Title

Long-term health-related quality of life in non-hospitalised COVID-19 cases with confirmed SARS-CoV-2 infection in England: Longitudinal analysis and cross-sectional comparison with controls

Authors

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Summary:

Losses of health-related quality of life in non-hospitalised COVID-19 cases increase with age and for cases with persistent symptoms. At a population level, the health loss from morbidity contributes at least 18% of the total COVID-19-related disease burden in England.

Abstract

Background: We aimed to quantify the unknown losses in health-related quality of life of COVID-19 cases using quality-adjusted life days (QALDs) and the recommended EQ-5D instrument in England.

Methods: Prospective cohort study of non-hospitalised, PCR-confirmed SARS-CoV-2(+) cases aged 12-85 years and followed up for six months from 01 December 2020, with cross-sectional comparison to SARS-CoV-2(-) controls. Main outcomes were QALD losses; physical symptoms; and COVID-19-related private expenditures. We analysed results using multivariable regressions with post-hoc weighting by age and sex, and conditional logistic regressions for the association of each symptom and EQ-5D limitation on cases and controls.

Results: Of 548 cases (mean age 41.1 years; 61.5% female), 16.8% reported physical symptoms at month 6 (most frequently extreme tiredness, headache, loss of taste and/or smell, and shortness of breath). Cases reported more limitations with doing usual activities than controls. Almost half of cases spent a mean of £18.1 on non-prescription drugs (median: £10.0), and 52.7% missed work or school for a mean of 12 days (median: 10). On average, all cases lost 13.7 (95%-CI: 9.7, 17.7) QALDs, while those reporting symptoms at month 6 lost 32.9 (24.5, 37.6) QALDs. Losses also increased with older age. Cumulatively, the health loss from morbidity contributes at least 18% of the total COVID-19-related disease burden in England.

Conclusions: One in 6 cases report ongoing symptoms at 6 months, and 10% report prolonged loss of function compared to pre-COVID-19 baselines. A marked health burden was observed among older COVID-19 cases and those with persistent physical symptoms.

Keywords: SARS-CoV-2; COVID-19; long COVID; health-related quality of life; QALYs

Introduction

The prevalence of persistent symptoms in some individuals who recover from coronavirus disease 2019 (COVID-19), sometimes called post-acute COVID-19 syndrome or "long COVID", is reported with 20-30% after one month and at least 10% after three months [1]. Cases with post-acute COVID-19 syndrome also report a worsened health-related quality of life (HRQoL) [2]. However, few studies have quantified the quality-adjusted life years (QALYs) lost with COVID-19.

QALYs integrate the duration of different health states expressed in years with the health-related quality of life experienced in those health states. Robust estimates of the COVID-19-related QALYs lost are needed to inform policy and intervention evaluations. The disease-generic EQ-5D is a validated, patient-reported instrument and is the recommended method in England [3, 4] and many other countries [5]. The importance of COVID-19-specific estimates of QALY losses is growing [6], particularly as countries face the impact of post-acute COVID-19 syndrome [1].

Therefore, we aimed to assess the HRQoL impact of infections with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and COVID-19-like symptoms using the EQ-5D. The primary aim was to provide COVID-19-specific estimates of the acute and long-term QALY loss of non-hospitalised confirmed cases in England. We also explored the physical symptom status and any private expenditures due to COVID-19 of the cases over 6 months. Lastly, we compared the SARS-CoV-2(+) cases cross-sectionally at month 6 to SARS-CoV-2(-) controls.

Methods

Study design and patient population (SARS-CoV-2 positive cases)

We report on a prospective observational study of individuals with SARS-CoV-2 infection and COVID-19 symptoms in England, with a cross-sectional comparison to controls at month 6 (see next section). Infections with SARS-CoV-2 were laboratory-confirmed by real-time polymerase chain reaction (RT-PCR) in November 2020. Participants aged 12 to 85 years inclusive were randomly selected from the Second Generation Surveillance System (SGSS; the routine laboratory reporting system in England [7]) to be proportionately representative of the geographical regions in England from all those who requested a test through community testing with a specimen date of 26-27 November 2020. At the time, the lineage of cases in England were predominantly formed by wild type and increasingly the Alpha variant (S-gene negative B.1.1.7) [8-10]. Laboratory confirmed cases were invited by email and post to this study on or shortly after December 01, 2020. Other than non-fatal outcome, non-hospitalised, PCR-positive, and aged between 12 and 85 years there were no formal recruitment restrictions. The study is an interim evaluation of ongoing surveillance.

Control population recruited in June 2021 (SARS-CoV-2 negative individuals)

In June 2021 we recruited a control group of individuals who had a negative SARS-CoV-2 PCR test in SGSS on 26-27 November 2020 and had no subsequent positive SARS-CoV-2 PCR test. The controls were randomly selected for a match of three controls per case, and frequency-matched to the cases by geographical region to reflect the spatial distribution of the cases. To reduce the administrative burden, we invited controls by email.

Survey design and data collection in cases and controls

The initial survey sent to cases enquired about baseline demographics (age, sex, pregnancy, ethnicity, and comorbidities), physical symptoms (in the first 7 days of illness given the potential delay in symptom onset, getting PCR tested, and receiving the survey; and at the time of filling out the survey), resource use and personal expenditures due to COVID-19 not falling on the healthcare system (like absence days from work or school, time used to care for others or being cared for, and costs for medication and other help due to the COVID-19 illness episode), and the HRQoL impact as measured through the adult version of the EQ-5D-5L, which collects information about 5 dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) on 5 levels (no problems, slight problems, moderate problems, severe problems, extreme problems). Given that cases were recruited after having tested positive for SARS-CoV-2, we used the EQ-5D three times in the initial survey for participants to self-report their health at three time points: 1) health on the day they filled in the survey, 2) pre-COVID-19 baseline health, and 3) health on the worst day of COVID-19.

After the initial survey, participating cases received short follow-up surveys asking about any change in symptoms and resource use since the last survey, and about the EQ-5D-5L on the day they filled in the survey. The follow-up surveys were sent out at week 2, week 4, week 6, week 8, week 12 and month 6.

