Appendix

Supplement to document 'What is the disease burden of COVID-19 by age-group and occupation category?'

Version of 16 Feb 2021

In this supplementary disease burden calculation, we estimate the impact on DALYs when the expected morbidity contributed by post-acute COVID-19 health states is included in the total disease burden. This is preliminary work based on very limited data sources, and so results should be considered in this context, as a first step towards computing the burden of post-acute consequences of COVID-19.

Methods

We estimate disease burden by age-group and by occupation category as before (see main report). The difference is the inclusion of an additional health outcome 'Post-acute consequences', and transition, after each of the Mild, Moderate and Severe health outcomes. Based on a non-exhaustive survey of the published and unpublished literature, we propose that post-acute consequences of COVID-19 can be divided into three distinct health states (Table S1), each with different disability weight, progression risk, and mean disability duration (where the latter two values can depend on the preceding health outcome; i.e. non-hospitalised vs. hospitalised COVID-19 disease; see Fig. S1). Given values for these parameters, the YLD calculation is straightforward; persons who survive each of the Mild, Moderate and Severe health outcomes have a certain probability to transition to one of these post-acute health states; YLD is then the product of the expected number of persons progressing to the health state, the mean duration in that state, and the assigned disability weight. The disability weights for the Persistent symptoms health state was chosen to match the health outcome Mild (acute) symptomatic infection, and the Post-acute syndrome health state has been previously put forward (Wyper et al., 2020); the disability weight for Anxiety was selected based on the GBD-2013 description (Table S1).

A non-systematic literature review was conducted to locate suitable parameter values for each health state among two groups: non-hospitalised and hospitalised (including ICU) ever-SARS-CoV-2 positive patients. (Note that we provisionally assign the same parameter values for post-acute health states following non-ICU (ie. Moderate) and ICU admissions (ie. Severe), as almost no study differentiated adequately between these two patient groups.) Ideally contributing studies should (i) be minimally affected by selection bias and so would be representative of the underlying populations of Mild and Moderate/Severe cases to allow the progression risk to be estimated, (ii) have sufficiently long follow-up time to estimate the mean duration of the health outcome, and (iii) report the risk of progression to the same health state among SARS-CoV-2 negative persons, so that progression probabilities can be

adjusted to indicate COVID-19 attributable risk. However, almost no study found to date met all of these criteria.

When multiple studies were available to inform a single parameter, the individual studies' parameter values were pooled using standard methods. 95% confidence intervals were derived assuming the patient counts are binomially distributed. The studies currently selected for inclusion are provided in Tables S2 and S3. For the health states Anxiety and Post-acute Syndrome following the Mild (non-hospitalised) infection health outcome, no suitable studies were found.

Below we describe the evidence available to inform the required parameters for each health state.

Health state* Persistent symptoms *following Mild symptomatic infection

For this health state three studies were available to inform the absolute risk among SARS-CoV-2 positives. This was the prevalence of one or more symptom at 4 weeks after the first week in which symptom(s) were reported (ONS), and 'LC28' (duration of symptom(s) 28 days or longer; Sudre et al.). For one study the prevalence of persistent symptoms among SARS-CoV-2 negative persons was available; this was 2.4% (C. Sudre, pers. comm.), which meant a risk ratio of 5.54 for symptom(s) associated with positivity could be applied to this study (and the other two), to yield an SARS-CoV-2 attributable risk (as the risk difference).

Sudre et al. (Suppl. Table 2) report odds ratios for persisting symptoms (LC28) among SARS-CoV-2 positives separately by sex and age-group (6 different age-groups, with <30 years as the reference category). Assuming these age-group ORs are identical for SARS-CoV-2 negatives, an absolute risk can be estimated for each age-group separately (see Foroutan et al., 2020). However, as solving for >2 unknowns requires numerical optimisation methods, we provisionally simplified by computing separate risks for two age-groups only: <30 and 30+ years, assuming an OR of 5.4 for 30+ years. We applied this method to the attributable risks for all three studies.

Disability duration was computed from the ONS study only, as prevalence was reported weekly until 12 weeks following week of first symptom; this allowed a more precise duration estimate to be made; right-censoring was a constraint for the other two studies. Given the lack of evidence for differing duration by age, we assume an age-independent parameter value.

