are therefore prevented from advocating changes to clinical case definitions, as such decisions inevitably require a balance of false-positive and false-negative rates. However, given the prevalence of atypical symptoms in our cohort, we can confidently suggest that reliance on clinical case definitions may result in missing cases of COVID-19, especially among children and older adults. Non-healthcare professionals making decisions regarding isolation may be especially vulnerable to missing cases of COVID-19 by adhering to a clinical case definition too strictly.

The reported prevalence of COVID-19 may also rely on a strict interpretation of case definitions. In settings where comprehensive contact tracing is planned, or there is easy access to microbiological testing, a highly sensitive case definition is desirable. However, where decisions are based on clinical diagnoses, it is important to recognize other pathogens that can cause similar constellations of symptoms. The addition of symptoms such as confusion or gastrointestinal symptoms to the COVID-19 case definition could increase sensitivity, but at the cost of reduced specificity. Changes in the senses of taste and smell have recently been added to case definitions. Our data suggest that these criteria would detect only a small proportion of patients admitted to hospital with COVID-19 who were omitted by other definitions.

These results highlight the need to consider COVID-19 even if individuals do not display typical symptoms of the disease. This is especially the case in children and older adults. Given that our results are likely to overestimate the sensitivity of the clinical criteria currently used to identify patients for testing, our results suggest a lower limit to the