Controls received a survey in June 2021 also enquiring about baseline demographics, the symptom status between March and June 2021, resource use and personal expenditures due to illnesses, and the HRQoL impact as measured through the EQ-5D-5L on the day of the survey.

Estimated sample size and observed response rates in cases and controls

We estimated the sample size required with 300-350 cases based on the quality-adjusted life-day (QALD) lost from acute illness during the H1N1pdm2009 influenza pandemic [11, 12]. Of the 1,500 laboratory-confirmed cases invited to participate, we analysed the responses of 548 cases (with 157 cases still responding at month 6). Of the nearly 5,000 laboratory-confirmed controls invited to participate, we analysed the responses of 651 individuals for the cross-sectional analysis at month 6.

Statistical analysis: Baseline characteristics and changes in EQ-5D responses

We summarised the baseline characteristics of respondents in terms of demography. To evaluate representativeness, we compared these with (1) the limited demographic information we had for non-respondents, and (2) the population in England. For respondents, we further analysed the symptom status, COVID-19-related resource use and private expenditures, and the health-related quality of life as measured on the 5 domains of the EQ-5D and the VAS. Changes of the EQ-5D responses over time were also described as compared to the pre-COVID baseline [13].

Statistical analysis: Longitudinal QALY losses per patient

We calculated individual patient-level QALYs lost due to COVID-19 over up to 6 months using the utility value set of the EQ-5D-5L and the EQ-5D-3L in England [14-16]. In sensitivity analysis, we used different international value sets [17-20] (see Appendix for details). We estimated QALY losses per patient based on dis-utilities, i.e. the difference of a utility value indicating perfect health (of 1.0).

We analysed the total individual patient-level QALY loss as the dependent variable in linear regression models with bias-corrected and accelerated confidence intervals based on the nonparametric bootstrap [21]. We explored adjusting for the impact of age, sex, pregnancy status, ethnicity, the presence of comorbidities, having been told to shield in the early phase of the pandemic ("shielding") [22], reporting being symptomatic at month 6, the household size, geographical region, the mode of survey submission (online or postal), the reason for being tested, the strain variant (Wildtype or Alpha), being vaccinated against seasonal influenza in 2020-2021, being fully vaccinated against COVID-19, and the pre-COVID-19 baseline utility [23]. No responses were imputed given the large proportion of missing values [24].

We then calculated the COVID-19-related burden at the population-level using our estimated QALY losses per case by age, which we compared to the QALY losses per death by age [25] (considering the 6.4 million confirmed cases and 118,858 COVID-19-related deaths in England by September 19, 2021; https://coronavirus.data.gov.uk/). We also used post-hoc weighting by age group and sex to account for the imbalances in our sample versus the population in England.

For ease of presentation, we converted the results in the main text to quality-adjusted life days (QALDs) by multiplying the QALYs with a value of 365.25 days.

Statistical analysis: Comparison of EQ-5D responses between cases and controls at month 6

For the cross-sectional analysis at month 6, we used conditional logistic regression models based on the matched geographical regions to investigate the association of each symptom and EQ-5D dimension with the persistence of symptoms reported by month 6 (with the EQ-5D dimensions coded as 0 = no limitation, 1 = any limitation). For the continuous EQ-5D health utility index values at month 6, we used multivariable linear regression models (similar to above), after finding no heterogeneity between regions when using a mixed-effects regression model. We included an additional indicator variable to distinguish cases from controls.

Given that the respondents reported on results for fewer than 12 months we did not apply discount rates [3, 4].

All analyses were conducted in R (R Core Team, Vienna, Austria).

Ethics

Ethical approval for this study was not required as the collection of information on patients' quality of life is part of the statutory tasks and routine surveillance activities of Public Health England and its legal successor, the UK Health Security Agency.

Results

Participant characteristics and descriptive statistics

The mean age of cases was 41.1 years at baseline (95% uncertainty interval, 95%-UI: 13.0-74.0), and 61.5% identified as female (81.6%; Table 1). At month 6, the mean age of responding cases was 49.4 years (13.9-78.1), and 61.8% identified as female. This compares with the controls who had a mean age of 45.4 years (16.0-72.8) and 70.7% identifying as female. Further demographic details of the participants are summarised in Table 1. Our respondents over-represented middle-aged adults, women, people of white ethnicity and individuals from London than the non-respondents and the population in England (Supplementary Figures 1 to 4). Post-stratification weights by age and sex were applied to partially correct for these differences.

Physical symptoms, healthcare resource use and private expenditures

Over 95% of cases reported any symptom in the first 7 days of being tested or onset of being ill, which decreased to a weighted mean of 35.7% (183/548) at week 4, 20.4% (109/548) at week 12 and 19.7% (92/548) by month 6. More than 50% reported symptoms of headache, extreme tiredness/lack of energy, loss of taste and/or loss of smell, and muscle aches (Figure 1). At month 6, the most frequently reported symptoms were extreme tiredness, headache, loss of taste and smell, and shortness of breath. Unweighted estimates were very similar to the weighted estimates (Supplementary Figure 5).

In terms of healthcare resource use (excluding hospital care), cases most frequently reported GP visits (15.5%; Table 2). Furthermore, 45.3% of cases reported taking non-prescription medicines to manage their COVID-19 illness, with private expenditures of a mean of £18.07 (median: £10.00, range: £0.50, £200.00). 38.0% of cases reported being cared for and/or caring for someone else with COVID-19. In both situations, the duration of caring was for a mean of 11 days (Table 2). Another 52.7% of cases missed work or school due to their COVID-19 episode, for an estimated total of a mean of 12 days (which may partly reflect infection control legislation that required 10 days of self-isolation). 20.8% of cases reported receiving other paid help, with mean expenditures of £61.35 (median: £25.00, range: £2.00, £1,000.00).