Health state* Persistent symptoms *following Moderate/Severe symptomatic infection

Four studies were selected to inform the absolute risk of Persistent symptoms among previously hospitalised COVID-19 patients; all provided a proportion at study end (Huang et al.; Chopra et al.; Carfi et al.; Garrigues et al.). No data on the proportion with the same indicator among SARS-CoV-2 negative patients were available; therefore attributable risks could not be estimated. Median follow-up ranged from 60 to 186 days; mean disability duration was therefore taken from the study with the longest follow-up, adjusted to 168 days after subtracting the mean time in Mild and Moderate health outcomes (following Moderate; for Persistent symptoms following Severe (ICU admission) 39 days for time spent in the preceding health outcomes was subtracted, ie. 147 days).

Health state* Anxiety *following Moderate/Severe symptomatic infection

One study had data on the proportion with 'anxiety or depression' (Huang et al.), among positives only (meaning attributable risk could not be estimated). The mean disability duration was also taken from this study's reported median follow-up time after symptom onset (186 days); duration was adjusted to 168 days after subtracting the mean time in Mild and Moderate health outcomes (following Moderate; for Anxiety following Severe (ICU admission), 39 days for time spent in the preceding health outcomes was subtracted, ie. 147 days).

Health state* Post-acute syndrome *following Moderate/Severe symptomatic infection

Two studies provided data on the proportion with this health state among positives only (meaning attributable risk could not be estimated); however, the match between the selected indicators ('problems with usual activity' and 'New or worsening difficulty with daily life activities') and the description of post-acute syndrome (Table S1) was not particularly close. Mean disability duration was taken from the study with the longer follow-up (Huang et al.), adjusted to 168 days after subtracting mean time in Mild and Moderate health outcomes (following Moderate; for Post-acute syndrome following Severe (ICU admission), 39 days for time spent in the preceding health outcomes was subtracted, ie. 147 days).

To estimate the proportion of persons within each age-group who survived following Mild, Moderate and Severe infection and who could progress to post-acute health outcomes, we adapted age-group specific mortality probabilities among non-ICU and ICU patients that have been used in other modelling (supplied by D. Klinkenberg) to roughly estimate the number of survivors per age-group, and then subtracted the known numbers of persons admitted to hospital (or ICU, as appropriate). The progression risk was then applied to this number to estimate the number of persons in each post-acute health state. For now, we ignore the possibility that a given person could experience >1 simultaneous post-acute health state.

Results and discussion

The estimated number of persons developing a post-acute health outcome within the analysis period 27 Feb through 31 Dec 2020 is 170,800 (95% CI: 162,400 - 179,900). With the inclusion of these post-acute health states, the total DALYs is estimated at 108,600 (95% CI: 106,300 - 110,900) and the proportion of total DALYs contributed by YLD is 3.1% (Fig. S2). The proportion of total YLD due to post-acute consequences is estimated at 50.5%. For comparison, the estimated total burden without post-acute health states was 106,900 DALYs (95% CI: 104,600–109,300).

Fig. S3 shows the cumulative incidence per age-group and health state. The YLD per 100,000 attributed to Persistent symptoms, Anxiety and Post-acute syndrome differed by age, reflecting the age-dependence in the number of non-hospitalised (Mild) and hospitalised patients, and the differing progression probabilities between these groups (Fig. S4). Overall, the greatest YLD was due to the Persistent symptoms health state (Fig. S5).

We have not attempted to address the possible consequences of heterogeneity across studies regarding country of study, and particularly relevant for studies of previously hospitalised patients, variation in the treatment provided (e.g., frequent antibiotic usage: Huang et al.), variation in the distribution of underlying health problems/comorbidites, and variation in potentially important demographic factors such as sex, age, and ethnicity. We did incorporate age-related differences in risk for Persisting symptoms following Mild infection, but only (crudely) distinguished two age-groups.