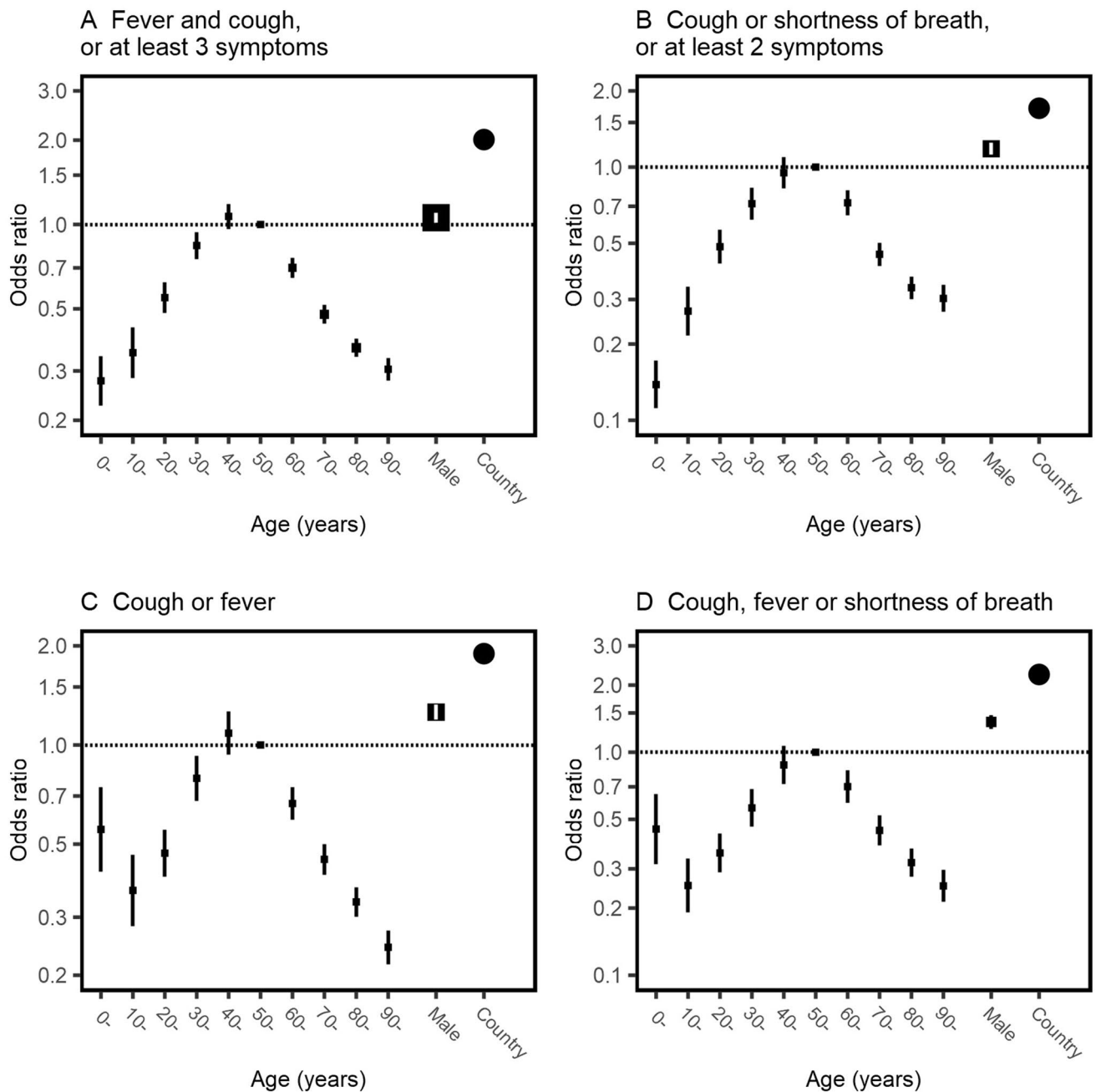


Fig. 5 Age- and sex-specific odds of meeting clinical definitions among patients admitted to hospital with COVID-19, stratified by age and sex. Each plot is the result of a logistic regression with a composite group of symptoms as an outcome. Fixed effects of age in ten-year bands (baseline group 50–60 years) and sex are shown in black boxes with 95% confidence intervals. The size of each square is inversely proportional to the variance of the log odds ratio, so larger boxes indicate greater certainty. Clustering by country is included as a ran-

dom intercept and heterogeneity is depicted by circles showing the median odds ratio. In panel A, the three symptoms are from the list of fever, cough, fatigue, headache, myalgia, sore throat, rhinorrhoea, shortness of breath, nausea and vomiting, diarrhoea, and confusion; in panel B the two symptoms are from the list fever, myalgia, headache, and sore throat. Patients with missing data for cough, fever or shortness of breath are excluded from all four plots

proportion of people in the community with COVID-19 who would not be identified. Addition of confusion as a symptom would increase the sensitivity of case definitions for older adults; and inclusion of nausea and vomiting or

abdominal pain would increase sensitivity for children and young adults. The high proportion of asymptomatic patients identified in patients aged 10–20 years suggests that universal screening in these ages could be beneficial when there is

widespread community circulation of COVID-19. Ongoing data collection outside high-income countries is needed to establish whether alternative case definitions are needed in different settings. Work is also ongoing to determine whether some constellations of symptoms are associated with better or poorer outcomes than others.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s15010-021-01599-5>.

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Availability of data and materials We welcome applications for UK data through the ISARIC 4C Independent Data and Material Access Committee (<https://isaric4c.net>). Requests for access to non-UK data can be sent to covid19@iddo.org.

Declarations

Conflict of interest M. Cheng declares grants from McGill Interdisciplinary Initiative in Infection and Immunity, and Canadian Institutes of Health Research; and personal fees from GEn1E Lifesciences (as a member of the scientific advisory board) and nplex biosciences (as a member of the scientific advisory board); M. Cummings and M. O'Donnell participated as investigators for completed and ongoing clinical trials evaluating the efficacy and safety of remdesivir (sponsored by Gilead Sciences) and convalescent plasma (sponsored by Amazon), in hospitalized patients with COVID-19—support for this work is paid to Columbia University; J. C. Holter declared grants from Research Council of Norway [grant 312780], and Vivaldi Invest A/S owned by Jon Stephenson von Tetzchner, during the conduct of the study; A. Kimmoun declared personal fees (payment for lectures) from Baxter, Aguetant, Aspen; D. Kumar declared grants and personal fees from Roche, GSK and Merck, and personal fees from Pfizer and Sanofi; F.X. Lescure declared personal fees (payment for lectures) from Gilead, MSD; and travel/accommodation/meeting expenses from Atellas, Eumedica, MSD; A. Pesenti declared personal fees from Maquet, Novalung/Xenios, Baxter, and Boehringer Ingelheim; S. Shrapnel reported grants from Prince Charles Hospital Foundation during the conduct of the study, and concurrently performed data analytics for the COVID-19 Critical Care Consortium; R. Tedder reports grants from MRC/UKRI during the conduct of the study, and has a patent United Kingdom Patent Application No. 2014047.1 “SARS-CoV-2 antibody detection assay” issued; J. Troost declared personal fees from General Electric and Procter and Gamble.

Ethics approval This observational study required no change to clinical management and permitted enrolment in other research. The study was approved by the World Health Organization Ethics Review Committee (RPC571 and RPC572). Local ethics approval was obtained for each participating country and site according to local requirements.

Consent to participate Informed consent was sought where required by local ethics committees. In many jurisdictions, ethics committees and public health authorities approved a waiver of consent to collect anonymised clinical data in the context of this public health emergency.

Consent for publication Not applicable.

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