Changes in health-related quality of life (EQ-5D), VAS and index utilities

The proportion of cases reporting any problems on the EQ-5D was lowest before the COVID-19 episode (Figure 2a). In comparison, on the worst day of the COVID-19 episode more than 80% of cases reported experiencing pain or discomfort. By week 2, the proportion who reported problems with self-care was restored to pre-COVID-19 baseline levels, while problems on the other dimensions returned to pre-COVID-19 baselines around week 8. Slight-to-moderate anxiety / depression were observed most frequently at the pre-COVID-19 baseline and again after week 2 through month 6 (Figure 2a, Supplementary Figure 6).

Compared to the pre-COVID-19 baseline, 81% of cases reported a worse health state on the worst day of their illness, which decreased to 27% by month 6 (Figure 2b). However, 69.3% of cases reported no issues at their last recorded observation.

Using the VAS and the EQ-5D index utility values, responses followed a similar trend to the responses on the individual domains in dropping off sharply on the worst day of illness, and

recovering by week 4-6 (Figure 2). Index utilities mapped to the EQ-5D-3L were slightly lower than those of the EQ-5D-5L for the UK, and at similar levels to the other international value sets (Supplementary Figure 7).

Longitudinal QALY losses in SARS-CoV-2(+) cases

With a mean follow-up duration of 77.9 days (weighted mean: 84.5 days), the unadjusted health loss due to COVID-19 ranged between 8.8 and 13.9 QALDs with the EQ-5D value sets of different countries (Supplementary Table 1). The unadjusted health loss for just the recovered individuals was lower between 4.7 and 7.3 QALDs (Supplementary Table 1).

The adjusted health losses of the COVID-19 cases were 13.7 (95%-CI: 9.7, 17.7) QALDs with the EQ-5D-3L (Table 3), which also resulted in the highest losses among international value sets (Supplementary Table 2). Notably, the health losses were higher for cases who returned surveys by post than online (Supplementary Figure 8), despite being of similar age (47.9 vs 43.0 years) and sex (60.2% female vs 63.8%, respectively). Generally, the health loss of cases increased by age from 7.2 (5.5, 9.0) QALDs in ages 12-24 years to 22.4 (14.6, 30.2) QALDs in ages 65+ years, and it was higher for cases who reported symptoms at month 6 (32.9, 95%-CI: 24.5, 37.6) versus cases who did not report symptoms at month 6 (8.8, 95%-CI: 5.8, 12.1); see Figure 3a, Table 3, and Supplementary Table 3. Cumulatively, the COVID-19-related QALY loss from morbidity contributes 18.2% of the total QALY loss attributed to COVID-19 morbidity and mortality in England by mid-September 2021, and the morbidity was higher than the losses from COVID-19-related mortality in age groups younger than 45-54 years (Figure 3b).

Cross-sectional analysis at month 6 of SARS-CoV-2(+) cases and SARS-CoV-2(-) controls

Cases were more likely to report physical symptoms than controls, particularly extreme tiredness, headache, loss of taste and/or smell, shortness of breath, and cough (Figure 3). Cases with persistent symptoms also had more difficulties with muscle aches and other symptoms than controls or recovered cases (Figure 4). In separate EQ-5D dimensions, cases more frequently reported problems with doing usual activities than controls, while controls more frequently reported problems with pain / discomfort and anxiety / depression than cases but differences were not significant (Figure 5). The adjusted utility index values improved for cases without symptoms but were worse for symptomatic individuals, irrespective of using the EQ-5D-3L (Table 4) or the EQ-5D-5L (Supplementary Table 4).

Discussion

This study explored the health-related quality of life impact of non-hospitalised, laboratory-confirmed COVID-19 cases in England prior to the implementation of a national vaccination programme. We estimated substantial long-term health impacts for cases, and QALY losses that increased by age. Cumulatively, the total COVID-19-related QALY loss from morbidity in England was higher than the loss from mortality in age groups younger than 45-54 years. This estimate ignores the QALY loss of hospitalised, non-fatal cases [26], and the under-reporting of non-fatal COVID-19 cases [27]. However, it stresses the importance of the COVID-19-related morbidity [25], and the shortcoming of using deaths and hospitalisations as the main metrics for the severity of an epidemic.

Furthermore, cases without symptoms were in better health than controls without symptoms at month 6. These results may point towards coping in cases and potential mental health impacts felt from the COVID-19 pandemic and resultant restrictions (once the physical health is restored), as previously shown for the general populations in multiple countries [28-30]. Some of the HRQoL loss in controls may also come from isolation and reporting symptoms of other respiratory diseases. Our covariates on the seasonal influenza and COVID-19 vaccines may also capture the impact of any non-fatal side effects. However, we caution about the predictive ability of the models.

Previous studies on the QALYs lost in COVID-19 cases have been limited and focussed on the acute illness [31]. Differences to previous studies on the H1N1pdm2009 pandemic influenza virus in the UK [12] and in Spain [11] may partly be explained by a more severe and/or longer-lasting health impact of COVID-19, and how the general population values their health differently during the COVID-19 pandemic [32].

Strengths and Limitations

This study is one of the first to provide longer-term QALY estimates associated with non-hospitalised COVID-19 in the UK. We also recruited a control group for the cross-sectional analysis, which is not often available in other studies. The study is ongoing, and longitudinal results for the cases and controls over 12 months will be reported separately later.

As cases were recruited after testing positive for SARS-CoV-2, they completed versions of the EQ-5D retrospectively about their pre-COVID-19 baseline health. Such a design is common, and while this may introduce recall bias most cases in our sample completed the initial survey within 4 weeks of symptom onset. Also, the retainment of cases with worse health may be higher in those who return surveys by post (which we accounted for in the models). Although all respondents were randomly sampled from the group of individuals in the population who were PCR-tested in November 2020, and we applied post-hoc weighting by age group and sex for more representative results, we also cannot rule out that controls are not representative of the general population on account of their being PCR tested.

We also provided results for both utility value sets in England given that mapping from the responses on the EQ-5D-5L to the EQ-5D-3L is currently recommended [14, 15], but this position has been criticised [33].

Our drop in responses after the initial survey may partly be the result of responders' fatigue, and cases who recovered and stopped returning follow-up surveys (as more than two-third of cases

reported no issues at their last recorded observation). We did not calculate QALYs for children aged younger than 12 years in the absence of a validated EQ-5D value set, and the adult value sets likely being inadequate to be used in children [34]. Furthermore, we did not enquire about the impact on other family members and partners who have shown to be impacted, too [35].