We emphasise that these results very likely underestimate the true disease burden associated with post-acute consequences of COVID-19, as for two proposed health states crucial progression risk parameter values could not be located, and for all health states the disability duration parameters were influenced by administrative right censoring of follow-up. However, this underestimation will be counteracted by overestimation of progression risks, as except for one health state, adjustment for post-acute health states experienced by SARS-CoV-2 negative persons could not be made.

Little information is available to date to evaluate the plausibility of the estimated number of persons suffering from post-acute consequences of COVID-19 (n=171,000). The national Physiotherapists' Association estimate that at least 28,000 ex-COVID-19 patients aged between 20 and 60 years are being treated by their members (https://www.kngf.nl/actueel/2021/febr/cijfers-onderbouwen-ad-artikel-over-herstelzorg.html); this suggests a lower bound for the expected numbers.

References

Amenta EM, Spallone A, Rodriguez-Barradas MC, El Sahly HM, Atmar RL, Kulkarni PA. Postacute COVID-19: An Overview and Approach to Classification. Open forum infectious diseases 2020 Dec (Vol. 7, No. 12, p. ofaa509)

Carfì A, Bernabei R, Landi F. Persistent symptoms in patients after acute COVID-19. Jama. 2020 Aug 11;324(6):603-5.

Chopra V, Flanders SA, O'Malley M, Malani AN, Prescott HC. Sixty-Day Outcomes Among Patients Hospitalized With COVID-19. Annals of Internal Medicine. 2020 Nov 11.

Foroutan F, Iorio A, Thabane L,Guyatt G. Calculation of absolute risk for important outcomes in patients with and without a prognostic factor of interest. J Clin Epidemiol. 2020;117:46-51.

Garrigues, E., Janvier, P., Kherabi, Y., Le Bot, A., Hamon, A., Gouze, H., et al. Post-discharge persistent symptoms and health-related quality of life after hospitalization for COVID-19. Journal of Infection 2020;81(6): e4-e6.

Greenhalgh T, Knight M, Buxton M, Husain L. Management of post-acute covid-19 in primary care. BMJ. 2020 Aug 11;370

Huang C, Huang L, Wang Y, 5.1.2e, Ren L, Gu X, Kang L, Guo L, Liu M, Zhou X, Luo J. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. The Lancet. 2021.

Nehme M, Braillard O, Alcoba G, Aebischer Perone S, Courvoisier D, Chappuis F, Guessous I. COVID-19 Symptoms: Longitudinal Evolution and Persistence in Outpatient Settings. Annals of internal medicine. 2020 Dec 8.

Office for National Statistics (ONS). Estimating the prevalence of long COVID symptoms and COVID-19 complications. 16 Dec 2020. https://www.ons.gov.uk/releases/estimatingtheprevalenceoflongcovidsymptomsandcovid19complications

Sudre CH, Murray B, Varsavsky T, Graham MS, Penfold RS, Bowyer RC, Pujol JC, Klaser K, Antonelli M, Canas LS, Molteni E. Attributes and predictors of Long-COVID: analysis of COVID cases and their symptoms collected by the Covid Symptoms Study App. medRxiv. 2020. https://doi.org/10.1101/2020.10.19.20214494.

Wyper GM, Assunção RM, Colzani E, Grant I, Haagsma JA, Lagerweij G, et al. Burden of disease methods: a guide to calculate COVID-19 disability-adjusted life years. Int J Public Health. 2020.

Table S1. Proposed post-acute health states, definitions, and GBD-2013 disability weight (Salomon et al., 2015). GBD-2013 = Global Burden of Disease Study, 2013.

Health state	Definition	Disability weight
Persisting symptoms	Continuation of relatively mild symptom(s) characteristic of those experienced during acute infection phase	0.051
Anxiety	GBD-2013: "feels anxious and worried, which makes it difficult to concentrate, remember things, and sleep. The person tires easily and finds it difficult to perform daily activities."	0.133
Post-acute syndrome	A debilitating illness; daily activities are severely affected (person typically experiences fatigue, dyspnoea, headache, pain). GBD-2013: "is always tired and easily upset. The person feels pain all over the body and is depressed." Similar examples are: dengue, post-acute consequences; and post-acute Lyme disease syndrome.	0.219

Table S2. Non-hospitalised cases: included studies and absolute risk parameter values