In conclusion, our study quantified the QALY loss due to COVID-19 in England for a prolonged time after the acute illness episode, which increased by age and was higher for cases who reported symptoms at 6 months. We also showed that there is a substantial quality of life burden due to non-fatal COVID-19 at a population level, and particularly in younger ages.

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Potential conflicts of interest

The Immunisation Department at PHE (and the UK Health Security Agency as the legal successor) has provided post-marketing surveillance reports to Marketing Authorisation Holders which they are required to submit to the UK Licensing authority in compliance with their Risk Management Strategy. A cost recovery charge is made for these reports. FS reports salary from UK Health Security Agency and LSHTM until October 31st, 2021 and salary since November 1st, 2021 from European Centre for Disease Prevention and Control (but works on this paper in own time and personal capacity; it is not supported/funded by ECDC in any way). WJE reports support for the current study from Medical Research Council and European Union, Horizon 2020 paid to the institution. MK reports consulting fees from Gilead Sciences Inc. MR reports the Immunisation Department provides vaccine manufacturers (including Pfizer) with post-marketing surveillance reports about pneumococcal and meningococcal disease which the companies are required to submit to the UK Licensing authority in compliance with their Risk Management Strategy, a cost recovery charge is made for these reports. GD reports their employer was previously known as Public Health England and previously received funding from GSK for a research project related to influenza antiviral treatment that preceded and had no relation to COVID-19, however, they have had no role in this work or received any funding from this project. RE reports funding for the current study from MRC paid to the institution as a regular grant.

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Figure Legends

Figure 1: Physical symptoms reported in each survey by the SARS-CoV-2(+) cases over 6 months weighted by age and sex of the population in England. Symptoms that have been seen as key indicators in the UK for members of the public to request a PCR test for COVID-19 are indicated in a darker colour and starred (i.e., fever of 38.8 C or higher, a new cough, or loss of taste and/or smell). The panels are rank-ordered by the proportion of symptoms in the first 7 days (top-left panel). Given the potential delay in symptom onset, getting PCR tested, and receiving the initial survey, the first survey enquired about the symptom status of cases within the first 7 days of feeling ill as well as if still feeling unwell today (week 0).

Figure 2. Results on the EQ-5D by the SARS-CoV-2(+) cases in each survey. Proportion of cases without any limitations reported per survey (panel a); percentage change of health states per survey (panel b); mean value of the visual analogue scale (panel c); EQ-5D utility index values using the UK value sets (panel d).

Figure 3. COVID-19-related quality-adjusted life day (QALD) losses per case by age group and presence of reported symptoms at month 6 (panel a ; raw data versus fitted results that were post-hoc weighted by sex), and the total COVID-19-related quality-adjusted life years (QALY) loss of cases versus deaths by age group in England at population-level (panel b). QALDs are equivalent to the number of QALYs*365.25 days.

Figure 4. Comparison of the physical symptoms reported by the SARS-CoV-2(+) cases and SARS-CoV-2(-) controls at month 6 (panel a), and the association between cases (and cases with persistent symptoms) and physical symptoms (panel b). Panel a) shows the unadjusted results with 95% binomial confidence intervals (unweighted, and weighted by age and sex), and panels b) shows the conditional logistic regression results.

Figure 5. Comparison of the limitations per EQ-5D dimension reported by the SARS-CoV-2(+) cases and SARS-CoV-2(-) controls at month 6 (panel a), and the association between cases (and cases with persistent symptoms) and limitation per EQ-5D dimension (panel b). Panel a) shows the unadjusted results with 95% binomial confidence intervals (unweighted, and weighted by age and sex), and panels b) shows the conditional logistic regression results.

Tables

Table 1. Demographic characteristics and summary of the SARS-CoV-2(+) cases at baseline, and of the SARS-CoV-2(+) cases and SARS-CoV-2(-) controls at month 6.

		SARS-CoV-2(+) cases		SARS-CoV-2(-) controls
		Baseline (n=548)	Month 6 (n=157)	Month 6 (n=651)
Parameter	**Category**	**n (%)**	**n (%)**	**n (%)**
Age group	12-24	110 (20.07%)	14 (8.92%)	62 (9.52%)
	25-34	84 (15.33%)	15 (9.55%)	104 (15.98%)
	35-44	105 (19.16%)	23 (14.65%)	137 (21.04%)
	45-54	123 (22.45%)	42 (26.75%)	148 (22.73%)
	55-64	81 (14.78%)	40 (25.48%)	142 (21.81%)
	65+	40 (7.30%)	23 (14.65%)	58 (8.91%)
	unknown	5 (0.91%)	0 (0.00%)	0 (0.00%)
Sex	Female	337 (61.50%)	97 (61.78%)	460 (70.66%)
Pregnant	Yes	7 (1.28%)	6 (3.82%)	5 (0.77%)
Ethnicity	Asian/Asian British	61 (11.13%)	11 (7.01%)	42 (6.45%)
	Black/African/ Caribbean/Black British	15 (2.74%)	2 (1.27%)	24 (3.69%)
	Mixed/Multiple	14 (2.55%)	1 (0.64%)	13 (2.00%)
	Other ethnic group	7 (1.28%)	0 (0.00%)	7 (1.08%)
	unknown	4 (0.73%)	1 (0.64%)	0 (0.00%)
	White British/Other White	447 (81.57%)	142 (90.45%)	565 (86.79%)
Region	East Midlands	49 (8.94%)	16 (10.19%)	56 (8.60%)
	East of England	45 (8.21%)	16 (10.19%)	58 (8.91%)
	London	78 (14.23%)	21 (13.38%)	100 (15.36%)
	North East	26 (4.74%)	12 (7.64%)	41 (6.30%)
	North West	52 (9.49%)	14 (8.92%)	72 (11.06%)
	South East	86 (15.69%)	30 (19.11%)	117 (17.97%)
	South West	34 (6.20%)	12 (7.64%)	42 (6.45%)
	unknown	70 (12.77%)	0 (0.00%)	0 (0.00%)
	West Midlands	59 (10.77%)	20 (12.74%)	95 (14.59%)
	Yorkshire and The Humber	49 (8.94%)	16 (10.19%)	70 (10.75%)
Comorbidities	Asthma	72 (13.14%)	13 (8.28%)	83 (12.75%)
	Diabetes	21 (3.83%)	8 (5.10%)	37 (5.68%)
	Heart condition	15 (2.74%)	1 (0.64%)	19 (2.92%)
	Hypertension	53 (9.67%)	8 (5.10%)	66 (10.14%)
	Low immunity	7 (1.28%)	0 (0.00%)	19 (2.92%)
	Lung breathing	8 (1.46%)	4 (2.55%)	22 (3.38%)
	Neurological	9 (1.64%)	2 (1.27%)	20 (3.07%)
	None of these	397 (72.45%)	128 (81.53%)	456 (70.05%)
	Other major health	28 (5.11%)	11 (7.01%)	29 (4.45%)

Shielding	Yes	64 (11.68%)	10 (6.37%)	36 (5.53%)
Household size	1	93 (16.97%)	33 (21.02%)	137 (21.04%)
	2	114 (20.80%)	49 (31.21%)	170 (26.11%)
	3	113 (20.62%)	27 (17.20%)	142 (21.81%)
	4	128 (23.36%)	30 (19.11%)	129 (19.82%)
	5+	100 (18.25%)	18 (11.46%)	73 (11.21%)
Vaccinated	Seasonal influenza (2020-2021)	106 (19.34%)	20 (12.74%)	335 (51.46%)
	COVID-19 (2 doses)	0 (0.00%)	107 (68.15%)	643 (98.77%)
Mode of response	Online	357 (65.15%)	106 (67.52%)	651 (100.00%)
	Postal	191 (34.85%)	50 (31.85%)	0 (0.00%)
	Online & postal	0 (0.00%)	1 (0.64%)	0 (0.00%)
Test reason	In contact with a case	106 (19.34%)	27 (17.20%)	NA
	Other reason/ illness	30 (5.47%)	10 (6.37%)	NA
	Suspected coronavirus	374 (68.25%)	112 (71.34%)	NA
	Tested for work	20 (3.65%)	2 (1.27%)	NA
	Tested in a care home	14 (2.55%)	5 (3.18%)	NA
	unknown	4 (0.73%)	1 (0.64%)	NA
Variant	Alpha	84 (15.33%)	30 (19.11%)	NA
	Wildtype	269 (49.09%)	84 (53.50%)	NA
	unknown	195 (35.58%)	43 (27.39%)	NA

Coronavirus disease 2019 (COVID-19), NA: not applicable, SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

Table 2. Frequencies of healthcare resource use, care taking, work and school absences, and receiving other help due to the COVID-19 illness episode, and personal costs of the SARS-CoV-2(+) cases over 6 months.

Parameter	**Category**	**Value** [b]
Healthcare utilisation [a]	Remote healthcare calls (NHS111)	69 (12.6%)
	Primary care (GP) visits	85 (15.5%)
	A&E visits	15 (2.7%)
	Other	68 (12.4%)
Drugs	Pain killers (i.e., ibuprofen, paracetamol, cough medication)	223 (40.7%)
	Antibiotics	10 (1.8%)
	Pain killers plus antibiotics	7 (1.3%)
	Other medication	33 (6.0%)
	None or unknown	300 (54.7%)
Caring due to the COVID-19 illness episode (received, or given to others)	I cared for someone else with coronavirus	91 (16.6%)
	Someone cared for me when I was ill	88 (16.1%)
	Both	29 (5.3%)
	No	331 (60.4%)
	Unknown	16 (2.9%)
Missing work or school due to the COVID-19 illness episode	Yes	289 (52.7%)
	No	253 (46.2%)
	Unknown	6 (1.1%)
Other help due to the COVID-19 illness episode (e.g. cleaner or deliveries)	Yes	114 (20.8%)
	No	423 (77.2%)
	Unknown	11 (2.0%)
Caring for someone (do we need n=? here)	Days, mean	10.74 (weighted mean: 9.44, sd: 9.44; median: 10; min: 1.00, max: 50.00)
Someone cared for you (do we need n=? here)	Days, mean	10.84 (weighted mean: 9.72, sd: 6.54; median: 10; min: 1.00, max: 35.00)
Days missed from work or school (do we need n=? here)	Days, mean	12.09 (weighted mean: 12.35, sd: 12.69; median: 10; min: 1.00, max: 164.00)
Drug costs	Expenditures (£), mean	18.07 (weighted mean: 18.08, sd: 24.01; median: 10; min: 0.50, max: 200.00)
Costs on other help	Expenditures (£), mean	61.35 (weighted mean: 76.90, sd: 118.20; median: 25; min: 2.00, max: 1000.00)

A&E: accident and emergency, COVID-19: coronavirus disease 2019, GP: general practitioner, NA: not applicable, NHS: National Health Service, SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

a: The small number of cases receiving hospital care after recruitment were excluded from this analysis.

b: Number and proportion, unless indicated otherwise.

Table 3: Adjusted QALD losses of the SARS-CoV-2(+) cases, and by SARS-CoV-2(+) cases who report symptoms at month 6.

Value set (EQ-5D)	Group	Unweighted results			Weighted results		
		Estimate	Lower 95%-CI	Upper 95%-CI	Estimate	Lower 95%-CI	Upper 95%-CI
UK (3L)	All cases	12.5	11.4	13.6	13.7	9.7	17.7
UK (5L)		9.2	8.4	10.0	10.1	7.1	13.2
UK (3L)	Cases without symptoms at month 6	8.1	7.4	8.8	8.8	5.7	11.9
UK (5L)		6.0	5.5	6.6	6.6	4.1	9.2
UK (3L)	Cases with symptoms at month 6	34.4	32.3	36.6	32.8	24.4	37.6
UK (5L)		24.8	23.0	26.6	23.4	16.9	27.6

CI: confidence interval, QALD: quality-adjusted life day, QALY: quality-adjusted life year, UK: United Kingdom.