Health state	Study indicator used	Estimated absolute risk in SARS-CoV-2 pos.	Lower 95%	Upper 95%	Source	Absolute risk in SARS-CoV-2 neg.*	Estimated absolute risk difference	Lower 95%	Upper 95%
Persisting symptoms	Prevalence of any of a long symptom list at 4 weeks following first week	0.239	0.228	0.249	ONS	*0.043*	0.196	0.187	0.204
Persisting symptoms	Prevalence of 1+ mild symptoms of mild infection "... which cause some difficulty with daily activities"	0.133 (558/4182)	0.123	0.144	Sudre et al.	0.024	0.109	0.101	0.118
Persisting symptoms	Proportion with 1+ symptoms ("fatigue, dyspnea, and loss of taste or smell were the main persistent symptoms")	0.32 (214/669)	0.285	0.357	Nehme et al.	*0.058*	0.262	0.233	0.292
Anxiety	*No studies located*								
Post-acute syndrome	*No studies located*								

Note. The ONS symptom list consist of fatigue, cough, headache, loss of taste, loss of smell, myalgia, sore throat, fever, shortness of breath, nausea/vomiting, diarrhoea, abdominal pain

Table S3. Hospitalised cases: included studies and absolute risk parameter values

Definition	Study indicator used	Estimated absolute risk in SARS-CoV-2 pos.	Lower 95%	Upper 95%	Source
Persisting symptoms	Proportion with "Fatigue or muscle weakness" (the most frequently reported symptom)	0.627 (1038/1655)			Huang et al.
Persisting symptoms	Proportion with "Cardiopulmonary symptoms (such as cough and dyspnea)"	0.326 (159/488)			Chopra et al.
Persisting symptoms	Proportion with fatigue (the most frequently reported symptom)	0.53 (76/143)			Carfi et al.
Persisting symptoms	Proportion with fatigue (the most frequently reported symptom)	0.55 (66/120)			Garrigues et al.
Anxiety	Proportion: "Anxiety or depression" (EQ-5D-5L)	0.227 (367/1617)			Huang et al.
Post-acute syndrome	Proportion: "Usual activity: problems with usual activity" (EQ-5D-5L)	0.016 (25/1611)			Huang et al.
Post-acute syndrome	Proportion: "New or worsening difficulty completing activities of daily living"	0.119 (58/488)			Chopra et al.

Fig. S1. Proposed clinical pathway progression model, including post-acute health states.

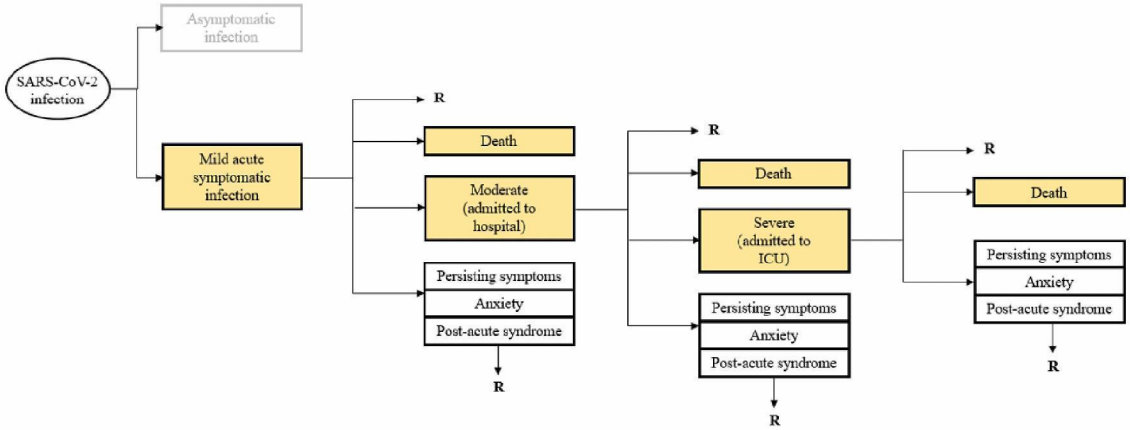

Fig. S2. Estimated DALY (split into YLD and YLL) when including post-acute health states, per 5-year age-group with 95% CIs, up to 31 Dec 2020. The inset plot zooms in on age-groups <1 years through 30-34 years