Results are based on the final regression models of the QALY loss per EQ-5D value set and adjusted for baseline utility, reporting symptoms at month 6, age, pregnancy, household size, mode of response, having received the influenza vaccine in 2020-2021, and having received 2 COVID-19 vaccine doses. We post-hoc weighted results based on age and sex of the population in England.

Table 4. Multivariable linear regression models of the EQ-5D-3L utility index values of the SARS-CoV-2(+) cases and SARS-CoV-2(-) controls at month 6.

		Full model		Final model	
Parameter	**Category**	**Estimate**	**95%-CI**	**Estimate**	**95%-CI**
Intercept	Constant	0.9514***	0.7886, 1.0869	0.9233***	0.8540, 0.9862
Group	Cases	0.0759**	0.0234, 0.1341	0.0712***	0.0298, 0.1094
Symptomatic	Month 6	-0.0813***	-0.1308, -0.0417	-0.0919***	-0.1241, -0.0612
Age	numeric	-0.0010	-0.0024, 0.0005	-0.0009	-0.0018, 0.0001
Sex	Female	-0.0065	-0.0403, 0.0334	-	-
Pregnant	Yes	0.0346	-0.0460, 0.2001	-	-
Ethnicity [a]	Asian/Asian British	Reference	Reference	-	-
	Black / African/ Caribbean/ Black British	0.0640	-0.0032, 0.1367	-	-
	Other ethnic group	0.0242	-0.0665, 0.1155	-	-
	White British/ Other White	-0.0238	-0.0780, 0.0367	-	-
Region	East Midlands	Reference	Reference	-	-
	East of England	-0.0146	-0.1156, 0.0812	-	-
	London	0.0575	-0.0050, 0.1461	-	-
	North East	0.0388	-0.0264, 0.1233	-	-
	North West	0.0269	-0.0496, 0.1132	-	-
	South East	0.0378	-0.0382, 0.1311	-	-
	South West	0.0154	-0.0541, 0.1078	-	-
	West Midlands	0.0163	-0.0687, 0.0989	-	-
	Yorkshire and The Humber	0.0481	-0.0124, 0.1363	-	-
Comorbidities	None	0.0351	0.0047, 0.0797	0.0382*	0.0080, 0.0738
Shielding	Yes	-0.0863**	-0.1653, -0.0196	-0.0706**	-0.1407, -0.0159
Household size	numeric	-0.0043*	-0.0120, 0.0027	-0.0043**	-0.0128, 0.0020
Vaccinated	Seasonal influenza (2020-2021)	-0.0222	-0.0588, 0.0205	-0.0191	-0.0475, 0.0113
	COVID-19 (2 doses)	-0.0238	-0.1192, 0.0814	-	-
adj. R-squared			0.085		0.093
AIC			-197.5		-407.2
BIC			-99.3		-365.3

Note: Negative values represent worse HRQoL and positive values represent improved HRQoL.
a: Answers of "Mixed/Multiple ethnicity" were combined with "Other ethnic group" given very small numbers.
COVID-19 vaccination status not being significant in the final model may be impacted by the partial protection in vaccinated individuals, and our sample having been tested before the vaccination rollout started in England in December 2020.
Bias-corrected and accelerated (bca) confidence intervals (95%-CI) were based on the nonparametric bootstrap. Covariates with significance levels below $p < 0.1$ were entered in the multivariable analysis.
*** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$

Figure 1

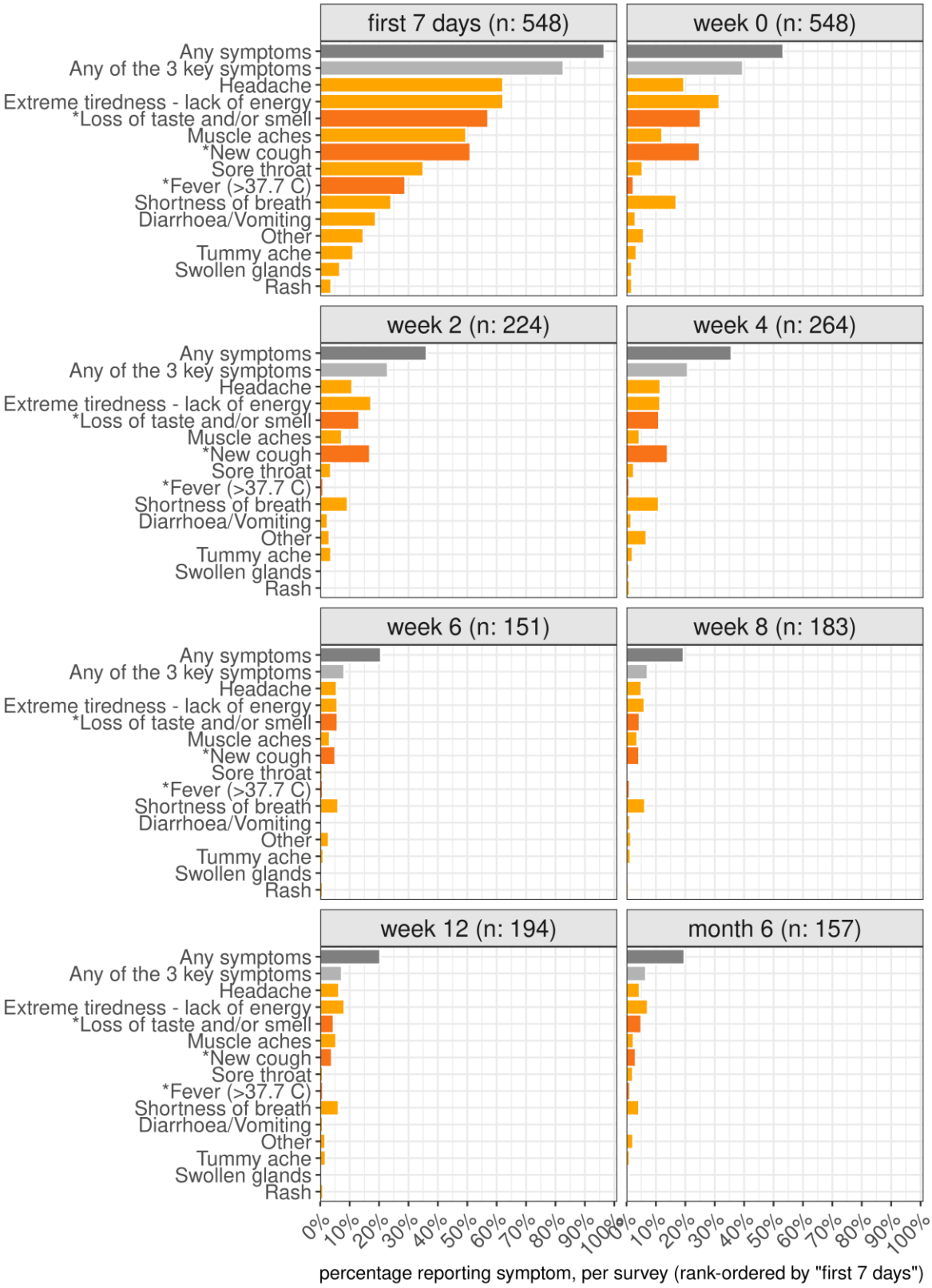
first 7 days (n: 548)
week 0 (n: 548)
week 2 (n: 224)
week 4 (n: 264)
week 6 (n: 151)
week 8 (n: 183)
week 12 (n: 194)
month 6 (n: 157)
Any symptoms
Any of the 3 key symptoms
Headache
Extreme tiredness - lack of energy
*Loss of taste and/or smell
Muscle aches
*New cough
Sore throat
*Fever (>37.7 C)
Shortness of breath
Diarrhoea/Vomiting
Other
Tummy ache
Swollen glands
Rash
0%
10%
20%
30%
40%
50%
60%
70%
80%
90%
100%
percentage reporting symptom, per survey (rank-ordered by "first 7 days")

Figure 2

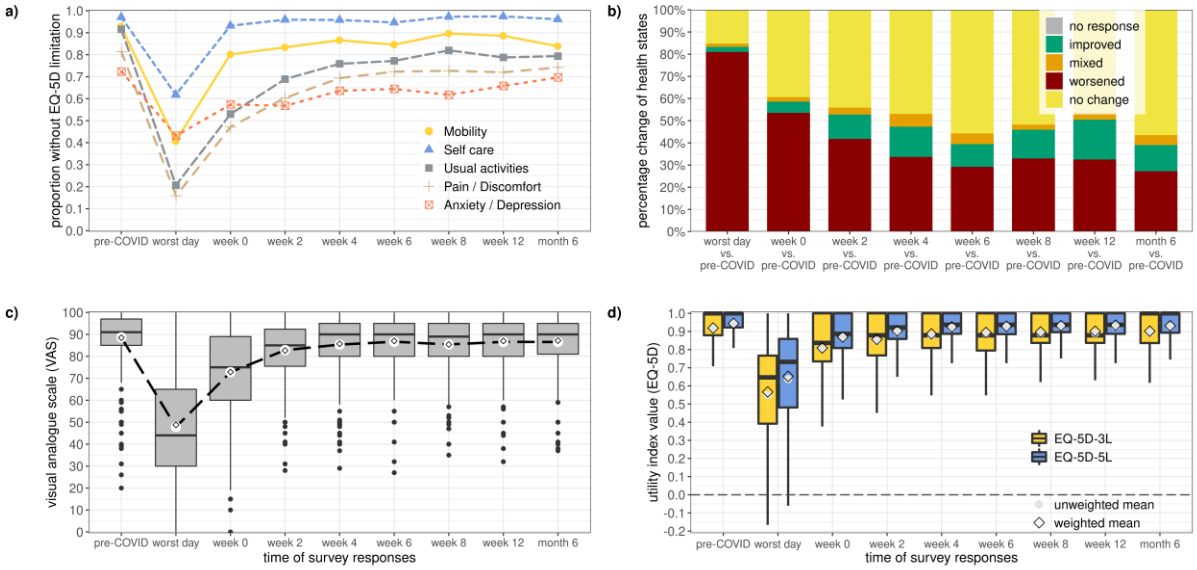

Figure 3