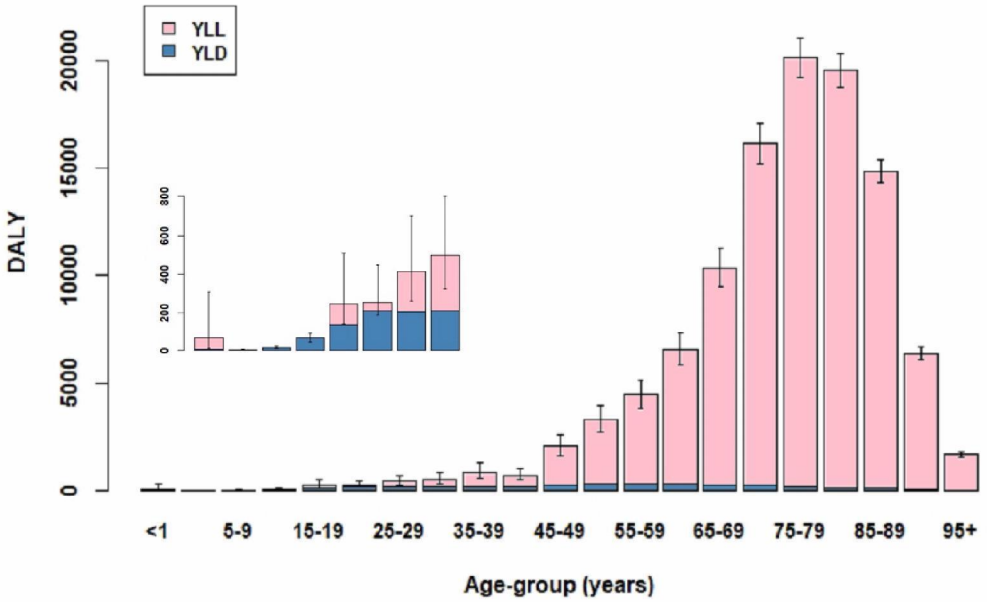

Fig. S3. Estimated cumulative incidence of post-acute health states only, per 5-year age-group with 95% CIs, up to 31 Dec 2020.

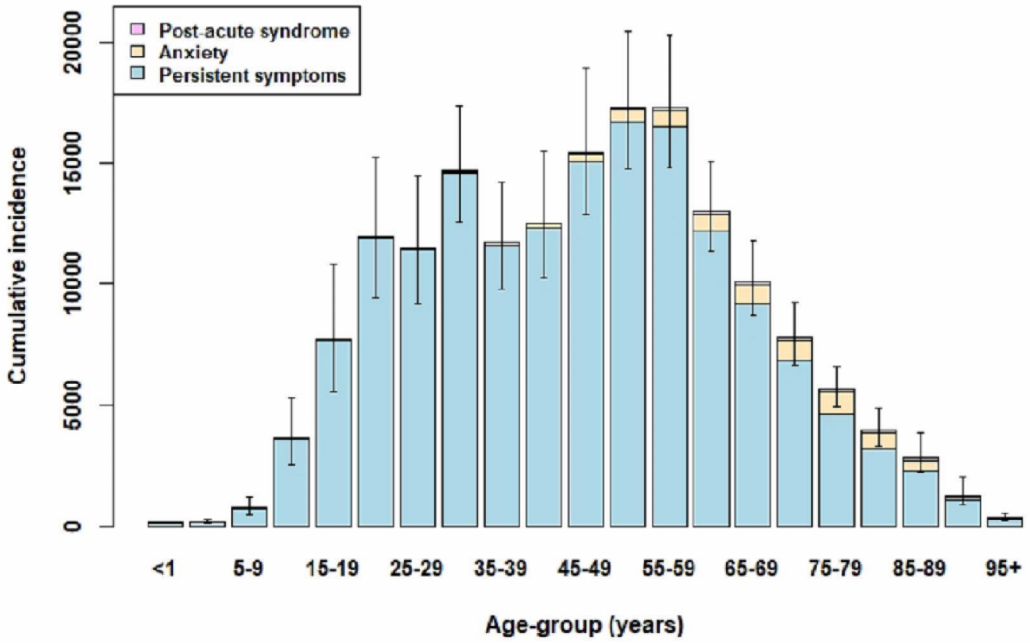

Fig. S4. Estimated YLD for post-acute health states only, per 5-year age-group with 95% CIs, up to 31 Dec 2020.