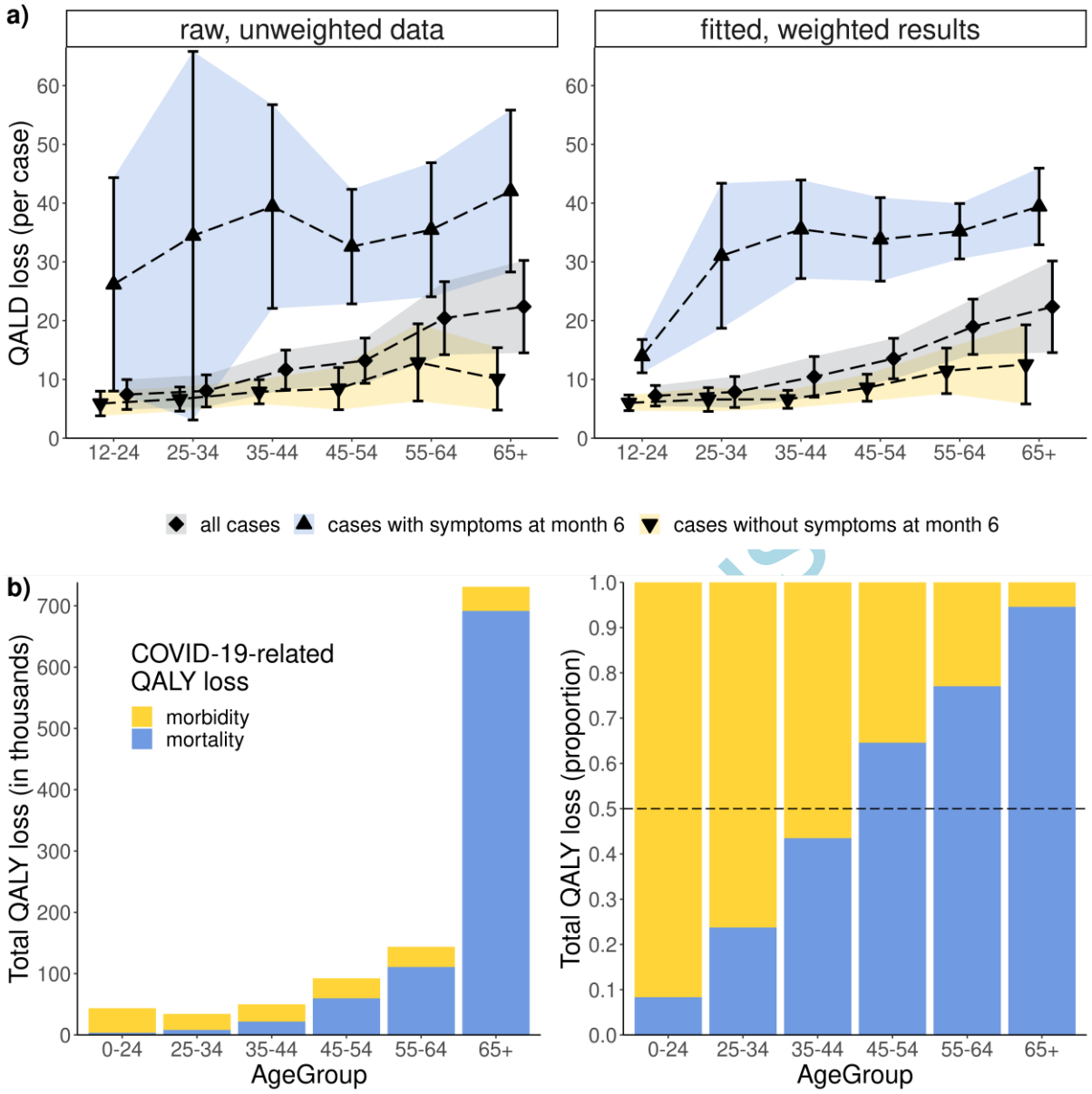

Figure 4

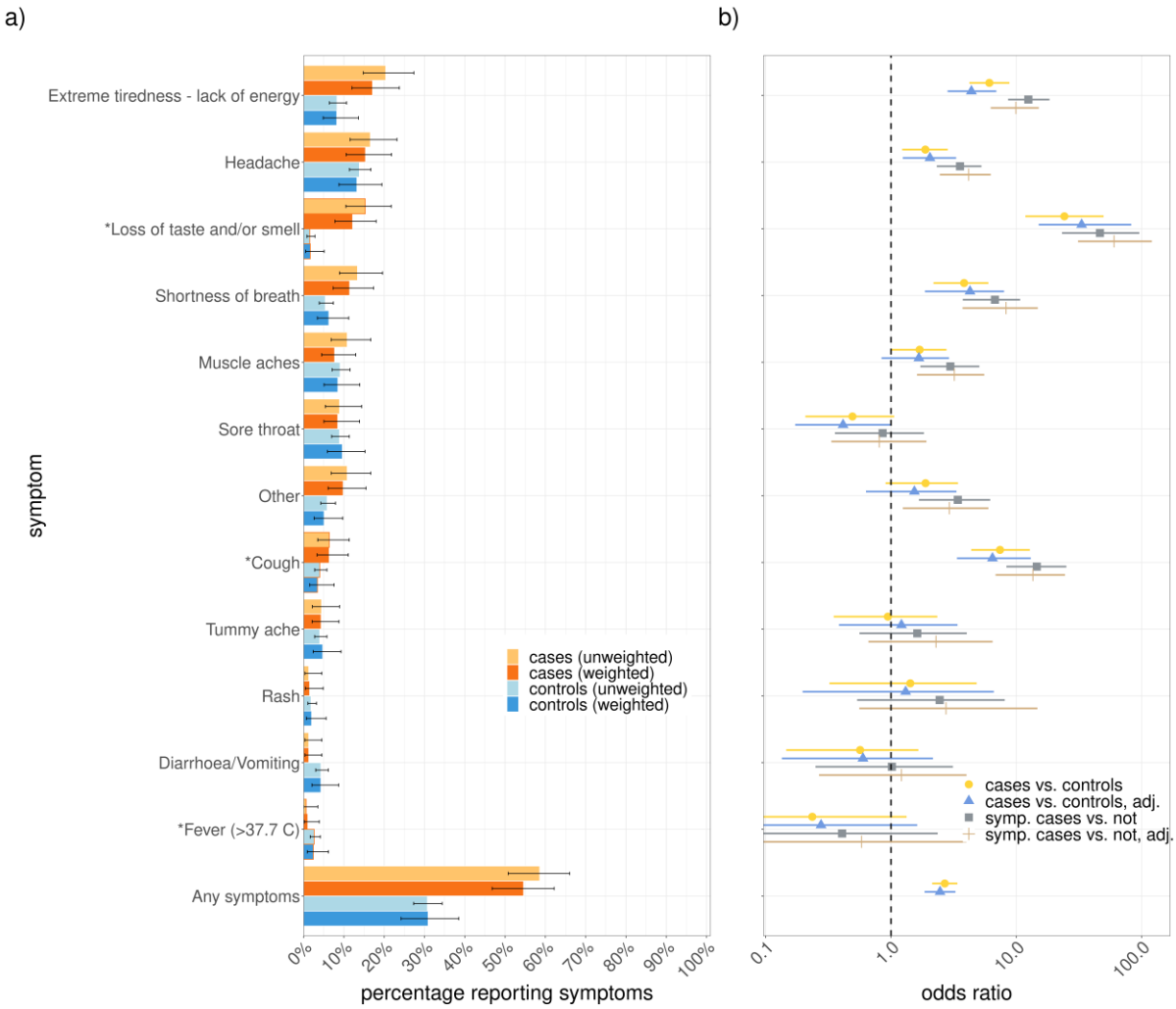

Figure 5