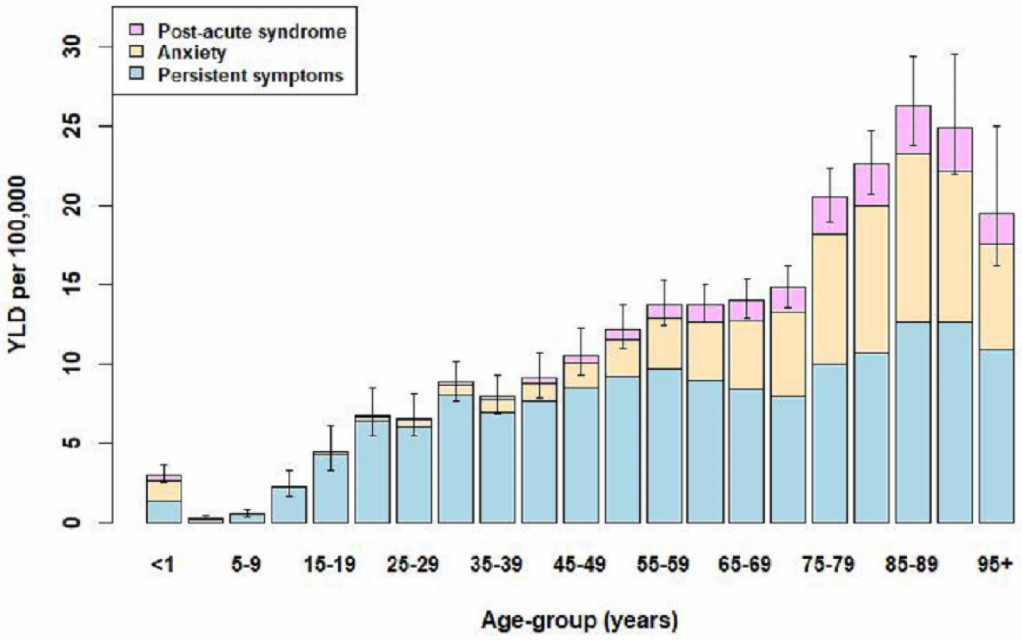

Fig. S5. Estimated YLD per post-acute health state (left panel) and estimated cumulative incidence (right panel), age-aggregated, with 95% CIs, up to 31 Dec 2020.

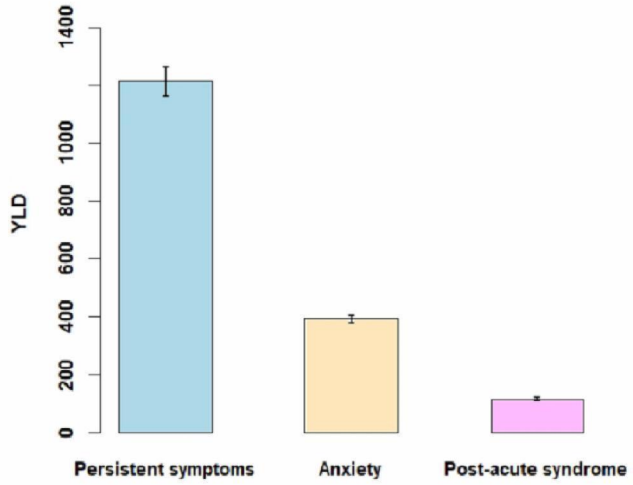

Fig. S6. Estimated relative disease burden per occupation category and 5-year age-group (as DALYs per 100,0000 persons in each category within each age-group, **including post-acute health states**), within 'full' analysis period (i.e., 27 Feb 2020 through 31 Dec 2020), and shown for the age range 20-69 years only. 'Not known' occupation imputed.